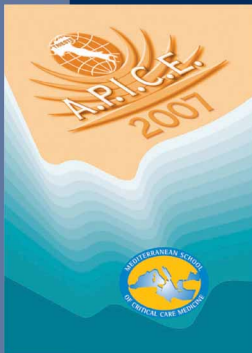


A. Gullo (Ed)

A.P.I.C.C.E. 22 Anaesthesia Pain Intensive Care and Emergency Medicine



Springer

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Anaesthesia, Pain, Intensive Care and Emergency – A.P.I.C.E.

Proceedings of the

22nd Postgraduate Course in Critical Care Medicine

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ANTONINO GULLO, M.D.

Head, Department of Anaesthesia and Intensive Care

Head, Postgraduated School of Anaesthesia and Intensive Care

Catania University Hospital

Catania, Italy

Library of Congress Control Number: 2007939172

ISBN 978-88-470-0772-7 Springer Milan Berlin Heidelberg New York

e-ISBN 978-88-470-0773-4 Springer Milan Berlin Heidelberg New York

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Printed in Italy

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Cover design: Simona Colombo

Typesetting and printing: Arti Grafiche Stella, Trieste, Italy

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List of Contributors

Abate M.G.

UO Neuroanestesia e Neuroranimazione, Dipartimento di Medicina Perioperatoria e Terapie Intensive, H San Gerardo, Monza (Italy), and Division of Anaesthesia, University of Cambridge, Addenbrooke's Hospital, Cambridge (UK)

Alexander R.

Department of Anaesthetics, Worcestershire Royal Hospital, Worcester (UK)

Astuto M.

Department of Anaesthesia and Intensive Care, "Policlinico" University Hospital, Catania (Italy)

Berlot G.

Department of Perioperative Medicine, Intensive Care and Emergency, Trieste University Medical School, Trieste (Italy)

Brodsky J.B.

Department of Anesthesia, Stanford University School of Medicine, Stanford, CA (USA)

Busoni P.

Department of Anaesthesia and Intensive Care, A. Meyer Hospital, Florence (Italy)

Calderan C.

Department of Perioperative Medicine, Intensive Care and Emergency, Trieste University Medical School, Trieste (Italy)

Cammarata G.

Department of Anaesthesia and Intensive Care, University of Catania, Cannizzaro (Italy)

Camporesi A.

Paediatric Anaesthesia and Intensive Care, Children Hospital "Vittore Buzzi", Milan (Italy)

Cannesson M.

Department of Anaesthesiology, Hôpital Louis Pradel, Bron (France)

Cariello C.

Department of Cardiothoracic Anaesthesia and Intensive Care, Azienda Ospedaliera Universitaria Pisana, Pisa (Italy)

Citerio G.

UO Neuroanestesia e Neuroranimazione, Dipartimento di Medicina Perioperatoria e Terapie Intensive, H San Gerardo, Monza (Italy)

Demetriades D.

Division of Trauma and Surgical Critical Care, Department of Surgery, University of Southern California, Los Angeles (USA)

DeVita M.A.

Department of Critical Care Medicine, University of Pittsburgh (USA)

DiGiacomo P.

Department of Critical Care Medicine, University of Pittsburgh (USA)

Disma N.

Department of Anaesthesia and Intensive Care, "Policlinico" University Hospital, Catania (Italy)

DuBose J.

Division of Trauma and Surgical Critical Care, Department of Surgery, University of Southern California, Los Angeles (USA)

Eich C.

Department of Anaesthesiology, Emergency and Intensive Care Medicine, University of Göttingen (Germany)

Foëx P.

Nuffield Department of Anaesthetics, University of Oxford (UK)

Frova G.

Emergency Department of Anaesthesia and ICU, Civili Hospital, Brescia (Italy)

Grüne F.

Department of Anaesthesiology, Erasmus University Medical Centre, Rotterdam (The Netherlands)

Guarino A.

Anaesthesia and Intensive Care, PO "Villa Scassi", Genoa (Italy)

Guarracino F.

Department of Cardiothoracic Anaesthesia and Intensive Care, Azienda Ospedaliera Universitaria Pisana, Pisa (Italy)

Gullo A.

Department of Anaesthesia and Intensive Care, "Policlinico" University Hospital, Catania (Italy)

Howard-Alpe G.

Nuffield Department of Anaesthetics, University of Oxford (UK)

Jevtovic-Todorovic V.

Departments of Anesthesiology and Neuroscience, University of Virginia Health System, Charlottesville (USA)

Klimek M.

Department of Anaesthesiology, Erasmus University Medical Centre, Rotterdam (The Netherlands)

Lehot J.-J.

Department of Anaesthesiology, Hôpital Louis Pradel, Bron (France)

Leykin Y.

Department of Anaesthesia, S.M. degli Angeli Hospital, Pordenone (Italy)

Marshall J.C.

Department of Surgery, and the Interdepartmental Division of Critical Care Medicine, University of Toronto, Li Ka Shing Knowledge Institute, St. Michael's Hospital, Toronto, Ontario (Canada)

Merli G.

Centro Cardiologico Monzino, Milan (Italy)

Moggia L.

Anaesthesiology and Intensive Care, University G. D'Annunzio Chieti-Pescara, Chieti (Italy)

Morello G.

Department of Anaesthesia and Intensive Care, "Policlinico" University Hospital, Catania (Italy)

Munari M.

Department of Pharmacology and Anaesthesiology, Anaesthesia and Intensive Care Unit, University of Padua, Padua (Italy)

Murabito P.

Department of Anaesthesia and Intensive Care, "Policlinico" University Hospital, Catania (Italy)

Noal N.

Department of Anaesthesia, S.M. degli Angeli Hospital, Pordenone (Italy)

Ori C.

Department of Pharmacology and Anaesthesiology, Anaesthesia and Intensive Care Unit, University of Padua, Padua (Italy)

Ottens T.H.

Department of Anaesthesiology, Erasmus University Medical Centre, Rotterdam (The Netherlands)

Paratore A.

Department of Anaesthesia and Intensive Care, "Policlinico" University Hospital, Catania (Italy)

Pellegrino S.

Department of Anaesthesia and Intensive Care, "Policlinico" University Hospital, Catania (Italy)

Petrini F.

Anaesthesiology and Intensive Care, University G. D'Annunzio Chieti-Pescara, Chieti (Italy)

Priebe H.-J.

Department of Anaesthesia, University Hospital, Freiburg (Germany)

Ristagno G.

Weil Institute of Critical Care Medicine, Rancho Mirage, CA (USA) and Department of Perioperative Medicine, Intensive Care and Emergency, Trieste University Medical School, Trieste (Italy)

Rubulotta F.

Department of Anaesthesia and Intensive Care, "Policlinico" University Hospital, Catania (Italy)

Russo S.

Department of Anaesthesiology, Emergency and Intensive Care Medicine, University of Göttingen (Germany)

Sala F.

UO Neuroanestesia e Neuroranimazione, Dipartimento di Medicina Perioperatoria e Terapie Intensive, H San Gerardo, Monza (Italy)

Salvo I.

Paediatric Anaesthesia and Intensive Care, Children Hospital "Vittore Buzzi", Milan (Italy)

Sanalitto E.

Department of Anaesthesia and Intensive Care, "Policlinico" University Hospital, Catania (Italy)

Saxena A.

Department of Anaesthesia, Worcestershire Royal Hospital, Worcester (UK)

Sorbello M.

Department of Anaesthesia and Intensive Care, "Policlinico" University Hospital, Catania (Italy)

Tang W.

Weil Institute of Critical Care Medicine, Rancho Mirage, CA (USA) and Keck School of Medicine, University of Southern California, Los Angeles, CA (USA)

Timmermann A.

Department of Anaesthesiology, Emergency and Intensive Care Medicine, University of Göttingen (Germany)

Ungerstedt U.

Dept of Physiology and Pharmacology, Karolinska Institutet, Stockholm (Sweden)

van der Voort P.H.J.

Department of Intensive Care, Onze Lieve Vrouwe Gasthuis, Amsterdam (The Netherlands)

van Houdenhoven M.

Director Beatrix-Hospital, Gorinchem (The Netherlands)

Vergolini A.

Department of Perioperative Medicine, Intensive Care and Emergency, Trieste University Medical School, Trieste (Italy)

Vincent J.-L.

Department of Intensive Care, Erasme Hospital, Free University of Brussels (Belgium)

Volpin S.

Department of Pharmacology and Anaesthesiology, Anaesthesia and Intensive Care Unit, University of Padua, Padua (Italy)

Wang T.

Weil Institute of Critical Care Medicine, Rancho Mirage, CA (USA)

Zoia E.

Paediatric Anaesthesia and Intensive Care, Children Hospital "Vittore Buzzi", Milan (Italy)

List of Abbrevations

α -MNE	α -Methylnorepinephrine
A wave	Atrial Peak Velocity
A	Adenine
ABP	Arterial Blood Pressure
ABS	Analgesia-Based Sedation
AC	Alternating Current
ACC	American College of Cardiology
ACE	Angiotensin-Converting Enzyme
ACLS	Advanced Cardiac Life Support
ACS	Abdominal Compartment Syndrome
ACS	Acute Coronary Syndrome
ACUITY	Acute Catheterization and Urgent Intervention Triage Strategy
AE	Accidental Extubation
AECOPD	Acute Exacerbation of COPD
AGNB	Aerobic Gram Negative Bacteria
AHA	American Heart Association
AHRQ	Federal Agency Healthcare Research and Quality
ALI	Acute Lung Injury
Am	Late Diastole
AMAF	Airway Management Assessment Forms
APACHE	Acute Physiology Chronic Health Evaluation
AR	Aortic Regurgitation
ARDS	Acute Respiratory Distress Syndrome
ARF	Acute Renal Failure
ATLS	Advanced Trauma Life Support
AVDO ₂	Arteriovenous Oxygen Content Difference
BAEP	Brainstem Auditory Evoked Potentials

BBB	Blood-Brain Barrier
BDNF	Brain-Derived Neurotrophic Factor
BGA	Blood Gas Analysis
BIS	Bispectral Index
BMI	Body Mass Index
BV	Blood Volume
C	Cytosine
CABG	Coronary Artery Bypass Grafting
CAS	Central Anticholinergic Syndrome
CBF	Cerebral Blood Flow
CBV	Cerebral Blood Volume
CCI	Controlled Cortical Impact
CCI	Corrected Colonisation Index
CCT	Critical Care Outreach Teams
CFD	Colour Flow Doppler
CI	Cardiac Index
CI	Confidence Interval
CMRO ₂	Cerebral Metabolic Rate of Oxygen
CNS	Central Nervous System
COPD	Chronic Obstructive Pulmonary Disease
CPA	Cardiopulmonary Arrest
CPAP	Continuous Positive Airway Pressure
CPK	Creatine Phosphokinase
CPP	Cerebral Perfusion Pressure
CPR	Cardiopulmonary Resuscitation
CQI	Continuous Quality Improvement
CRRT	Continuous Renal Replacement Therapy
CSA	Compressed Spectral Arrays
CSHT	Context-Sensitive Half Time
CSI	Cerebral State Index
CV-CI	Cannot Ventilate – Cannot Intubate
CVP	Central Venous Pressure
D wave	Diastolic Wave Velocity
DAM	Difficult Airway Management

DC	Decompressive Craniectomy
DISC	Death-Inducing Signalling Complex
DMV	Difficult Mask Ventilation
DNA	Deoxyribonucleic Acid
DSA	Density Modulated Spectral Arrays
DSE	Dobutamine Stress-Echocardiogram
DT	Deceleration Time
E wave	Early Filling Peak Velocity
EBM	Evidence Based Medicine
ED	Emergency Department
EEG	Electroencephalogram
EF	Ejection Fraction
EGD	Extra Glottic Devices
EGDT	Early Goal-Directed Therapy
EGR1	Early Growth Response Factor-1
Em	Early Diastole
EMS	Emergency Medical Service
EORs	Estimated Odds Ratios
EPs	Evoked Potentials
ER	Emergency Room
ERV	Expiratory Reserve Volume
ETC	Esophageal-Tracheal-Combitube
ETI	Endotracheal Intubations
FE	Failed Extubation
FRC	Functional Residual Capacity
FV	Flow Velocity
G	Guanine
GA	General Anaesthesia
GCS	Glasgow Coma Scale
GEB	Gum Elastic Bougie
GERD	Gastroesophageal Reflux Disease
GOS	Glasgow Outcome Scale
GSW	Gunshot Wounds
HBS	Hypnotic-Based Sedation

HELP	Head Elevated Laryngoscopy Position
HFV	High Frequency Ventilation
HICP	High Intracranial Pressure
HPV	Hypoxic Pulmonary Vasoconstriction
HS	Hypertonic Saline
IAP	Intra-Abdominal Pressure
IBW	Ideal Body Weight
ICN	Intercostals Nerve
ICP	Intracranial Pressure
ICU	Intensive Care Unit
IE	Infective Endocarditis
IHCA	In-Hospital Cardiac Arrest
IHI	Institute for Healthcare Improvement
IIT	Intensive Insulin Therapy
ILMA	Intubating Laryngeal Mask Airway™
IOM	Institute of Medicine
IOM	Intraoperative Monitoring
IPM	Intraperitoneal Microdialysis
IRAK-M	IL-1 Receptor-Associated Kinase
JCAHO	Joint Commission on Accreditation of Healthcare Organizations
LAD	Left Anterior Descending Coronary
LAP	Left Atrium Pressure
LBW	Lean Body Weight
LEMON	Look - [e] Mallampati class – Obstruction - and Neck mobility
LMA	Laryngeal Mask Airway
LOS	Length of Stay
LT	Laryngeal Tube™
LV	Left Ventricle
LVEDAI	Left Ventricular End Diastolic Area Index
LVEDP	Left Ventricular End-Diastolic Pressure
MABP	Mean Arterial Blood Pressure
MaVS	Metoprolol after Vascular Surgery
MCA	Middle Cerebral Artery
MDPE	Median Performance Error

MEP	Motor Evoked Potentials
MET	Medical Emergency Team
MET	Metabolic Equivalent Task
MI	Myocardial Infarction
MOANS	Mask seal poor - Obesity - Aged - No teeth – Stiff
MODS	Multiple Organ Dysfunction Score
MPM	Mortality Probability Models
MR	Mitral Regurgitation
MSCs	Mesenchymal Stem Cells
NAS	Nursing Activities Score
NF-kappa B	Nuclear Factor Kappa B
NFR	Not-For-Resuscitation
NGF	Nerve Growth Factor
NIMV	Non Invasive Mechanical Ventilation
NIPV	Non-Invasive Positive Ventilation
NIRS	Near-Infrared Spectroscopy
NIV	Non Invasive Ventilation
NMBD	Neuromuscular Blocking Drugs
NNT	Numbers Need to Treat
NO	Nitric Oxide
NSAID	Nonsteroidal Anti-Inflammatory Drugs
NSTEACS	Non-ST-segment Elevation Acute Coronary Syndromes
NSTEMI	Non-ST-segment Elevation Myocardial Infarction
NT	Neurotrophic Factor
OAA/S	Observer's Assessment of Alertness/Sedation Scale
OHCA	Out-of-Hospital Cardiac Arrest
OHS	Obesity Hypoventilation Syndrome
OLV	One-Lung Ventilation
OR	Operation Room
OSA	Obstructive Sleep Apnoea
PaCO ₂	Arterial Carbon Dioxide Tension
PACU	Post Anaesthesia Care Units
PAOP	Pulmonary Artery Occlusion Pressure
PAP	Pulmonary Artery Pressure

PBEF	Pre-B-cell colony-Enhancing Factor
PbrO ₂	Brain Tissue Oxygen Tension
PBS	Phosphate Buffer Solution
PCI	Percutaneous Coronary Intervention
PCWP	Pulmonary Capillary Wedge Pressure
PD	Pharmacodynamic
PEA	Pulseless Electrical Activity
PEEP	Positive End-Expiratory Pressure
PIC	Pulmonary Infection Control
PICU	Paediatric Intensive Care Unit
PIRO	Predisposition, Infection, Response, Organ dysfunction
PK	Pharmacokinetic
PNI	Penetrating Neck Injuries
POBBLE	Perioperative Beta-Blockade
POISE	PeriOperative ISchemic Evaluation
PONV	Postoperative Nausea and Vomiting
POP	Pulse Oximeter Plethysmographic
PPM	Potential Pathogenic Microorganisms
PR	Rules Rate
PRIS	Propofol Infusion Syndrome
PSV	Pressure Support Ventilation
PVB	Paravertebral Block
P _v O ₂	Mixed Venous O ₂ Tension
PVR	Pulmonary Vascular Resistance
RCRI	Revised Cardiac Risk Index
RCT	Randomised Controlled Trial
RML	Rhabdomyolysis
ROC	Receiver Operating Characteristic
ROSC	Return of Spontaneous Circulation
RR	Relative Risk
RR	Respiratory Rate
RRS	Rapid Response System
RRT	Rapid Response Team
RSI	Rapid Sequence Intubation

RTP	Reverse-Trendelenburg Position
RV	Right Ventricle
RWMA	Regional Wall Motion Abnormalities
S wave	Systolic Wave Velocity
SAH	Subarachnoid Haemorrhage
SAM	Systolic Anterior Motion
SAPS	Simplified Acute Physiology Score
SBP	Systolic Blood Pressure
SCCM	Society of Critical Care Medicine
SCD	Sudden Cardiac Death
ScvO ₂	Central Venous Oxygen Saturation
SDD	Systemic Digestive Decontamination
SEF	Spectral Edge Frequency
SEPs	Somatosensory Evoked Potentials
SjO ₂	Jugular Venous Oxygen Saturation
SjvO ₂	Jugular Venous Bulb Oxygen Saturation
Sm	Systolic Velocity Signal
SMR	Standardised Mortality Ratio
SNP	Single Nucleotide Polymorphism
SOFA	Sequential Organ Failure Assessment
SV	Stroke Volume
T	Thymine
TBI	Traumatic Brain Injury
TBW	Total Body Weight
TCD	Transcranial Doppler
TCI	Target Controlled Infusion
TDA	Traumatic Disruption of the thoracic Aorta
TEE	Transoesophageal Echocardiography
TENS	Transcutaneous Electric Nerve Stimulation
TISS	Therapeutic Intervention Scoring System
TIVA	Total Intravenous Anaesthesia
TLR	Toll-Like Receptor
TLV	Two-Lung Ventilation
TNF	Tumour Necrosis Factor

TNF- α	Tumour Necrosis Factor Alpha
TP	Trendelenburg Position
Trk	Tropomyosin Receptor Kinase
TTE	Transthoracic Echocardiography
UMSS	University of Michigan Sedation Scale
UPMC	University of Pittsburgh Medical Center
V/Q	Ventilation/Perfusion ratio
VATS	Video-Assisted Thoracoscopy Surgery
VEGF	Vascular Endothelial Growth Factor
VF	Ventricular Fibrillation
Vp	Propagation Velocity
VRE	Vancomycin Resistant Enterocci
VT	Tidal Volume
VT	Ventricular Tachycardia
WHO	World Health Organization
WM	Wall Motion
ZEEP	Zero End-Expiratory Pressure

ADVANCES ON CRITICAL CARE

Organization of the Rapid Response System

P. DI GIACOMO, M.A. DE VITA

The patient admitted to the hospital is already an individual who is at risk because of an underlying pathology that requires inpatient care. When patients decline, they have evidence of clinical deterioration (hypoxia, hypotension, tachypnoea, tachycardia, altered level of consciousness) that is often documented in the medical record 8 to 48 hours prior to a crisis being detected. Furthermore, even if symptoms of critical illness are discovered, they may be undertreated [2, 3]. This gap between needs and resources can lead to death. The best hospitals are able to find and treat sudden-onset critically ill patients (often with transfer to the intensive care unit – ICU) before harm occurs [1]. In essence, these sudden-onset critically ill patients have an immediate increased need of the resources available for their care. The failure to resolve the mismatch between patient needs and available resources is the cause of the medical emergency [4]. This chapter discusses the system for detecting patients with sudden critical care needs outside the intensive care unit (ICU), and then reliably and efficiently provide them with the resources their lives depend upon.

The Medical Emergency Team (MET), Rapid Response Team (RRT), and Critical Care Outreach Teams (CCO) represent the response mechanisms employed by institutions to provide needed resources to patients with medical emergencies. While much of the literature has described this efferent (response) limb of the Rapid Response System (RRS), a comprehensive approach to in-hospital medical emergencies requires clinical detection and response activation (Afferent Limb), and resource response (Efferent Limb). The “mature” system has also linked their process improvement mechanism to review cases so as to identify underlying trends leading to emergencies and enable the prevention of future events. Finally, an administrative component is needed to oversee the system and provide it with resources and a capacity for self improvement. The First Consensus Conference on Medical Emergency Teams described these four components and recommended that the term Rapid Response System (RRS) be used to describe such a multifaceted approach to ensure that a mismatch between the needs of critically ill patients and the available resources is prevented, and whenever it does occur, ensure that the imbalance is rapidly rectified [4].

The nomenclature for the Rapid Response System has four major components or “limbs” [4].

1. Afferent Limb: Event detection and response trigger
2. Efferent Limb: Resources immediately made available to the patient’s bedside,

including both equipment and personnel with specific critical care skills (the response team)

3. Evaluative, Patient Safety and Process Improvement Limb
4. Governance and Administrative Structure

The *Afferent Limb* (triggering mechanism) is responsible for recognizing the existence of a medical emergency and activating the RRS. Activating the afferent limb may on the surface appear to be the easiest of the four components. Hospital staff routinely record data in the medical record such as vital signs, urine output, and oxygen saturation. However, although the data is recorded, crisis recognition is often lacking. In other words, the patient can become critical, but the hospital staff fail to respond, possibly due to a failure to recognize critical illness. Alternatively, the staff may recognize the patient is critically ill, but have no ability to bring the needed resources to bear (this is taken up below in the Efferent Limb). Recognizing physiological derangements and translating that information into intervention is essential for the success of the RRS. The MERIT study reported that for individuals suffering adverse events and simultaneously meeting criteria to trigger a MET response, only 30% actually had the MET response triggered [5]. The afferent limb must employ calling criteria. Calling criteria can be subjective and/or objective. The subjective criteria allow for the activation of the RRS by any staff member who has “concern” for the safety of a patient who does not satisfy the objective criteria. Objective criteria are also useful to help staff recognize critical illness. Various MET calling criteria exist and are generally based on physiological derangements of airway protection, breathing, circulation, and neurological status [6, 7]. An example of calling criteria from the MERIT Trial is provided in Table 1 [5].

Table 1. Calling Criteria (PR = Pulse Rate, RR = Respiratory Rate, SBP =Systolic Blood Pressure) [5]

	MERIT STUDY
Airway	Threatened airway
Breathing	All Respiratory Arrests RR < 5/min RR > 36/min
Circulation	All Cardiac Arrests PR > 140 PR < 40 SBP < 90
Neurology	Sudden fall in level of consciousness (Fall in GCS of 2 points) Repeated or prolonged seizure
Other	Any patient that you are seriously worried about that does not fit the above criteria

No matter which system or collection of calling criteria is used, it is essential that the ability to trigger the RRS be available to all hospital personnel on a 24 h a day basis. The mechanism for triggering the RRS should employ technology familiar to all caregivers at a given institution. Examples include hand-held or

pocket cards, high visibility posters, calling criteria attached to staff identification badges, the utilization of the hospital pager system individually or (for redundancy) in conjunction with the hospital overhead speaker system, and creation of a MET or RRS hotline or single telephone number. Additionally, triggering the RRS should never be accompanied by a punitive response from the MET toward the individual triggering the RRS. A negative response would be one that challenges the need for the call. This challenge will decrease the probability that the next call is made. It is inherent in the system that sometimes a team response will be triggered when not needed. In this situation, the team should commend the caller for caring for the patient.

The *Efferent Limb* of the RRS is charged with responding to the triggering of the RRS. The efferent limb of the RRS must (1) provide an initial diagnosis, (2) initiate the appropriate intervention, and (3) have the ability to make patient placement decisions and access the equipment and additional caregivers to provide definitive treatment [4].

Response teams typically employ one of two models in delivering care. One model, the MET, is considered to be a high capability team. This model is usually physician led, often larger in number of responders and more diverse in the range of skills brought to the bedside [9, 10]. Competencies in critical care allow for the initiation of a wide range of therapeutic options such as difficult airway management, the placement of invasive arterial and venous catheters and advanced cardiac life support. By bringing a large, diverse, and highly skilled team to the bedside the MET has the ability to “ramp down” the response if the level of decision making and intervention does not require the full competencies of the individuals responding.

The second model will be referred to as a “rapid response team” or RRT. This system may be nurse-led with intermediate capabilities: better than the floor staff, but not as good as a critical care physician led team. This model has been employed in both the community hospital setting as well as tertiary referral teaching hospitals [11, 12]. The RRT members may include an ICU nurse as well as respiratory care personnel, but do not include a physician. Following the initial evaluation of the patient, the members of the RRT have the ability to call upon additional resources to meet the needs of the patient [11]. These resources may include the primary attending physician, physicians with critical care skills, or additional consultants. The hallmark of this model is the ability of the RRT to “ramp-up” the level of care once the initial evaluation is completed, and titrate the resources as the situation requires.

There is another form of the efferent limb response, which can be staffed in the ramp-down (MET) style or the ramp-up (RRT) style. Called Critical Care Outreach (CCO), it is different from MET and RRT in that the members of this team plan *in advance* to visit and treat selected high risk patients rather than waiting for a crisis call. The goal is to prevent the patient deterioration and critical resource mismatch from occurring. Patient groups visited routinely include any patient transferred out of the ICU within the last 24 hours, any patient on oxygen greater than 40%, or any patient a floor nurse has “questions” about.

Like the afferent limb (triggering mechanism), optimally the efferent limb should be available 24 hours a day. Some hospitals have not been able to provide this level of capability immediately, and they may opt for a partial coverage plan. Once experience is gained, usually they are able to acquire resources to make the coverage better. At a minimum, responders should have the potential to perform the initial evaluation, generate a working diagnosis, and begin therapy or access additional resources. They should also have the ability to triage the patient to the appropriate level of care. The goals of the RRS remain the same irrespective of whether the responders are a MET or an RRT: bring a resolution to the mismatch between the patient's needs and the available resources.

One of the benefits of the RRS is that it employs an *Evaluative, Patient Safety and Process Improvement Limb*. If structured properly, the RRS will have the ability to generate an abundance of information about the antecedent events leading up to the medical emergency. An example of such an effort was provided by Braithwaite et al at the University of Pittsburgh Medical Center (UPMC), who utilized the MET model to identify the percentage of MET calls at an academic tertiary referral centre that were associated with medical errors [9]. A more in-depth analysis demonstrated that 67% of the adverse event associated METs were related to diagnostic errors, 59.6% were related to treatment errors, while 26.3% were from failure to institute preventive measures [9]. Quality improvement programmes that have been born from the MET programme at UPMC include hypoglycaemia protocols, standardized airway protocols, and guidelines for the transfer of patients from one level of care to another. The same group has in-press a manuscript showing the decline in the rate of "avoidable" crisis events over time. They attributed this reduction to the preventive efforts they implemented over a 5 year time frame.

The evaluative component should also serve to critique the performance of the RRS itself. The ease of triggering the afferent limb, the response time for the efferent limb (MET/RRT), the time to definitive therapy, and barriers to the use of the RRS are all potential aspects of the RRS that can be improved upon with a proactive evaluative process.

Hospitals employ different modalities to try and improve patient safety. Root Cause Analysis, quality improvement committees, morbidity and mortality conferences, and peer review are examples of such attempts. The evaluative component of the RRS should compliment these efforts by providing the collection, analysis, and interpretation of data generated from the activation of the RRS. Root cause analysis and quality improvement efforts can be directed and focused on the basis of data generated by the RRS.

The final component of the RRS is the *Governance and Administrative Structure*. The development of an RRS that is well integrated into the culture of your hospital can be a difficult undertaking. Nevertheless, without appropriate resources, the system cannot succeed. For example, for all hospital members to know the crisis criteria and respond appropriately to them by calling the team requires a huge work effort. The criteria have to be agreed upon, then taught to professionals, and mnemonic devices like posters and pocket cards need to be made. A call number

must be established and each staff member must be taught who to call, and the number to call, and what to do while waiting for the responders. The responders have to be identified before the call, and must know their duty. All these items must be decided by a leadership group, and then resources provided to ensure that they are successfully implemented. Education and more conclusive evidence that RRS can help in the management of critically ill patients will be necessary to overcome barriers such as territorialism, the current culture and hierarchy of care at various institutions, as well as the uncertainty of what form of RRS will be the most appropriate for a given institution.

At present, financial and staffing resource constraints specific to each institution will also dictate the model and make-up of the RRS that is implemented in the beginning. The evolution of the RRS will require oversight as barriers and unexpected issues are encountered. The governance and administrative structure should comprise a group of individuals or a formal committee responsible for all phases of the programme, including but by no means limited to education, promotion of cultural change, design and development of institution specific afferent and efferent limbs, financial and process review and improvement. This group should include physicians, nurses, administrators and respiratory care and pharmacy personnel. It may also include quality improvement staff, equipment supply staff, and even hospital operators. Ideally a coordinator for the RRS should be a member of the ICU staff who is familiar with the resources and culture available and present at each institution. A member of the RRS committee or coordinator of the committee should be involved in all aspects of the hospital connected with patient safety such as quality improvement, patient safety committee, "Code Blue" or cardiac arrest team committees, root cause analysis endeavours and morbidity and mortality conferences. For institutions utilizing multiple response teams such as a chest pain team, stroke team and difficult airway team, involvement of the governance component will be needed to define roles as well as utilize and maximize shared resources for the benefit of patients.

Much like the afferent limb, efferent limb, and evaluative/process improvement/patient safety limb, the governance and administrative limb will be unique to the institution. There is no clear definition or proof of the best method for a RRS. The resources, level of care provided by the institution and support from hospital administration and medical staff will help to dictate what structure for the RRS is best for the individual institution. Ongoing evaluation and process improvement of the system will allow for integration of the RRS into the culture of the institution.

Conclusions

RRS are rapidly emerging as a standard of care in many countries, most notably in Australia, New Zealand, the United States, the United Kingdom and Canada. It is likely that other countries will begin to utilize the system to avoid preventable and unexpected hospital deaths. To be successful, more than a response team is needed. A system including the four limbs seem to be required to achieve optimal benefits.

While not every hospital can create the same system, there is accumulating data to suggest that some type of system to identify sudden-onset critically ill patients outside the ICU which can provide them with ICU-type resources will reduce mortality.

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Transoesophageal Echocardiography: Clinical Assessment, Techniques and Procedures in Critical Care and ICU

F. GUARRACINO, C. CARIELLO

Transoesophageal echocardiography (TOE) was introduced into the operating room in the late 1980s as a tool for monitoring the left ventricle (LV) and for supporting the haemodynamic management of patients during general anaesthesia.

Soon it became evident that TOE could provide much more information than just the state of the LV. In recent years its use has largely expanded and it is now recognized as an excellent diagnostic and monitoring tool [1].

TOE is considered to be non-invasive and relatively easy to use: manipulation of the probe or of the transducer through the three-dimensional extent of a structure permits the heart to be examined completely.

Echocardiography is at the moment the only method which can provide bedside real-time imaging of the heart.

All patients studied with TOE should have a full and comprehensive examination of the heart. The great vessels should also be explored as much as can be seen. This systematic approach makes it less likely that unsuspected abnormalities will be missed.

Several sets of guidelines for a comprehensive examination have been published [2, 3].

The role of TOE in the intensive care unit (ICU) and in critical care medicine is increasing. It is of particular value in managing haemodynamic optimization in ICU: according to the practice guidelines for perioperative TOE published in Anesthesiology in 1996, TOE is recommended in the ICU setting for "unstable patients with unexplained haemodynamic disturbances, suspected valve disease or thromboembolic problems" to detect postoperative complications, specially when data are compared to the intraoperative exam.

In the ICU, where most patients are intubated and often have drainage, obtaining clear acoustic windows and images is often problematic using regular transthoracic echocardiography (TTE). Because the cardiac structures are in close proximity to the oesophagus, TOE provides better image quality through an oesophageal probe.

TOE allows us to assess ventricular function, both the systolic and diastolic, volume state, pericardial effusion and pulmonary embolism, all of which are important features in circulatory failure. Other important indications for TOE in the ICU are: suspected endocarditis, assessment of valvular function, evaluation of

aortic dissection, complication of myocardial infarction, hypoxaemia, and evaluation of chest trauma. Thus, TOE should be the technique of first choice instead of many other expensive examinations [4].

Basic Approach

A complete examination includes the following ultrasound modalities [2, 3]:

1. two dimensional imaging to examine cardiac anatomy
2. colour flow Doppler imaging to visualize blood flow velocities
3. spectral Doppler: pulsed wave, to measure blood flow velocities at specific locations
4. continuous wave, to measure high velocities that exceed the limits of pulsed Doppler and are commonly associated with abnormal flow jets.

The complete examination should include the 20 standard views [2].

The sequence may start with the upper oesophageal views, proceed to midoesophageal views, and end with transgastric views.

The complete examination will focus in turn on the following structures:

1. left ventricle
2. mitral valve
3. aortic valve, aortic root and left ventricle outflow tract
4. left atrium and pulmonary veins, right atrium and atrial septum
5. right ventricle, tricuspid valve and pulmonary valve
6. thoracic aorta

Most important rules of TOE in critical care medicine are in the fields of heart failure, septic patients and in the emergency department.

In the ICU, critical care and in the emergency department, TOE may be very useful for diagnosing and treating heart failure and septic shock.

Heart Failure

Acute or chronic heart failure may be due to several causes, such as myocardial dysfunction, myocardial ischaemia, arrhythmias, valve abnormalities, pericardial disease, tamponade, and aortic dissection [5].

TOE can be useful in understanding reasons for heart failure by studying systolic and diastolic function, valvular dysfunctions, pulmonary hypertension, pericardial space and the anatomy of the thoracic aorta.

LV Systolic Function

Segmental models of the LV are needed to accurately describe the location and extent of regional wall motion abnormalities.

The standard views in most systematic TOE examinations include at least four

views of the LV. The guidelines use a model with 16 anatomical myocardial segments [3]. The model divides the LV in three levels from base to apex: basal, mid and apical. The basal level extends from the mitral valve annulus to the tips of papillary muscles, the mid level extends from the tips of the basis of the papillary muscles and the apical level comprises the remaining part of the LV. The basal and mid levels are each divided circumferentially into six segments, and the apical level into four. This allows assessment and quantification of global LV function. Individual myocardial segments are observed for systolic thickening and for motion. Areas which do not thicken in systole or which do not move towards the centre of the ventricle in systole are described as regional wall motion abnormalities (RWMA). The analysis of wall motion (WM) can be quantitative by using a grading scale for motion and thickening, which leads to a scoring system.

The grading of motion is based on the evaluation of segmental radial shortening of the distance from the endocardium to the centre of the LV cavity during systole.

Thickening is graded on the increase in the distance between the endocardial and epicardial border during systole. This increase is estimated by eyeball on a scale from + to +++ (Table 1).

Table 1	% radial shortening	Thickening	Score
Normal	>30	+++	1
Mild hypokinesis	10-30	+	2
Severe hypokinesis	<10, >0	+	3
Akinesis	0	0	4
Dyskinesis	Paradoxical	Thinning	5

TOE was found to be good at detecting new LV RWMAs, associated with ischaemia in particular using the transgastric midpapillary short-axis view of the LV [6].

TOE allows measurements of the ejection fraction (EF) based on the volume change of the LV. EF is obtained in the midesophageal four-chamber view, by measurements of end-diastolic and end-systolic volumes normalized for end-diastolic volume. This method can be performed by Simpson's rule which assumes that the LV volume can be obtained by summing the volumes of multiple slices of known thickness that make up the ventricle itself.

TOE can detect LV wall motion abnormalities before other modalities such as ECG could demonstrate evidence of ischaemia [7].

The development of newer modalities, such as acoustic quantification and automated border detection, may provide real-time estimates of stroke volume (SV) and EF [8, 9].

The main factor in critically ill patients is cardiac output. So far, the thermodilution technique is considered the gold standard for the ICU environment. SV may be calculated using complex mathematical calculations and measurements of the aortic valve area and the area under the curve of the Doppler flow profile. The cardiac output may, thus, be obtained noninvasively by multiplying the SV with

the heart rate. This technique has been shown to correlate well with the thermodilution technique [10]. By combining specific views to estimate aortic flow and end-diastolic area, cardiac contractility may also be assessed. Although this technique is still inaccurate, it provides hope for a contractility index with significant clinical applications [11].

LV Diastolic Function

Diastolic dysfunction can be evaluated using 4 different well documented echo methods [12-14]:

1. transmitral flow velocity: the probe is positioned at the midesophageal four-chambers view and the sample volume placed at the level of the open leaflets in diastole. All the following measurements can be obtained:
 - early filling peak velocity (E wave),
 - atrial peak velocity (A wave),
 - E/A ratio
 - Deceleration Time (DT).
- The isovolumetric relaxation time (IVRT) – the period from the end of aortic systolic flow to the start of mitral inflow – is measured with continuous wave Doppler between the aortic and mitral valves in the deep transgastric long-axis view.
2. pulmonary vein flow: the probe is positioned in the midesophageal two-chambers view with the sample volume placed 1 cm from the pulmonary vein orifice. All the following measurements can be obtained:
 - the systolic wave velocity (S wave)
 - the diastolic wave velocity (D wave)
 - the atrial wave velocity (A wave)
3. Colour M-mode to measure propagation velocity (Vp): the colour M-mode modality provides the spatiotemporal distribution of blood flow velocity within the LV across a vertical line. This method enables the study of the propagation velocity of the flow within the LV during the rapid and slow filling phases.
4. Tissue Doppler of mitral annulus velocity. In the midesophageal four-chambers view with sample volume positioned on the lateral wall of the mitral annulus a systolic velocity signal (Sm) and two diastolic velocities can be measured, one during early (Em) and the other during late (Am) diastole.

Diastolic dysfunction has been classified according to ESC guidelines (1998):

	E/A	Dt _s	IVRT _s	S/D	Vp _{cm/s}	Em/Am	Em _{cm/s}
Normal	E>A	140-220	60-100	S>D	>55	>1	>8
Delayed relaxation	E>A	>220	>100	S>D	<55		<8
Pseudonormal	E>A	140-220		S>D	<55		<8
Restrictive	E>A	<140	<60	S<D	<55		<8

Right Ventricular Failure

The right ventricular (RV) function is very difficult to evaluate by TOE; moreover the RV is strongly influenced by the preload. Generally, RV failure involves a decrease in LV preload and thus a reduction in cardiac output. The consequent hypotension causes coronary hypoperfusion and then a worsening in cardiac function.

All the situations leading to a sudden increase in pulmonary pressure (pulmonary embolism) or acute myocardial infarction of the RV can cause an acute RV failure. Progressive hypertrophy and dilatation of the RV secondary to chronic pulmonary hypertension such as in case of parenchyma and vascular lung diseases can cause chronic RV failure such as chronic obstructive pulmonary disease.

In the case of acute ischaemia of the RV, distension and acute overload of the ventricle cause tricuspid insufficiency, even without pulmonary hypertension.

The four-chamber view evaluates the RV dimension and its relationship with the LV: if the RV is dilated and hypokinetic, a paradoxical movement of the septum towards the left septum will appear. By rotating the probe 60-90° the RV outflow tract appears, thus enabling the evaluation of the presence of thromboembolism.

In the transgastric view, either short and long-axis, the RV function and its size and septal motion can be evaluated. An abnormal movement of the interventricular septum is often the first signal of RV failure. The septum bellows to the LV and maintains a convex curve toward the RV. With the increase in RV volume, the septum flattens and assumes a paradoxical movement toward LV during the end-diastolic phase. In the case of pressure overload (pulmonary hypertension), this paradoxical movement is maximal during the end-systolic phase. The study of the RV should be completed with an evaluation of the tricuspid valve, which is mostly insufficient.

Valvular Dysfunction

Valvular abnormalities may be acute or chronic in an unstable, critically ill patient. The patient may not be aware of the chronic valvulopathy, and the valvulopathy may not be related to the acute condition of the patient. When evaluating valves, the abnormality should be correctly diagnosed, quantified, and the underlying disease identified.

Regurgitation is screened with colour Doppler, and a turbulent retrograde flow can be detected. Alternatively, when stenosis is the question, flow acceleration through a stenotic valve is measured by spectral Doppler interrogation.

Acute subaortic stenosis is a relatively rare condition that is rarely diagnosed, but which may have devastating consequences if left unrecognized. TOE can help in the diagnosis of this condition, which occurs in patients with LV hypertrophy when there is a reduction in preload. Acute obstruction may be triggered by anaesthesia, pericardial effusion, or hypovolaemia and may cause shock. It is usually reversible if volume substitution is started immediately. What is important is that this condition may require the discontinuation of inotropes in a hypotensive patient, so the diagnosis should be firmly established [17].

Colour-flow mapping is a useful method for the detection of valvular regurgitation. However, since it may not be accurate enough for reliable quantification in some circumstances, a volumetric approach is preferable. In cases of massive mitral regurgitation (MR) or aortic regurgitation (AR), any measurement may be difficult.

Aortic and mitral stenosis are satisfactorily assessed by the volumetric, continuous wave and pulsed wave Doppler methods [18].

Ischaemic mitral valve insufficiency is very common in the ICU. Today, many agree that the pathophysiological mechanism is due to a pathology of the LV based on changes of the LV geometry. The valve becomes regurgitant because there is a displacement of the implant base of papillary muscles towards the ventricle apex and also an involvement of the basal level of the LV, which is the annular region.

So the measurement of the tenting area, of the coaptation depth, of the regurgitant jet are important steps for understanding the mechanism. The colour Doppler evaluation gives useful information by showing the direction of the regurgitant jet. Mostly it is a central jet, as in annuloaortic ectasia and symmetric tethering. When the tethering is asymmetric, the regurgitant jet is eccentric, in the direction of the leaflet which is affected [19].

The evaluation of the mitral valve by TOE is based on a systematic examination of the entire mitral valve apparatus: it includes a comprehensive evaluation of anatomy and function in the standard views by 2-D examination, followed by the colour Doppler evaluation of the regurgitant jet.

Haemodynamically Unstable Patients

TOE is often useful in the management of haemodynamically unstable patients in emergency medicine and in the ICU. Even with the help of invasive monitoring,

when managing the hypotensive patient there are often circumstances when it is difficult to distinguish the hypotensive patient from one with primary pump failure. TOE can demonstrate a small under-filled LV in which the papillary muscles are almost touching or can show a dilated ventricle in a patient with LV failure. TOE can estimate standard haemodynamic variables (e.g., filling pressures, cardiac output) that are normally obtained by other invasive techniques, such as pulmonary artery catheterization; TOE is also used to quantify cardiac dimensions, intracardiac flow rates, and overall cardiac performance.

TOE may be useful for understanding incomprehensible reasons for heart failure as in systolic anterior motion (SAM).

SAM may occur after mitral valve plasty, because of the LV outflow tract obstruction when the mitral coaptation line is displaced anteriorly. Understanding the geometry of this phenomenon by the use of TOE may facilitate heart failure diagnosis and SAM can be managed by volume loading and discontinuation of beta-stimulants and/or administration of beta-blockers.

Preload Assessment

In clinical practice, LV end-diastolic pressure (LVEDP) is used as an equivalent to LV preload and is equated with left atrium pressure (LAP). The assumption that pulmonary artery occlusion pressure (PAOP) reflects LAP and LVEDP is not always true because LV diastolic compliance can vary, as in myocardial ischaemia, and PAOP may overestimate LAP [20]. Various attempts have been made to estimate LVEDP noninvasively. In a study by Garcia et al [21], transmitral Doppler flow and colour M-mode Doppler flow propagation velocities correlate well with PAOP measurements. Another study showed that by using various echocardiographic indices, the SV may be consistently estimated [22]. Finally, a combination of transmitral pulsed Doppler and colour M-mode Doppler flow propagation velocity or deceleration time of diastolic pulmonary venous flow allows a close approximation of PAOP [23].

Hypoxaemia in the ICU

TOE may be helpful for the early diagnosis of hypoxaemia in the ICU. Intracardiac right-to-left shunt through a patent foramen ovale (PFO) may result in the development of hypoxaemia in the ICU. Cardiac tamponade and mechanical ventilation with high positive end expiratory pressure are the most common factors responsible for enhancing intracardiac right-to-left shunt through a PFO. TOE can reveal right-to-left shunting via a PFO. Surgical closure of the PFO must be done without delay. Hypoxaemia may be caused by a pulmonary embolus. Prompt diagnosis is essential to initiate the therapy in haemodynamically unstable patients. TOE can visualize the thrombus, RV dilatation and hypokinesis, interventricular septal flattening and paradoxical movement, pulmonary hypertension, PFO, etc [24]. Acute increase in pulmonary artery pressure may result in RV dysfunction due to

chamber dilatation, and hypokinesis, while chronic pulmonary hypertension will result in RV hypertrophy (the wall may be thicker than 5 mm). As RV pressure and volume increase, the LV develops a “D” shape. As a result of increased pressure in the RV, the right atrial pressure exceed LAP, hypoxaemia may results from right-to-left shunting across a PFO. Tricuspid regurgitation occurs as a result of an increased RV afterload and/or RV dilatation. The definitive diagnosis is made by direct visualization of the thrombus in the pulmonary artery, with distinct borders, different echogenicity from the blood or vascular wall, evidence of protrusion into the arterial lumen and alteration of flow on Doppler imaging [25].

Emergency Department

TOE in Aortic Disease (Acute Traumatic Aortic Disruption and Dissection)

TOE is very sensitive in evaluating the thoracic aorta due to the proximity of the oesophagus to this great vessel in the thoracic and upper abdomen. It is only limited in an adequate visualization of the total ascending segment, leaving a small blind spot along its distal portion due to trachea interference.

Important information can be obtained regarding aortic atherosclerosis, and patients who are asymptomatic but at high risk for perioperative stroke and peripheral embolization can be identified.

Moreover, patients with dissections involving the ascending aorta (Stanford Type A) have a very high mortality if not treated with urgent surgery, while patients with acute dissection not involving the ascending aorta (Stanford Type B) in general do better without surgery. The principal benefits of TOE during aortic dissection diagnosis are: its ability to identify the dissection flap and the site of intimal tear, to determine disruption of the aortic valve by aortic regurgitation, to evaluate the involvement and integrity of the coronary artery in cases with very proximal aortic dissection, to distinguish the true lumen from the false lumen, and to study cardiac function [26].

Acute traumatic disruption of the thoracic aorta (TDA) is a highly lethal but treatable injury that usually occurs as a result of high-speed deceleration accidents. Abrupt deceleration injuries generate shearing forces that act maximally in the region of the aortic isthmus. Because the major complication of TDA is adventitial rupture, usually resulting in immediate death secondary to massive haemorrhage, early diagnosis of TDA followed by immediate surgical repair is imperative to improve survival rates.

Aortography, which is currently considered the gold standard diagnostic technique, is invasive and extremely difficult to perform in haemodynamically unstable patients with multiple trauma and delays the initiation of aortic surgical repair by an average of 60 minutes. TOE appears to be a rapid, safe, and accurate alternative diagnostic approach for this condition. TOE can be performed safely in patients who have sustained severe blunt chest trauma, resulting in clinical information that can be used for determining the immediate management of patients [27]. Because of its

accuracy, portability, and safety, TOE is better suited than aortography as the first-line imaging modality for evaluation of patients with multiple trauma and suspected acute TDA. TDA may present as intimal flap, contained rupture (pseudoaneurysm), intramural haematoma, branch vessel injury (avulsion of an intercostal artery, injury to a brachiocephalic artery), and rarely as an aortic dissection [28].

TOE in Cardiac Tamponade

Cardiac tamponade is defined as significant compression of the heart by accumulating pericardial contents which include blood and clots (chamber perforation, dissecting aortic aneurysm, trauma or anticoagulant therapy), exudative effusions (malignant states, infective pericarditis, or idiopathic pericarditis), non exudative effusions (uraemia, systemic lupus erythematosus, rheumatoid arthritis, etc) and air. Clinically, it is described by hypotension, increased jugular venous pressure and muffled heart sounds. TOE can be very helpful in the diagnosis and clinical management of cardiac tamponade. Several echocardiographic features may be detected by TOE: diminished LV dimension and mitral valve excursion during inspiration, shifting of the interventricular septum towards the LV, changes in transvalvular (mitral and aortic) flow characteristics seen by Doppler, and diastolic posterior motion of the right ventricle wall [29]. The best view is the transgastric mid papillary short-axis view at 0° to assess for the presence of an echolucent fluid-filled space surrounding one or both ventricles. When the effusion is significant, ventricular function can be normal or depressed. The transgastric long-axis view at 90° visualizes the anterior and inferior walls of the LV and if present a pericardial collection appears as an echolucent space separating the LV walls from the parietal pericardium. Loculated pericardial collections can exist around the right atrium or the left atrium, so other views may be needed. Cardiac tamponade reduces compliance of the various cardiac chambers affecting filling and their systolic and diastolic functions. Transvalvular and transpulmonary vein filling patterns can be interrogated with Doppler echo.

TOE in Septic Patients

Septic shock is associated with important haemodynamic alterations, including an absolute or relative decrease in central blood volume, systolic alterations of LV and RV function, and severe peripheral vasodilatation responsible in part for alterations in regional blood flow distribution and probably linked to outcome [30, 31].

For a long time, assessment of haemodynamic instability in sepsis has been based on right heart catheterization at the bedside. Recently, the Task Force of the American College of Critical Care Medicine reiterated the usefulness of right heart catheterization in guiding haemodynamic support despite its invasiveness and associated specific complications [32].

TOE enables the inspection of the superior vena cava, the RV and LV cavities, and can identify the precise cause of haemodynamic instability in septic shock,

which may be hypovolaemic, cardiogenic, or distributive. This diagnosis is required for an adequate treatment, which may be rapid fluid administration, infusion of an inotropic agent, infusion of a vasoconstrictor agent, or various combinations of the above. Repeated bedside echocardiography can also assess the adequacy and efficacy of therapies implemented.

A large spectrum of changes in ventricular systolic function can be observed in septic shock.

With TOE, a long-axis view enables the examination of the four cardiac cavities. From this view it is possible to measure LV and RV end-diastolic and end-systolic size and calculate the LVEF. A short-axis view of both ventricles by a transgastric approach also enables the measurement of LV size, the calculation of LV fractional area contraction, and the examination of septal shape and kinetics. In the long-axis view of the superior vena cava, TOE is able to examine the variation in its diameter during the respiratory cycle. A long-axis view of the LV outflow tract, by a transgastric approach, and a long-axis view of the RV outflow tract enable Doppler measurement of both left and right stroke outputs by simultaneously measuring aortic and pulmonary artery diameters.

Doppler aortic flow velocity measurement, as well as Doppler pulmonary artery flow velocity measurement, can be used to assess cardiac stroke index.

Evaluation of Volume Status

Central blood volume may be inadequate in a patient with hypovolaemia, as a result of an excessive airway and/or pleural pressure displacing blood from the intrathoracic vessels toward the extrathoracic vessels. In such cases, LV diastolic filling is insufficient and LV stroke is reduced.

The inadequacy of volume status should be rapidly detected and corrected in patients with sepsis. Indeed, blood volume expansion has been shown to improve prognosis significantly.

Evaluation of LV Systolic Function

Septic shock has long been considered as hyperkinetic shock. Even if this concept remains largely true, a hypokinetic state of septic shock is now well recognized, as illustrated by a significant decrease in LV systolic function measured by echocardiography. In this situation, patients with sepsis have a markedly depressed LVEF.

Incidence of Hyperkinetic State and Specific Vasoactive Treatment

Hyperdynamic shock is characterized by the combination of a low arterial pressure with marked tachycardia and, from an echocardiographic point of view, by a hyperkinetic LV on echocardiography and/or a high Q' by Doppler measurement.

The thermodilution method has probably contributed to the assertion that septic shock is always hyperkinetic, whereas more than 30% of patients actually

have hypodynamic shock with increased systemic vascular resistance. This inaccurate technique has also led to the debatable concept of acute LV dilatation in septic shock. Abnormal LV in a supine subject is really close to its limit of distension and has not much additional preload to offer, and although LV systolic dysfunction is often observed, dilatation is rarely seen using TOE in septic shock.

Echocardiographic control is thus required after starting norepinephrine infusion. When the afterload effect of norepinephrine appears excessive, a reduced dosage associated with dobutamine may be appropriate [33].

The RV in Septic Shock

RV dysfunction has also been demonstrated in septic shock. RV dysfunction may be related not only to intrinsic depression in contractility producing hypokinesia, as described for the LV, but also to acute cor pulmonale. Acute cor pulmonale is produced by an acute increase in pulmonary vascular resistance, which from an echocardiographic point of view combines acute RV enlargement and septal dyskinesia [34]. However, this increase may be relative to the quality of the RV systolic function, and a minor rise in airway pressure, as produced by mechanical ventilation, may produce acute cor pulmonale when applied on a depressed RV. Severe RV dysfunction as a part of biventricular failure requires inotropic support, whereas pre-eminent RV dysfunction may be corrected by norepinephrine infusion (by way of restoring arterial pressure and coronary perfusion).

TOE in Patients with Endocarditis

TOE has made a huge contribution to the improvement of diagnostic accuracy in infective endocarditis (IE) in recent years. The early diagnosis of IE is established by the demonstration of endocardial involvement during a systemic infection. TOE has better spatial resolution than TTE and a better specificity (88-100%) and sensitivity (86-94%) for vegetation.

Three echo findings are thought to be important criteria in establishing a diagnosis of IE:

1. mobile echo dense mass attached to valvular or mural endocardium or to implanted material
2. demonstration of fistulae or abscess formation
3. new disruption or dehiscence of a prosthetic valve

The role of TOE in IE is to screen suspected IE patients, to identify lesions, to follow up patients when medically treated and to select patients for surgery [35].

Conclusions

Echocardiography appears to have a definite role in the critical patient. The technique can offer quick bedside assessment of the unstable patient with thoracic

trauma and suspected cardiac or major vessel injury. Echocardiography often helps clarify the heart's function and its pathophysiology. The major problem appears to be operator education. Echocardiography may well be described as an extension of the physical examination in the ICU and emergency department.

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Use of Pulse Oximeter Waveform as a Non Invasive Functional Haemodynamic Monitoring Technique

M. CANNESSON, J.-J. LEHOT

Recently published studies have shown that intraoperative fluid optimization decreases postoperative morbidity and hospital stay [1]. On the other hand, if inappropriate, volume expansion may have deleterious effects. Therefore, preload dependence and fluid responsiveness assessments are of major importance during surgery. Static indicators of fluid responsiveness such as central venous pressure (CVP), pulmonary capillary wedge pressure (PCWP), or left ventricular end diastolic area index (LVEDAI) are invasive or uneasily available and have been shown to be poor predictors of fluid responsiveness [2-6]. Dynamic indicators, relying on the respiratory variations in stroke volume or its surrogates in mechanically ventilated patients, have been shown to be superior to static indicators for the prediction of fluid responsiveness [2-6]. However, they are either invasive (respiratory variations in arterial pulse pressure (ΔPP), stroke volume variations) with their associated complications [7, 8], technically challenging (respiratory variations in pulse Doppler aortic flow velocity, inferior vena cava diameter) or not widely available (oesophageal Doppler [9]).

The first noninvasive oximeter was invented by Carl Matthes in 1935 and was nonpulsatile. In 1970, engineers from Hewlett Packard developed the first commercially available device that allowed arterial oxygen saturation to be obtained non-invasively from the ear. This system required warming the tissues in order to increase local blood flow. In 1974, Takuo Aoyagi noted that the plethysmographic saturation in oxygen can be measured using the analysis of pulsatile light signals. This major discovery gave birth to the modern pulse oximeters we now know and use daily in intensive care units and operating rooms.

The pulse oximeter plethysmographic waveform depends on arterial pulsatility. In this chapter, after a brief overview regarding the concept of fluid responsiveness, we will see that: (1) the respiratory variations in the pulse oximeter plethysmographic waveform are related to the respiratory variations in the arterial waveform, (2) this waveform is able to detect changes in ventricular preload, and (3) the respiratory variations in this waveform are accurate predictors of fluid responsiveness in mechanically ventilated patients.

Fluid Responsiveness

Fluid responsiveness prediction has been extensively studied in the intensive care unit and operating room in mechanically ventilated patients. It is now well accepted that dynamic parameters (relying on the cardiopulmonary interactions in patients under positive pressure ventilation) are better predictors of fluid responsiveness than static indicators (such as CVP, PCWP, and LVEDAI). In patients under mechanical ventilation, positive pressure induces a decrease in right ventricle preload and, consequently, a decrease in right ventricle stroke volume (as described by the Frank-Starling relationship) and in pulmonary artery blood flow during inspiration. These phenomena are transmitted to the left ventricle (pulmonary transit time) and are responsible for a decrease in left ventricular stroke volume and output during expiration. These respiratory variations in left ventricular stroke volume or its surrogates have been shown to be predictive of response to volume expansion. Moreover, it has been shown that the respiratory variations in arterial pulse pressure are more predictive of response to volume expansion than the respiratory variations in systolic arterial pressure since systolic arterial pressure not only depends on respiration-induced changes in stroke volume, but also on respiration-induced changes in intrathoracic pressure. The main limitations of these indices are that they are invasive, technically challenging, or not widely available. Arterial catheters, which are mandatory for ΔPP calculation and monitoring, have been shown to be responsible for infections and thromboses and their use is limited to the operating room. On the other hand, transoesophageal echocardiography requires extensive training and is not widely available. Thus, these indices are not used daily in operating rooms.

Relationship between Respiratory Variations in Pulse Oximeter Plethysmographic Waveform and Respiratory Variations in Arterial Pressure

Pulse oximeters display a signal proportional to light absorption between the fingernail and the inferior portion of the finger. Light absorption increases with the amount of haemoglobin present in the fingertip. Thus, the pulse oximeter plethysmographic (POP) waveform amplitude depends on arterial pulse. Previous studies have shown a correlation between respiratory variations in POP waveform peaks and arterial systolic pressure [10], demonstrating that decreased preload resulted in waveform variation of the plethysmographic signal similar to the variation observed in the arterial waveform. However, like systolic pressure, POP waveform peaks also depend on the transmission of the intrathoracic pressure. Therefore, POP waveform amplitude analysis should be more accurate. Pulse pressure and POP waveform amplitude are related to stroke volume and vascular tone. As vascular tone is considered unchanged between inspiration and expiration, respiratory variations in POP waveform amplitude mainly reflect respiratory changes in left ventricular stroke volume. As pulse oximeters are already widely available in intensive care units and operating rooms, they could be a noninvasive and simple mean of predicting fluid responsiveness in patients with circulatory

failure, especially if they are not equipped with an arterial catheter. As most patients with shock have arterial catheters, POP waveform analysis could be utilized in patients not routinely monitored with such catheters.

The relationship between the respiratory variations in POP waveform amplitude (Δ POP) and Δ PP were first described in 2005 [11]. In this study, we analyzed Δ PP and Δ POP in 22 mechanically ventilated patients in the intensive care unit. A pulse oximeter was attached to the index or middle finger of either the right or left hand. POP waveforms were recorded using a M3150A monitor (Philips France). The plethysmographic gain factor was held constant throughout the procedure as the bedside monitor enables a choice between manual and automatic gain control. POP waveform amplitude was measured on a beat-to-beat basis as the vertical distance between a peak and the preceding valley of the waveform and was expressed in millimetres. Maximal POP (POPmax) and minimal POP (POPmin) were determined over the same respiratory cycle. The respiratory variations in POP waveform amplitude were calculated using a formula similar to that proposed to assess Δ PP: Δ POP (%) = $100 \times \{(\text{POPmax} - \text{POPmin}) / ([\text{POPmax} + \text{POPmin}] / 2)\}$. Finally, Δ POP was evaluated on three consecutive respiratory cycles simultaneously with Δ PP measurements. We found a fair agreement and a good relationship between Δ POP and Δ PP. Moreover, we found that the threshold Δ POP value of 15% allowed discrimination between patients with a Δ PP >13% and patients with a Δ PP $\leq$ 13% with a sensitivity of 87%, a specificity of 100%, a positive predictive value of 100% and a negative predictive value of 94%. These results were confirmed one year later by Natalini et al who found similar results in patients in the intensive care unit and operating room [12]. At the same time, Shelley et al found that the respiratory variations in the POP waveform depend on the site of measurements [13] demonstrating that this site should be standardized among patients and between studies [14].

Ability of the Respiratory Variations in the Pulse Oximeter Plethysmographic Amplitude to Detect Changes in Ventricular Preload

Showing that Δ POP is related to Δ PP was the very first step toward the demonstration that Δ POP was able to predict fluid responsiveness. The next step was to show the ability of Δ POP to detect changes in ventricular preload. We studied 25 patients under mechanical ventilation in the operating room. All the patients were studied after induction of anaesthesia and before surgery. All haemodynamic parameters were recorded at each step of the protocol, after at least 2 minutes of stabilization. First, patients were studied in the supine position. Then they were raised in the anti-Trendelenburg position (head-up 30°) to induce relative depletion of central blood volume and, lastly, in the Trendelenburg position (head-down 30°) to mimic a volume expansion [15, 16]. As expected we observed significant decreases in mean arterial pressure (from 66 ± 9 to 58 ± 9 mmHg; $p < 0.05$) from baseline to anti-Trendelenburg position. These changes were associated with increases in both Δ PP (from 10 ± 7 to $14 \pm 8\%$; $p < 0.01$) and Δ POP (from 11 ± 9 to $17 \pm 12\%$; $p < 0.01$). From the anti-Trendelenburg to Trendelenburg position we observed significant increases

in mean arterial pressure (from 58 ± 9 to 67 ± 10 mmHg; $p < 0.01$). At the same time we observed significant decreases in both ΔPP (from 14 ± 8 to $7 \pm 5\%$; $p < 0.01$) and ΔPOP (from 17 ± 12 to $9 \pm 5\%$; $p < 0.01$) showing that ΔPOP was influenced by changes in ventricular preload.

Ability of the Respiratory Variations in the Pulse Oximeter Plethysmographic Waveform Amplitude to Predict Fluid Responsiveness in Mechanically Ventilated Patients

Solus-Biguenet et al were the first to report the ability of ΔPOP to predict fluid responsiveness in mechanically ventilated patients [17]. While encouraging, their results were at the same time quite disappointing because they found that ΔPOP was a weak predictor of fluid responsiveness. However, their results were disputable since the waveform was not systematically recorded at the same site, information regarding the gain processing factor was not available and technical information was not broad enough to sustain the hypothesis that ΔPOP was a weak predictor [18].

More recently, ΔPOP was studied in the intensive care unit and in the operating room with positive results [19-21]. Natalini et al [21] studied patients in intensive care and found that a ΔPOP threshold value of 15% predicted fluid responsiveness with a positive predictive value of 55% and a negative predictive value of 100%. Feissel et al [20] found that a ΔPOP value of 14% discriminates between responders and non responders to volume expansion with a sensitivity of 100% and a specificity of 94% in patients in the intensive care unit. Our team studied patients in the operating room and found that a threshold ΔPOP value of 13% predicted fluid responsiveness with an 80% sensitivity and a 90% specificity [19]. Interestingly, all of these studies found similar ΔPOP threshold values and were published within the same year.

Conclusions

There is now much evidence showing that the respiratory variations in the pulse oximeter plethysmographic waveform amplitude are as accurate as other dynamic indicators for fluid responsiveness assessment in mechanically ventilated patients in the intensive care unit and the operating room. This technique is not yet easily measurable at the bedside but new devices will probably allow for automatic and continuous assessment of this parameter [22].

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Continuous Monitoring of Organ Chemistry – a Paradigm Shift in Management of Intensive Care

U. UNGERSTEDT

For decades we have discussed the possibilities that will open up once we have biosensors that can be implanted into individual organs providing us with invaluable bedside information about their metabolic state during intensive care. However, developing such sensors has proven much more difficult than anyone could have foreseen.

In 1974 we presented a simple solution: to implant a tiny dialysis tube into the brain of an animal, perfuse it with a physiological medium and collect the samples outside the body [1]. In this way all conceivable analytical techniques became available for analyzing essentially every kind of molecule present in the interstitial fluid. The technique was subsequently called *microdialysis*.

Since then the microdialysis technique has developed into a standard technique for recovering every conceivable endogenous and exogenous molecule from essentially every tissue in the body. In the early 1980s the technique became available for human use [2] and a simple check in PubMed shows that there are now close to 12,000 published articles including approximately 2,000 of the use of the technique in humans. Microdialysis has become a universal biosensor for monitoring the chemistry of tissues and organs.

In 1987 the first microdialysis “probes” were implanted in the human brain and subcutaneous tissue at the Karolinska institute in Stockholm. In these early studies we used sterilized animal probes [3, 4], however, in subsequent work new catheters were developed especially suited for human tissues [5].

Today there are CE-labelled catheters available for implantation in the brain, abdomen, liver, muscle, subcutaneous tissue as well as intravenously. There are miniature perfusion pumps, micro vials and analyzers suitable for intraoperative as well as bedside use in the intensive care unit (ICU). Tissue chemistry data can be presented as trend curves on bedside monitors together with physiological data in order to help the staff to decide about treatment and to evaluate the effect of their interventions in real time.

In this article I will give an overview of the different applications of clinical microdialysis. Some of these have reached the stage of clinical routine as in neurointensive care and reconstructive surgery, while others are being researched and evaluated e.g. the application to the intestine, liver and heart.

Markers of Tissue Biochemistry

There is a fundamental difference between blood chemistry and tissue chemistry. In a blood sample we analyze chemicals that may originate from essentially every organ of the body – usually excluding the brain due to the blood brain barrier. Because of this, we need to develop chemical assays for organ-specific markers i.e. chemical compounds that originate from a particular organ and have special relevance for the pathological state of that organ.

In the case of microdialysis we implant our microdialysis catheter in the particular tissue or organ of interest. It means that if we want to study, for example, changes in the energy metabolism, we can use the same marker substances for whichever organ we study. We monitor the environment of the cells in the organ regardless of whether the substances are produced from the cells themselves or imported from the local capillary blood flow. We sample the environment that tells us if the cells are functioning normally, if they are being supplied normally, the drug concentrations they are exposed to and the pathology they are suffering. We sample the environment of the cells regardless of whether they are inside or outside the blood brain barrier.

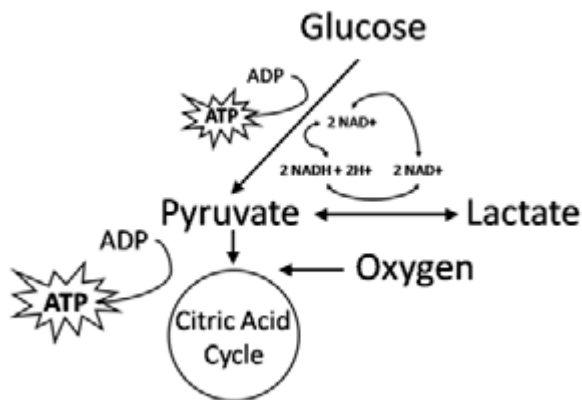


Fig. 1. The use of lactate/pyruvate as a marker of the cells ability to make use of oxygen and/or glucose is easily understood when considering the anaerobic and aerobic part of the glycolysis. In the anaerobic part of glycolysis glucose becomes pyruvate in several steps not requiring oxygen. The reaction needs NAD^+ and produces two molecules of ATP for every molecule of glucose. Pyruvate enters the citric acid cycle, where 32 molecules of ATP are produced, provided that oxygen is available. NAD^+ is regenerated from NADH when part of the pyruvate is metabolized to lactate. Ischaemia, that is an insufficient capillary blood flow, will limit the supply of oxygen and glucose forcing pyruvate to be metabolized to lactate in order to keep up the anaerobic energy production. The increase in lactate is soon followed by a decrease in pyruvate due to the decrease in glucose supplied by the capillary blood. The result will be an increase in the lactate/pyruvate ratio.

In the case of energy metabolism (Fig 1) it is of obvious value to sample glucose metabolism using markers such as glucose, lactate and pyruvate where the lactate/pyruvate ratio is a well known marker of the redox state of the tissue and an indicator of tissue ischaemia [6]. An important aspect of the lactate/pyruvate ratio is that changes in catheter recovery e.g. due to tissue oedema or changes in the flow of the perfusate through the catheter do not affect the ratio. The ratio is an absolute number, which can be used to compare one organ to another organ or one patient to another patient. In the brain we have rarely seen ratios above 25 in normal brain tissue and we therefore consider values above 25 as an indicator of the degree of ischaemia [5].

Another valuable feature of the lactate/pyruvate ratio is that increases in lactate due to an increase in cell metabolism are not misinterpreted as a sign of ischaemia as long as the lactate/pyruvate ratio remains the same. Furthermore, the lactate/pyruvate ratio tells us whether a decrease (or increase) in tissue oxygen has a real effect on cell metabolism. The tissue level of oxygen is dependent upon the supply from capillaries and the true impact on cell pathology can only be understood by analyzing the lactate/pyruvate ratio i.e. the change in cell metabolism that may or may not follow a change in tissue oxygen.

Once there is an increase in the lactate/pyruvate ratio we want to know if this is damaging to the cells. Cells may react differently to changes in their redox state depending on the type of cell as well as the degree of pathology from which it is suffering. We can then use indirect markers of cytotoxicity such as glutamate [7, 8] or a direct marker such as glycerol [9]. Cell membranes are largely built from glycerophospholipids and when they are under attack from phospholipases, glycerol is released as a sign of membrane decomposition (Fig. 2).

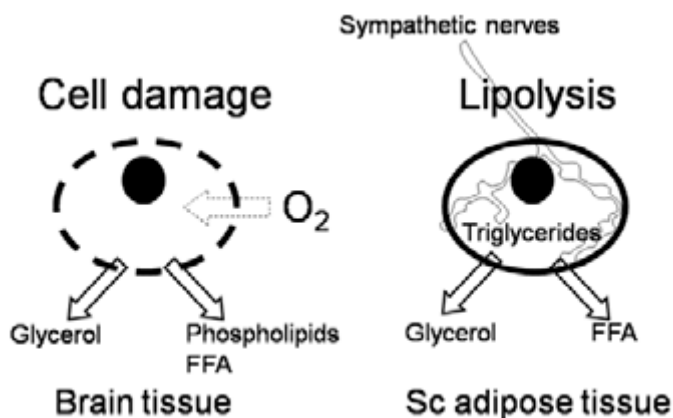


Fig. 2. Depending upon the tissue, glycerol may serve as a marker of cell membrane damage or lipolysis. In the brain, where there is little or no lipolysis, an increase in glycerol signals a breakdown of cell membranes due to a decrease in capillary perfusion and an insufficient supply of oxygen and glucose. In adipose tissue, e.g. when the microdialysis catheter is implanted subcutaneously, an increase in glycerol signals an increase in lipolysis, i.e. release of noradrenalin from sympathetic nerve endings stimulating adrenoreceptors on the adipocytes that trigger the breakdown of triglycerides (fat) to free fatty acid and glycerol. In this way glycerol in the dialysate signals an increased sympathetic tone.

In adipose tissue, however, glycerol is a marker of lipolysis [10] controlled by the local supply of sympathetic nerves [11]. This means that glycerol may serve as an important indirect marker of sympathetic stress once a microdialysis catheter is inserted subcutaneously in the patient. This is a still largely unexplored application of microdialysis and of potentially great value in the intensive care setting.

The interest in inflammatory processes in a number of clinical conditions such as brain trauma, sepsis and transplant rejection has led to microdialysis of inflammatory mediators such as cytokines (e.g. tumour necrosis factor (TNF)- α , interleukin (IL)-1b, IL-6 and IL-10a, 17-28 kDa) and chemokines (IL-8, MCP-1, IP-10 and MIG; m.w. 7-11 kDa). This has become possible when using microdialysis catheters with large pore membranes and a molecular cut-off of 100,000 Da or higher [12, 13].

Furthermore, microdialysis emerges as a truly unique tool for monitoring the free fraction of drugs in catheters placed in tissues and organs or in the blood using intravenous microdialysis catheters. It becomes possible to evaluate the penetration of drugs over the blood brain barrier both when it is intact and when it is damaged [14] and the extent to which antibiotics, for example, reach an infected organ. In the future we may be able to estimate the pharmacokinetic (PK) variables as well as the pharmacodynamic (PD) responses in an individual patient and in this way optimize our drug treatment to match the pathological process.

Finally, there are instances when microdialysis may be used to administer exogenous or endogenous compounds to an individual tissue or organ. An isotope such as ^{13}C -labelled glucose may be included in the perfusate with the aim of studying glucose metabolism in the tissue [15] or the tissue or organ may be fed with a substrate of an important enzyme reaction while recovering the product through the same microdialysis catheter. This may become especially interesting when used to evaluate the pathological state of the liver during the surgical resection of the organ for cancer and when harvesting a liver from a donor.

Why Monitor Tissue Biochemistry?

Before introducing a new technique into surgery and intensive care there must be excellent reasons based on evidence from outcome studies and cost benefit evaluations. Even to research the technique demands a clear vision of why such a technique might be useful in a reasonably near future.

In the case of microdialysis the vision is easy to understand: We want to detect pathological changes *before* we see them as clinical signs (Fig. 3). Ideally, we even want to detect those processes that eventually may lead to pathology. All of this comes down to the important fact that we need more time in order to successfully intervene. We need a window of opportunities.

It seems reasonable to assume that tissue and organ pathology starts with changes in tissue biochemistry – even when the primary damage may be physical – as in traumatic brain injury (TBI). We want to avoid the secondary damage whether it is due to ongoing chemical processes in the cells or due to the nature of our pharmacological and surgical interventions.



Fig. 3. By detecting a change in organ chemistry before clinical signs become apparent treatment can start hours or even days earlier than would have been the case when clinical signs is the only source of information. A “window of opportunities” is created that may dramatically alter outcome measured as “tissue outcome” and possibly outcome as measured by a traditional outcome scale.

Already at this stage of the microdialysis technique it is beyond doubt that we can detect pathological changes in tissue chemistry before we detect changes in clinical signs. Vasospasm after subarachnoid haemorrhage (SAH) is detected by changes in the lactate/pyruvate ratio on average 11 hours before clinical signs are evident as measured by transcranial Doppler [16]. Glutamate and lactate/pyruvate ratio have been found to be the earliest indicators of vasospasm in SAH patients [17]. Ischaemia in a free flap is detected as soon as a thrombosis compromises the capillary flow to such an extent that tissue ischaemia develops [18, 19]. This early detection of flap ischaemia gives the surgeon 5-6 hours to intervene and remove the thrombus.

With ongoing research we will increase our understanding of the pathological processes behind events such as ischaemia, vasospasm, thrombus formation and inflammation. We can intervene even earlier and thus increase the size of our window of opportunities. Above all we can monitor the impact of our interventions aiming to restore the normal physiology and chemistry of the tissue.

However, performing adequate outcome studies is difficult. The reason is obvious: Microdialysis is a diagnostic technique not a treatment. A proper outcome study can only be performed when the data derived from microdialysis is used to guide a treatment known to be effective. This could be the adjustment of cerebral perfusion pressure (CPP) in response to the lactate/pyruvate ratio in order to increase capillary perfusion, or changing the dose of a drug in response to the PK/PD in the tissue. In all such situations the purpose is to individualize the treatment in relation to the biochemistry of the tissue.

Another problem relates to the very definition of outcome. We all know that most of the procedures used in intensive care are not proven in outcome studies often because the tools we have for monitoring outcome are inadequate. In the case of microdialysis one might argue that a positive outcome is evident already when it is possible to restore normal physiology and biochemistry in the tissue not

necessarily when considering the wellbeing of the individual. It is, for example, obvious that a patient may not survive due to conditions unrelated to the successful normalization of the tissue while other patients may have an excellent outcome just because of the saving of tissue.

Microdialysis in Neurointensive Care

The application of microdialysis to brain monitoring was obvious for two reasons: The existence of the blood brain barrier, which made blood sampling uninteresting, and the fact that pathological processes in the brain were often local, e.g. tumours, contusions and haemorrhages. This demanded a technique capable of monitoring local processes, a technique capable of telling apart normal brain tissue from tissue with pathological metabolism.

After establishing the chemical characteristics of brain ischaemia in patients during resection of brain tissue [20] and in patients after TBI [6, 21] the single most important discovery was the great difference in metabolism between the normal tissue and the penumbra surrounding a contusion [22] or haemorrhage [23]. The penumbra tissue proved much more sensitive to secondary insults than normal tissue (Fig. 4). A seemingly normal CPP that was adequate for the normal tissue contralateral to the lesion could be highly inadequate for the penumbra resulting in infarction and death of tissue [22].

In view of the great local differences in brain pathology the placement of the catheters became of vital importance. Only after the launch of catheters with a gold

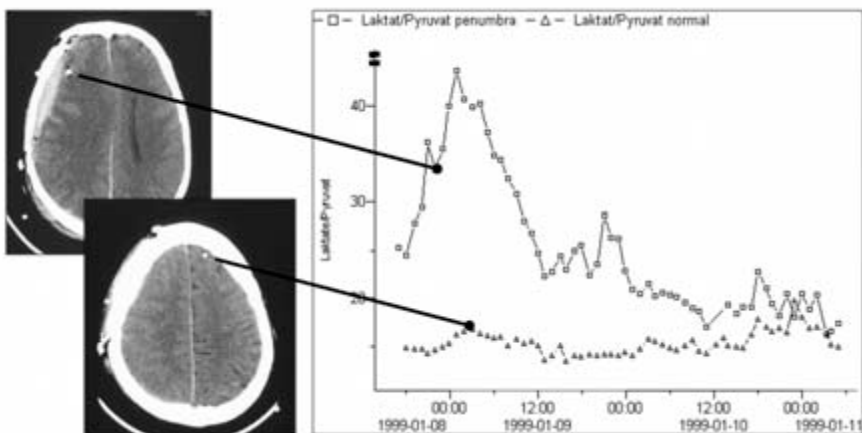


Fig. 4. The gold tip of the microdialysis catheter is visible on CT and shows that one catheter is positioned in the penumbra of the haematoma and the other in normal tissue contralateral to the lesion. The dramatic rise in the lactate/pyruvate ratio was due to an inadequate CPP. This was corrected by a blood transfusion which caused lactate/pyruvate to decrease and finally reach the normal level of the contralateral side. The data show the great difference in sensitivity to secondary damage between penumbra and normal tissue.

tip visible on CT was it possible to make proper use of the data from tissue chemistry monitoring in the brain. The catheter far from the lesion might signal normal brain metabolism while the catheter properly placed in the penumbra reveals the pathology relevant for guiding the treatment of the patient. In this way the technique of microdialysis has proven its true value by being able to monitor local events of direct importance for avoiding secondary damage of the penumbra as well as normal brain tissue.

Microdialysis in Reconstructive Surgery

The application of microdialysis to the monitoring of microsurgical flaps in reconstructive surgery is close to the ideal application. The blood supply to the flap is usually maintained by a single artery and vein. A thrombosis or torsion of the artery will affect the capillary perfusion of the entire flap and in this way the localization of the microdialysis catheter becomes less important. The diagnosis of a compromised capillary perfusion is detected early leading to appropriate treatment i.e. surgical removal of the thrombus or correction of the torsion [18, 19, 24, 25].

A decrease in capillary perfusion leads to decreased delivery of oxygen and glucose. The lack of oxygen causes a shift towards anaerobic metabolism with increasing lactate and a decreasing pyruvate due to lack of glucose i.e. an increase in lactate/pyruvate ratio.

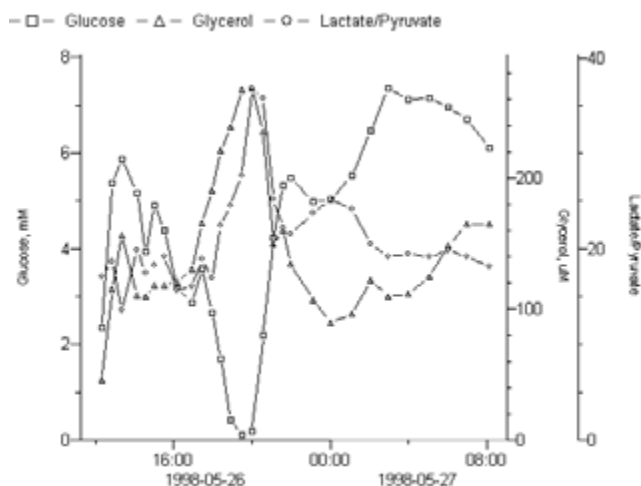


Fig. 5. During reconstructive surgery of a leg the microdialysis catheter is placed in the flap. As soon as the artery to the leg is clamped glucose starts to decrease due to the limitation of the glucose supply. Subsequently, when the artery supplying the flap is cut, the glucose drops to zero while the lactate/pyruvate ratio and glycerol increase. Once the anastomosis is prepared and the flap reperfused there is an immediate decrease in lactate/pyruvate as well as glycerol while glucose returns to normal levels.

Microdialysis may also be applied during reconstructive surgery showing the effect of clamping and cutting vessels and the reperfusion after completing the anastomosis (Fig. 5). Inadequate recovery of tissue chemistry after reperfusion will be noted and may lead to reopening the vessels and a renewed anastomosis.

After surgery the microdialysis catheter is left in place during the critical post-surgical period effectively alerting the staff to any change in the perfusion of the flap. Microdialysis is of particular value in buried flaps where it is difficult or impossible to visually inspect the flap. An added advantage of microdialysis is that patients can be mobilized without being tied to tubing or electrical wires.

The obvious connection between diagnosis and treatment has made it possible to identify improved outcome as well as calculating the cost-benefit of using microdialysis monitoring of free flaps in a plastic surgery clinic [26].

Microdialysis in Intestinal Surgery

In the literature there are several studies of microdialysis of the intestinal wall with the idea of capturing the first signs of ischaemia that may lead to sepsis and multi-organ failure. However, our own experience in a porcine model of sepsis convinced us that it would be too risky to place microdialysis catheters in the wall of the human intestine due to the possibility that the catheter may penetrate the wall and open the way for peritoneal infections [27].

We hypothesized that the intraperitoneal fluid might reflect ischaemic changes in the intestinal wall and this was tested by clamping the superior mesenteric artery as well as an arcus artery in a porcine model. Microdialysis catheters were placed freely in the immediate vicinity of the intestine where the artery was clamped and further away, adjacent to the normally perfused intestine [28].

Global ischaemia caused by clamping the superior mesenteric artery caused a dramatic increase in the lactate/pyruvate ratio and glycerol, signalling ischaemia and cell membrane breakdown. Regional ischaemia after clamping an arcus vessel showed ischaemic metabolism close to the affected region of the intestine while the catheter adjacent to the normal intestine showed no signs of ischaemia.

Intraperitoneal microdialysis (IPM) was then carried out in a pilot study in humans after abdominal surgery confirming the ability of microdialysis to detect intestinal ischaemia [29].

Subsequent studies have shown that a normal postoperative course results in a decreasing lactate/pyruvate ratio, while complications such as peritonitis, bowel ischaemia and urinary fistula are preceded by two to four days of increasing lactate/pyruvate ratio as an early marker of an impending complication [30]. By surgical placement of the catheter close to the anastomosis after colorectal surgery it has been possible to detect anastomosis leakage before serious complications occur [31]. Microdialysis is now also being tested for its ability in detecting complications after oesophageal anastomosis and pancreas surgery.

Further studies in animals and humans have shown that microdialysis may be performed in the intestinal lumen and that essentially the same chemical informa-

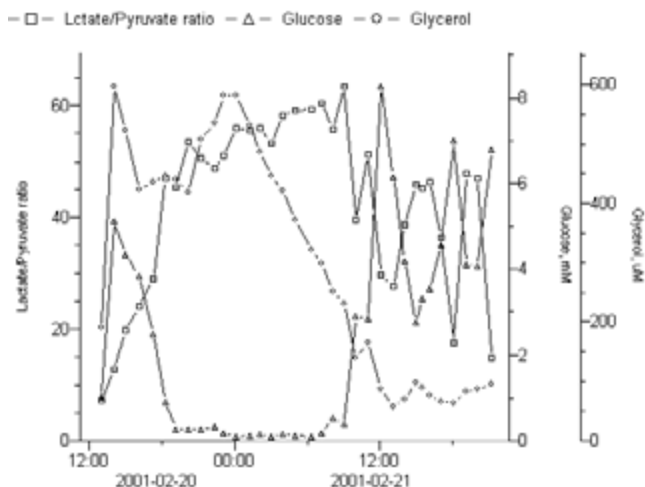


Fig. 6. After abdominal surgery intraperitoneal ischaemia develops approximately 4 hours before clinical signs are apparent. Glucose drops to almost zero and the lactate/pyruvate ratio as well as glycerol increases. The event was related to insufficient oxygen saturation and the chemistry returned to normal when this was corrected.

tion is derived from intraluminal, intramural and intraperitoneal placement of the microdialysis catheter [32, 33].

Microdialysis of the peritoneal cavity is of particular interest as it reveals the chemistry of a compartment between the intestine and the liver that so far has been accessed only by analyzing exudates from intraperitoneal drainage. It may lend itself to early diagnosis of changes in intestinal absorption of nutrients, translocation of bacteria and the development of sepsis.

Microdialysis of the Liver

Vascular and biliary complications related to ischaemia-reperfusion injury still remain a major problem after liver transplantation despite improvements in preservation, technical advances, and surgical skills. Early detection of impaired function of the transplanted liver is vital for a successful outcome.

The detection of vascular complications, such as arterial and portal vein thrombosis, is especially important in the early post transplantation period. Hepatic artery thrombosis is one of the most devastating complications in liver transplantation and occurs in 3% to 12% of all adult transplant recipients and up to 42% of paediatric patients.

Microdialysis of the liver parenchyma promised to be an ideal technique for metabolic monitoring over extended periods of cold storage and early after transplantation. We started by investigating each step of the procedure in a porcine model [34]. In a subsequent study in patients [35] we confirmed the results from

the porcine model. An interesting finding was that transient ischaemia in the human liver is followed by increasing glycerol levels indicating an ongoing damage to cell membranes [36]. This means that glycerol might also serve as an early marker of liver rejection. We are presently conducting a clinical trial investigating the predictive power of liver glycerol after transplantation. Recent studies have also investigated the metabolites of ischaemia-reperfusion injury and amino acids in the liver using microdialysis during transplantation [37].

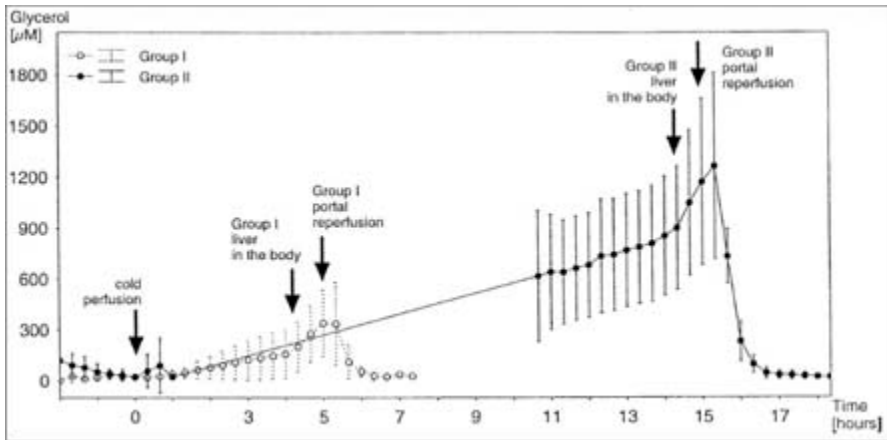


Fig. 7. In the this study [36] cell damage accelerated once rewarming started and the glycerol levels increased more rapidly in group II (15 h of ischaemia) compared to group I (5 h of ischaemia). The most likely source of glycerol is damaged cell membranes of hepatocytes because of the dominance of this cell type in the liver. The changes in glycerol concentration after rewarming/reperfusion is, to a large extent, the result of damage during cold ischaemia. Our study supports the theory that cold preservation increases the sensitivity of hepatocytes to rewarming injury in a time-dependent manner.

Monitoring Glucose, Lactate and Pyruvate in the ICU

So far we have limited our discussion to the monitoring of organ pathology during neurointensive and general intensive care. However, there are several global parameters that may be monitored simultaneously in these patients by placing microdialysis catheters subcutaneously or intravenously. This is especially interesting in view of the recent interest in keeping glucose within tight limits, which seems to be an important factor in improving outcome [38].

However, when evaluating our experience of subcutaneous monitoring of glucose in neurointensive care patients [39] it seems as if there is a discrepancy between blood and subcutaneous glucose. Similar findings have been reported recently in studies of critically ill children [40]. This is in contrast with diabetic

patients, where there is a good correspondence between blood and tissue glucose [41].

The reason for this discrepancy is in all probability because changes in capillary perfusion of subcutaneous tissue in the critically ill is often caused by pathological factors or the administration of vasoactive drugs, which redistribute blood between extremities, torso and internal organs. In order to faithfully record tissue concentration of glucose in the interstitial fluid the recovery of the microdialysis probe must be close to 100%. If not, the concentration of the particular substance in the dialysate will be dependent upon the supply of glucose. The supply of glucose over time will change if capillary flow changes and so does the concentration in the dialysate even if the concentration in the blood remains stable [42].

The solution to this dilemma is to place the microdialysis catheter in the blood stream i.e. intravenously. The constant flow of blood over the microdialysis membrane ensures that there will be no limitation in the supply of glucose and the microdialysis catheter will easily reach 100% recovery and thus faithfully reflect the true concentration in the blood.

The same catheter may be used to recover other markers of metabolism such as lactate and pyruvate as well as the free fraction of drugs in the blood. The main advantage of this is that blood can be sampled without removing blood from the patient and without the staff handling blood in connection with the analysis. A further advantage is that the dialysate is cleaned by the dialysis process making the sample ready for analysis without further purification steps.

Preliminary findings indicate that it is possible to distinguish sepsis from ischaemia when monitoring lactate and pyruvate in subcutaneous tissue. Lactate increases in sepsis as well as in ischaemia while the lactate/pyruvate ratio remains stable in sepsis and decreases in ischaemia e.g. in an ARDS patient.

Monitoring Stress in the ICU Patient

Microdialysis offers a unique possibility to sample glycerol from the subcutaneous tissue as an indicator of lipolysis (see also above). Lipolysis is predominately regulated by the release of noradrenalin from sympathetic nerves stimulating receptors on the adipocytes [11]. The innervation from the sympathetic trunk follows the dermatomes.

A catheter placed in the periumbilical region, for example, will primarily reflect sympathetic events related to abdominal function and secondarily the general activity of the sympathetic system as expressed in a sedated patient. After examining a large number of patients in the neurointensive care unit we were surprised to see large variations in glycerol over time in the individual patient. We interpret this as an inadequate control of the stress level experienced by our patients during intensive care in spite of “proper” treatment with sedative drugs.

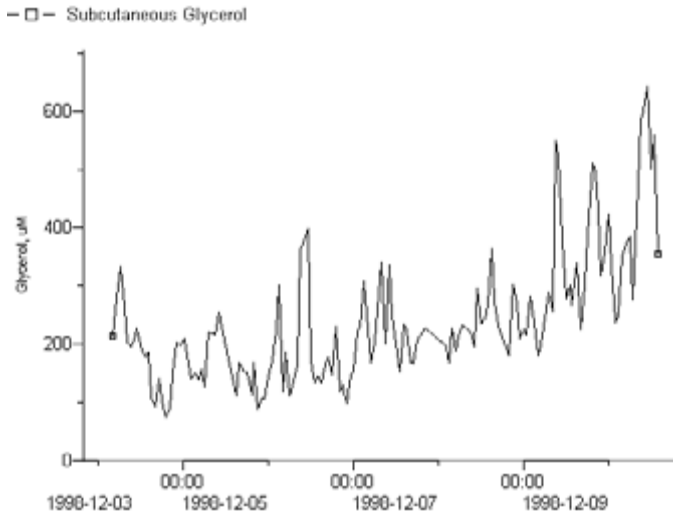


Fig. 8. A 7-day trend curve of subcutaneous glycerol from a catheter implanted in the periumbilical region in a patient suffering TBI. The expected concentration of glycerol in the dialysate in a well sedated patient is between 50 and 100 μM . In spite of following the ICU normal routines for sedation, the patient displays dramatic shifts in glycerol indicating great shifts in the activity of the sympathetic nervous system.

Interpreting Multimodal Data

It may seem that with every new technique added, the intensive care environment comes closer and closer to a situation when we are overloaded with information that we cannot make use of. I do not believe that this is the case. Many everyday situations, like driving a car through a city at rush hours, is equally or more information intensive – yet we still do it.

Data presented in the ICU must be interpretable. In the case of microdialysis it becomes frustrating if one tries to understand every swing in the chemistry trend curve. Our knowledge of tissue chemistry does not allow such a close look at data and the technology itself is probably not reproducible enough to allow such a close attention to details. We need to reform the way data is presented in the ICU where we mostly react to instantaneous data presented as numbers on a bedside monitor. This deprives us of the historical knowledge of what happened minutes, hours and days ago.

A well designed data system should be able to display all numerical information as trends where every parameter can be displayed against every other parameter by simple drag and drop. This must happen quickly and without effort in an effective dialogue between the computer and the nurse or doctor. There must also be some simple procedures to follow. We teach the LTC method: Start by looking at the LEVEL of the lactate/pyruvate ratio, for example. Is it above, below or within

normal range? Next look at the TREND over the last 8 to 12 hours: Is it moving into or out of the normal range? Finally, COMPARE the level and the trend with other recorded variables: If the lactate/pyruvate ratio is above normal range and still increasing while CPP is in the low range, consider increasing the CPP.

Monitoring the Heart

In all applications of microdialysis described so far CE-labelled catheters are available permitting the technique to enter into routine medical care in Europe. In the United States FDA approved catheters are so far only available for implantation into the brain. When microdialysis has been studied in patients undergoing heart surgery all studies have been done under ethics committee approval using mostly brain catheters or custom-made catheters with the intention of finding the ideal catheter that can be left in the beating heart for post surgical surveillance of the patient.

The microdialysis technique for in vivo studies in animals of myocardial energy metabolism has been extensively validated with impressive results [43] and applied to studies of dynamic changes of myocardial metabolism in response to ischaemia, cardioplegia, and extracorporeal circulation [44]. Porcine models have also been applied to the development of myocardial [45] and intravasal [46] catheters for future use in humans. Lastly, human studies have confirmed the power of myocardial microdialysis to monitor metabolic changes related to cardioplegic heart arrest [47, 48] and coronary artery bypass surgery [49, 50].

Concluding Remarks

Monitoring tissue and organ chemistry in the ICU is a logical and necessary step considering the rapid development of biochemical knowledge. We cannot limit ourselves to monitoring physical variables or relying on clinical observations at the same time as we spend a considerable amount of our time studying and researching the chemical pathology of the tissues and organs.

The problem is and has been that we still lack effective and economically feasible means of recording and displaying changes in organ chemistry bedside. To some extent we lack the knowledge to interpret the biochemical data; however, I am not impressed by this argument as essentially everything stated in this article is first-year medical school knowledge. Monitoring tissue chemistry with the simple technique of microdialysis is the beginning of a paradigm shift which will allow us to make use of all the knowledge of tissue and organ chemistry that is already available.

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General Anaesthesia and the Developing Brain

V. JEVTOVIC-TODOROVIC

Advances in modern anaesthesiology have enabled us to perform complex surgical interventions in the early stages of human development. General anaesthesia is routinely administered to neonates, infants, and very young children, and the use of anaesthesia in premature infants (as young as 20 weeks postconception), has steadily increased. It would be over-simplistic to consider the child as a small adult when it comes to anaesthesia management, and many concerns in paediatric anaesthesia are unique to the pathophysiology and psychology of a child. Of special interest for our research is the fact that the young brain undergoes immense growth during early childhood. Although its development begins during the last trimester of in utero life, the human brain is not fully developed at birth and continues to grow over the first couple of years of postnatal life [1].

Prolonged deep sedation in the intensive care unit and/or multiple surgical interventions are routine occurrences in daily paediatric practice which expose thousands of very young children to increasingly complex and often repetitive anaesthesia interventions. This common practice involves the use of numerous anaesthetic agents with the ultimate end point of achieving the level of comfort (unconsciousness and insensibility to pain) synonymous with massive and prolonged depression of neuronal activity. However, it is well known that all key elements of neuronal development, especially synaptogenesis (e.g. migration, synapse formation, differentiation, and maturation) depend upon constant neuronal signalling, communication, and feedback processing [2]. The very small percentage of unsuccessful neurons that do not make meaningful connections during synaptogenesis are considered redundant and are destined to die by the process referred to as programmed cell death (e.g. apoptosis, neuronal suicide) [3]. This raises the ultimate question regarding the prudence of our practice of exposing young individuals to general anaesthesia. Could anaesthesia-induced depression of neuronal activity constitute a generic signal for a developing neuron to commit suicide by “pushing” many immature neurons into a redundant category? Could clinical anaesthetics administered during the most critical and vulnerable period of brain development be causing harm to our youngest and most precious patient population?

Our basis for concern regarding the detrimental effects of general anaesthetics in the immature brain is not purely hypothetical or speculative. Based on our work and the work of others over the last few years, it is becoming widely accepted that the use of common general anaesthetics known to potentiate inhibitory transmis-

sion through GABA_A receptors (e.g. intravenous anaesthetics-benzodiazepines, barbiturates, propofol, and inhalational anaesthetics – isoflurane) [4, 5] and general anaesthetics known to decrease the excitatory transmission through NMDA glutamate receptors (e.g. nitrous oxide and ketamine) [6, 7] at the peak of synaptogenesis causes widespread apoptotic neurodegeneration in vulnerable brain regions in various mammalian species (e.g. rats, mice, guinea pigs, and non-human primates) [8-12]. Furthermore, based on extensive behavioural studies conducted with rats (and emerging studies conducted with non-human primates), it appears that exposure to general anaesthesia at the peak of synaptogenesis causes significant learning and memory deficiencies later on in life with the gap in learning abilities between control and anaesthesia-treated animals progressively widening in later adulthood [8].

Therefore, it is important to conduct diligent studies aimed at clearly understanding the mechanism(s) operative in anaesthesia-induced neuronal demise during early stages of brain development. Based on this growing body of evidence, the assumption that general anaesthetics do not have potentially worrisome neurotoxic side effects is not acceptable and should be carefully scrutinized, especially since these pharmacological agents are routinely used in neonatal and paediatric medicine. This review summarizes our present understanding of some of the key components responsible for anaesthesia-induced neuroapoptosis and offers some neuroprotective strategies that could be beneficial as an adjunct therapy in preventing anaesthesia-induced death of the developing neurons.

The Critical Components of Anaesthesia-Induced Apoptotic Cascade Activation

a. General anaesthesia activates mitochondria-dependent apoptotic cascade leading to effector caspases activation and apoptotic neurodegeneration.

Apoptosis can be executed via different biochemical pathways resulting in activation of effector caspases as the final step. The mitochondria-dependent pathway (also called the intrinsic pathway) involves the down-regulation of antiapoptotic proteins from the bcl-2 family (e.g. bcl-x_L), an increase in mitochondrial membrane permeability and an increased release of cytochrome c into the cytoplasm, which in turn activates caspase-9 and caspase-3 resulting in apoptotic damage [13]. To investigate the importance and timing of the intrinsic pathway activation in anaesthesia-induced neuroapoptosis, we used clinically-used general anaesthetics, isoflurane (at 0.75-vol%), nitrous oxide (at 75-vol%), and midazolam (1 mg/kg, s.c.) which were administered at the peak of rat brain development (7 days postnatal age) [14]. We found that mitochondria-dependent cascade gets activated early (within the first two hours of anaesthesia exposure) and is characterized by a significant fall in protein levels of bcl-x_L, a significant rise in cytochrome c and activation of caspases -9 and -3.

Melatonin, a hormone secreted by the pineal gland at night and one of the most commonly purchased over-the-counter drugs, was shown to modulate the mito-

chondria-dependent apoptotic cascade in vitro [15] by up-regulating the protein levels of bcl-x_L and down-regulating the protein levels of cytochrome c, thus protecting against apoptotic cell death. When melatonin was examined in vivo we found that it provides significant protection against anaesthesia-induced neurotoxicity in the immature rat brain [16], thus recommending for the first time a clinically attainable and readily available preventive strategy.

b. General anaesthesia activates death receptor-dependent apoptotic cascade leading to effector caspase activation and apoptotic neurodegeneration.

The extrinsic pathway is initiated by the activation of death receptors that involves the formation of a death-inducing signalling complex (DISC) which contains Fas, a member of the TNF- α superfamily. DISC formation results in the activation of caspase-8 which activates caspase-3, executing the cell. To investigate the importance and timing of the extrinsic pathway activation in anaesthesia-induced neuroapoptosis, we analyzed the changes in the expression of Fas and the activation of two key effector caspases - caspase-8 and caspase-3 [14]. We found that anaesthesia induced significant up-regulation of Fas protein levels and significant activation of both caspase-8 and caspase-3 although based on timing it appears that anaesthesia-induced activation of the intrinsic pathway occurs before activation of the extrinsic pathway.

c. General anaesthesia activates neurotrophic factor-dependent apoptotic cascade leading to effector caspase activation and apoptotic neurodegeneration.

The neurotrophins, a family of growth factors consisting of NGF (nerve growth factor), BDNF (brain-derived neurotrophic factor), NT (neurotrophic factor)-3 and NT4/5, are known to support neuronal survival, differentiation and several forms of synaptic plasticity and therefore play an important role in synaptogenesis of the mammalian brain. The signal transduction systems that mediate the diverse biological functions of neurotrophins are initiated via two different classes of plasma membrane receptors: the Trk (Tropomyosin receptor kinase) receptors and the p75 neurotrophic receptor (p75^{NTR}). Current data suggest that the main physiological functions of p75^{NTR} are not only the regulation of Trk receptor activation and signalling but also the activation of Trk-independent signal transduction cascade [17]. Both Trk-dependent and independent cascades modulate the activation (phosphorylation) of the Akt serine/threonine kinase, the pivotal factor in major survival pathway for neurons [18]. The neurotrophins are synthesized and released by neurons and both their biosynthesis and secretion depend on neuronal activity. Extensive depression of neuronal activity can impair survival-promoting signals that are regulated by neurotrophins and consequently promote apoptosis.

We presented evidence that clinically-used general anaesthetics, isoflurane, nitrous oxide, and midazolam, administered at the peak of rat brain development (7 days' postnatal age) induce neuroapoptotic damage in the developing brain of the immature rats that is mediated, at least in part, via a BDNF-modulated apoptotic cascade [19]. Anaesthesia-induced disturbances in BDNF-mediated neuronal survival pathways were significant and fairly rapid. Based on our experimental

evidence, we suggested a dual mechanism for anaesthesia-induced activation of neurotrophin-mediated apoptotic pathways: one via Trk-dependent and the other via Trk-independent, $p75^{\text{NTR}}$ dependent apoptotic cascade. The importance of either pathway seems to be brain region-specific. In the thalamus, anaesthesia causes a decrease in the protein levels of BDNF and the activated Akt levels (without any effects on $p75^{\text{NTR}}$ and ceramide levels) resulting in activation of caspase-9 and -3. On the other hand, in the cerebral cortex, anaesthesia causes an increase in BDNF levels while decreasing levels of the activated Akt and increasing caspase-9 and -3 activity, suggesting that activation of the TrkB signalling pathway is probably overridden by increased production of ceramide via activation of the Trk-independent $p75^{\text{NTR}}$ -dependent cascade.

A steroid hormone β -estradiol was shown to play an important role in up-regulating phosphorylated Akt levels, thus down-regulating the activation of caspase-3 and ultimately protecting against apoptotic cell death. When β -estradiol was examined we found that it provides significant protection against anaesthesia-induced neurotoxicity in the immature rat brain [19] offering another clinically attainable and potentially useful preventive strategy.

d. General anaesthesia induces permanent and significant neuronal deletion in vulnerable brain regions.

An important question regarding the significance of anaesthesia-induced neuronal damage during brain development is whether the observed anaesthesia-induced neuroapoptosis of the developing neurons results in permanent neuronal deletion or is only a transient and reversible phenomenon. To address this question, we studied fully-developed rat (postnatal day 23) [20] and guinea pig (first week postnatal life) [11] brains which were exposed to clinically-relevant anaesthesia (triple combination containing isoflurane, midazolam, and nitrous oxide) at the peak of their synaptogenesis (which coincides with the peak of their vulnerability – 7 days postnatal life in rats and 35-40 days in utero life in guinea pigs) and compared them to age-matched controls. After careful quantification of neuronal densities in the most vulnerable cortical and subcortical regions, we concluded that anaesthesia-treated rats and guinea pigs show a significant decrease in neuronal densities in all vulnerable brain regions compared to their respective controls (in rats as early as 3 days post-anaesthesia). Although physiological “pruning” of the redundant neurons is commonly observed in the developing mammalian brain, only a small percentage (estimated to be approximately less than 1% of the total neuronal population with some regional variations) is not expected to survive during normal synaptogenesis. Of grave concern is the fact that clinically relevant general anaesthesia severely jeopardizes the survival of many developing neurons leading to an alarming increase in neuronal deletion (as much as 50% in most vulnerable brain regions).

e. General anaesthesia induces effector caspase activation and apoptotic neurodegeneration despite adequate maintenance of cardiovascular and respiratory homeostasis.

Of paramount concern in clinical anaesthesia practice is the maintenance of adequate oxygenation/ventilation, tissue perfusion, and ultimately stability of vital and metabolic signs. Therefore, an ultimate concern was raised that the observed morphopathological changes in the developing brain, at least in part, could be due to inadequate maintenance of physiological [21, 22] or metabolic (e.g. hypoglycaemia) [23] homeostasis. To address this concern, we examined arterial blood gas values in infant mice or rats that were treated with a neuroapoptogenic dose of ketamine or a combined anaesthesia containing isoflurane, midazolam and nitrous oxide, respectively, and found that despite normal blood gas values, including arterial oxygen saturation, throughout the anaesthesia treatment the immature neurons undergo significant apoptosis [14, 24]. As for severe hypoglycaemia being the contributory factor for neuroapoptosis in infant rodents and immature guinea pigs it was reported that anaesthesia exposure condition triggered neuroapoptosis while blood glucose values remained equal to or higher than control values [11, 19].

Conclusions

Based on the intriguing and fast growing evidence that is being reported, the potentially alarming issue of anaesthesia-induced neuronal damage in the immature brain is gathering a lot of interest among practicing anaesthesiologists. By improving our understanding of the mechanism(s) by which anaesthesia induces neuronal damage in the immature brain we hope to devise the most effective preventive strategies so that existing anaesthetic drugs can be used to their full advantage without the risk of neurotoxic side effects since general anaesthetics in obstetric and paediatric anaesthesia are a necessity that cannot be avoided when pregnant mothers and newborn infants present with life threatening conditions requiring surgery and/or a prolonged stay in the intensive care unit.

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AIRWAY

Airway Management: The Essentials

G. FROVA, M. SORBELLO

*A kiss is yet a kiss. A breath is yet a breath.
Because essential things keep their value
for ever, despite time passing by.*
American proverb

The “essential” or the essence of an argument is what is absolutely necessary and/or fundamental (Oxford Dictionary, 9th ed. 1995).

There is a quantitative difference between what is “essential” for the patient and what is generally considered essential for the operator, either in terms of basic knowledge or in terms of experience and skills for successfully managing the airway, and particularly the difficult airway. The patient essentially needs to receive oxygen for his survival; this is effectively the true target in emergency management; the complete control of the airways (control of ventilation, prevention of inhalation, etc.) is not strictly necessary, but its achievement will contribute to improve the quality of assistance and to reduce risk.

Furthermore, in elective anaesthetic procedures, when a breathing and conscious individual is transformed by the anaesthesiologist into an apnoeic, unconscious and areflexic one, the complete control of the airway is an essential medico-legal duty for the operator, whereas oxygenation, carbon dioxide removal and inhalation prevention are mandatory targets for optimal airway management. To achieve these targets, anaesthesiologists should focus on some essential steps included among a wide, though less essential, knowledge of specific techniques and procedures. In the field of airway management, where a wide amount of information is available, many things could be considered essential, and only by recalling and focusing on the most important is it possible to keep in sight what is really essential.

This might be even more true and important if one considers how frequently and unexpectedly problems occur: in all those cases where the only thing missing is the time to think or decide what to do [1, 2], obtaining both the preliminary knowledge and the ability to apply the eight fundamental endpoints discussed in the following paragraphs becomes mandatory. The first cause of anaesthesia-related accidents is unpredicted difficulty in airway management, and its incidence seems to be underestimated because of reticence and because the occurrence of “near misses” is unknown [3]. What is known is that they occur mainly during anaesthesia induction, their incidence being double that during the intraoperative, extubation and post-anaesthesia phases, and that, probably thanks to the introduction of the ASA 1993 guidelines [4], the incidence of fatal accidents has been halved [5].

Predicting Difficulties

Even though no preoperative evaluation test is considered error-free, the choice of multiple measurements and tests has been widely accepted: in any case regardless of the result itself, time spent for pre-procedural evaluation might grant a significant reduction in unexpected difficulties and related accidents. Not all studies accept the importance of rigorous research of all predictive indices during preliminary clinical examination, because of the high grade of variability and subjectivity of some of them [6]; indeed these tests have a low sensitivity and therefore a large number of false positives, whereas if a certain number of tests are performed, the number of false negatives remains extremely low. For these reasons evaluation with the Mallampati test alone, as commonly occurs, is absolutely useless, whereas the following six parameters should be considered mandatory:

- a) Analysis of facial morphology, both frontal and lateral
 - b) Mouth opening measurement
 - c) Thyromental distance measurement
 - d) Mallampati test (static + phonation)
 - e) Mandibular subluxation capacity evaluation
 - f) Head and neck flexion and extension capacity evaluation
- According to these parameters difficulty might be recognized and graded in:
- Difficult face mask ventilation (DMV) (criteria a, d, f)
 - Difficult laryngeal mask airway ventilation (criterion b)
 - Difficult intubation (criteria b, c, d, e, f)

By following this approach, the question “What difficulties might I expect?” is integrated in the more comprehensive “How severe are the assumed difficulties?”

If only one of the above mentioned tests is largely abnormal, it might be stated that a certain manoeuvre will be either difficult if not impossible (Table 1); in other cases difficulty arises from the sum of small alterations of different parameters.

Table 1.

Predictors of difficult intubation (using single parameter)

- Mouth opening (interdental distance <3 cm)
- Thyromental distance <6 cm
- Mallampati class IV (phonating)
- Maxillary prognathism (not modifiable)
- Neck rigidity (flexion)

Predictors of difficult intubation (using multiple parameters)

- Mallampati class III (phonating)
- Thyromental distance 6-6.5 cm
- Mouth opening (interdental distance 3-3.5 cm)
- Limited neck flexion-extension (<90°)
- Maxillary prognathism (modifiable)
- Obesity

In terms of decision making, the predicted association of ventilation and intubation difficulty (Table 2) might strongly influence the operative procedures, suggesting narcosis refusal or in any case spontaneous breathing abolishment refusal, thus working with awake intubation techniques in local anaesthesia or with sedated but spontaneously breathing patients.

Table 2.

Predictors of difficult facial mask ventilation
Mallampati class IV
History of snoring or sleep apnoea
Presence of a beard
Overweight patient (BMI>26)
Large nose
Lack of teeth
Age (over 55 years)
Predictors of difficult laryngeal mask ventilation
Limited mouth opening (<2.0 cm)
Glottis opening oedema
Anatomical deformities and oropharyngeal pathology resulting in a poor LMA fit

The fundamental role of prediction, although known for a long time [7], is not widely recognized and accepted [8, 9]. The Italian guidelines [1] recognize the utmost importance of predictive tests and more generally of prediction difficulty, since their systematic use offers not only the obvious advantage of reducing unexpected difficulty, but also the less obvious (though even more important) consequence of focusing operator attention on airway management aspects, a still largely underestimated feature.

Evaluating the Patient and Recoding Parameters

Careful transcription of the measured parameters and clinical history of the patient in the anaesthesia record targeted at airway management should not be underestimated; it plays an essential role, especially wherever the physician administering anaesthesia is different from the one performing preoperative evaluations and in all cases of repeated procedures and definitively as a quality measurement instrument.

The results of the written record would clearly be much more effective if standardized measurements, scales and instruments were used: e.g. using the enhanced Cormack-Lehane laryngoscopic difficulty scale [10] with a recent video laryngoscope will provide different results from those obtained with a conventional Macintosh laryngoscope [11].

Being Familiar with and Possessing Mandatory Devices

The Italian Guidelines for difficult airway management [1] suggest some devices should be present wherever general anaesthesia is performed, so that some simple, well known, easily available and widely used devices have been identified and indicated as mandatory, with an advantageous cost/benefit ratio. The rigid Macintosh laryngoscope is still the most common and most used in all settings, despite several attempts to substitute it with newer prodigious devices, which are undoubtedly interesting but much more expensive, bulky and not always readily available, especially outside the operating room [11].

From this point of view video laryngoscope certainly provide better laryngeal exposure than conventional laryngoscopes, but even if they were commonly used and present in operating rooms, a standard laryngoscope would always be necessary in both intra- and out-of-hospital emergencies, in less developed countries and in any case whenever adequate skills for their use were not standardized. While on the one hand they provide great laryngoscopies, on the other intubation is not always easy, even in the hands of an expert, and always requires stylettes and guides which make less experienced operators much more prone to provoking laryngeal trauma.

Conversely, the main limitation of standard laryngoscopes is the occasional impossibility of obtaining a satisfactory glottic view, both because of lack of operator experience and because of the difficulty in obtaining the necessary oral, pharyngeal and laryngotracheal axis alignment, which is not needed when using video-devices, as they enable “look-around-the-corner” vision. In any case, such recent devices, despite their incredible didactic value, are not yet ready for routine use.

External laryngeal manoeuvres, such as BURP, might help in all cases of difficult laryngoscopy [1, 12], but they do require experience and optimal cooperation. Difficulty grading with standard laryngoscopy was first provided by Cormack and Lehane [13] and more recently enhanced by Yentis [10], and it remains a milestone in decision making during difficult airways management, providing maintenance of optimal oxygenation parameters.

The laryngoscopic view, in fact, suggests either repeating a laryngoscopic attempt in better conditions (changing the patient’s head position) and with different devices (different blades, stylettes, Magill forceps, introducers), or to waken the patient and programme different airway management strategies, since it is well known that repeated laryngoscopic attempts adversely affect new attempts and patient ventilability [14]. For these reasons the Italian guidelines limit to three and four the number of attempts for a skilled or for a non-skilled operator, respectively, before intubation attempts are withdrawn [1, 14].

As standard laryngoscopy might allow only a partial glottic view (2e, 3, 3e), knowledge of simple complimentary techniques and devices should be considered essential: these considerations, while being obvious for Magill forceps or for stylettes, are not yet obvious for devices such as the gum elastic bougie or hollow introducers, which might allow successful intubation even in cases where the glottic view is limited to the epiglottis alone [15].

The use of more complex devices is undoubtedly useful, but it cannot be considered essential. The Italian guidelines did not include the flexible fiberscope among the mandatory devices to be present in the operating room or to be used in an urgency/emergency setting, despite its unquestionable importance in certain situations, but they do consider mandatory the need to develop adequate skills and experience with this instrument [1].

Essential instruments and devices are shown in Table 3.

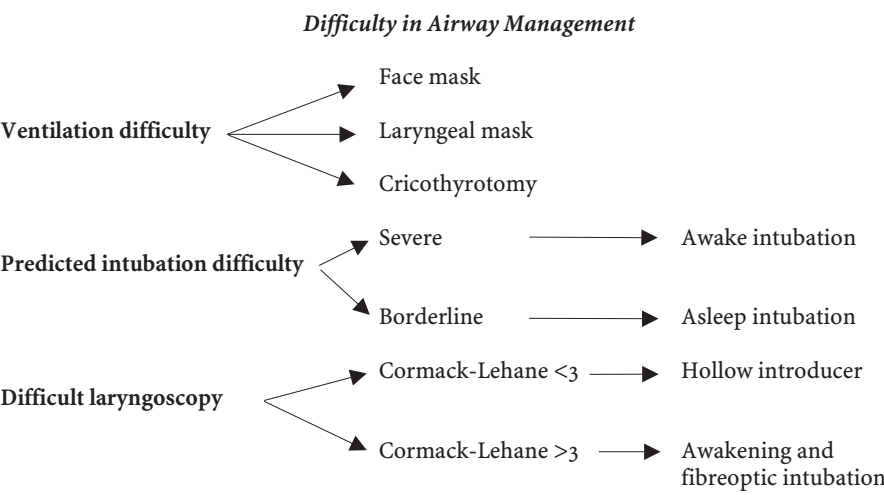
Table 3.
Essential devices for difficult airway management
Oxygen source
Rigid Macintosh laryngoscope
Tracheal tubes of different size
Facial mask
Laryngeal mask
Short stylette
Tracheal introducer
Flexible fibrescope
Cricothyrotomy set

Identifying a Behavioural Strategy

All algorithms and flow-charts accompanying difficult airway management documents and guidelines represent, per se, essential instruments: they enable the quick identification of criticality and propose essential decisional trees to address the problem [16]. While on the one hand this makes them perfect for mnemonic purposes and for practical management, on the other they require further discussion and deeper knowledge. Guidelines have demonstrated their importance for both patients safety [5] and for anaesthesiologists defence during legal claims [5]. The aim of the SIAARTI Difficult Airway Study Group publishing the first guidelines in 1998 [17] was to produce a simple but not simplistic document based on both the (low amount of) evidence available in the literature and on the experience of skilled operators and daily clinical good practice, and the solutions proposed for different difficulties were always the safest for patients and the simplest for anaesthesiologists. Table 4 shows a simplified version of a difficult airway algorithm, showing some essential concepts:

- type and grade of difficulty represent the milestone in decision making;
- face mask, laryngeal mask and cricothyrotomy are the three essential steps for oxygenation;
- severe predicted difficulty and borderline difficulty with predicted ventilation difficulty require fibreoptic approach and patient spontaneous breathing;
- unexpected difficulty requires the use of simple alternative devices or simply the use of good sense, meaning waking the patient and fibreoptic intubation with topical anaesthesia (if not in an emergency) when the laryngoscopic difficulty is above Cormack and Lehane grade 3.

Table 4.



The simple knowledge and application of these essential rules might be, essentially, life-saving [18, 19].

Checking Tube Position

Routine control of the correct tube position after any intubation manoeuvre is an unquestionable part of anaesthesiology daily practice, while it becomes mandatory after any case of difficulty in which direct vision of the tracheal tube passing the vocal cords was not possible.

Extubating Safely

A careful analysis of airway-related accidents shows different trends: while the number of fatal accidents during induction of anaesthesia has fallen, extubation and post-anaesthesia accidents over the same period have remained unchanged [5]. This means that after the introduction of guidelines for managing difficult intubation, something similar is required for managing (difficult) extubation, in order to standardize essential behaviour such as protected extubation on tube exchangers whenever particular difficulty was encountered during intubation attempts.

Checking the Patient after Difficult Intubation and Providing Written Information

As stated above, written consent from the patient before and written information for the patient after the procedure are mandatory steps of any difficult airway management, and therefore should be considered essential.

Post-procedural controls, especially in the event of difficulties and complex or potentially traumatic devices, are fundamental to provide both immediate diagnosis and treatment and to avoid future complications.

Developing Personal Experience

Direct experience in daily practice is probably the most important and effective way to develop skills and knowledge in the field of airway management. Unfortunately (or fortunately, according to the point of view), some situations occur so rarely that developing enough experience with daily practice alone appears impossible; the best example is the cannot ventilate – cannot intubate scenario. Its incidence is extremely low, indeed, and to date has been addressed with surgical (often late) access to the airway. Recently changes have been made, and only apparently is the situation more difficult than before.

The early use of extraglottic devices (so called as this definition is anatomically more correct than the American use of supra-glottic airways [20]) often solves most cases of difficult or impossible face-mask ventilation, with the sole exception of late use, when tissue swelling and oedema prevent their correct performance and ventilation.

In the rare cases of extraglottic ventilation failure, only rapid tracheal access allows patient oxygenation; unlike in the past, this manoeuvre is today easier for a non-surgeon operator, as the quite common experience with extraglottic devices and the specific experience of anaesthesiologists with the Seldinger-based approach make it almost natural to perform a percutaneous approach to the airway [21].

What is essential, then, is early recurrence to cricothyrotomy and its performance by the anaesthesiologist rather than by the surgeon.

The safest procedures are the Seldinger-based techniques after an aspiration test and introduction of either a cuffed or uncuffed > 4 mm ID cannula (which does not require jet ventilation and provides adequate ventilation for the patient) [22].

Despite being superficially described in the past as “*restaurant tracheostomy*” as “*it can be performed in a restaurant with a jack knife and the barrel of a pen for a tube*” [23], cricothyrotomy performance requires a certain amount of experience. Rarely performed in the operating room (6-200 per million anaesthetics [24]), but more frequent in emergency department (2000-5000 per million patients [25]), the only way to develop a certain skill might be simulation on cadavers or on mannequins with a quite low number of attempts [26] to achieve the ability of performing it in less than 40 seconds.

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Best Method to Establish the Grade of Difficult Airway. Clinical Assessment, Techniques and Procedures in Critical Care and ICU

F. PETRINI, L. MOGGIA, G. MERLI

Due to advances in training, technology and guidelines implementation, elective airway management within the setting of the Operating Room (OR) can be associated with very low complication rates [1]. There has been a heightened awareness and a steady rise in the amount of literature published on the prediction of difficult airways for anaesthesia purposes. Unfortunately none of the suggested methods provide satisfactory results in terms of sensitivity and specificity: at least for now, reliable prediction of difficult airway management (DAM) is likely to remain a decision-making process based on clinical judgment, and this is particularly true in emergency situations and critical illness [2]. Furthermore, the epidemiology of DAM varies according to the different definitions used and the population studied in the large amount of literature on the subject [3]. Complication rates in the Intensive Care Unit (ICU) environment are also much higher due to the inability, in the majority of cases, to perform a thorough evaluation of the patient's anatomy prior to airway instrumentation.

The Italian Society of Anaesthesia, Analgesia, Reanimation and Intensive Care (SIAARTI) Guidelines recommend performing multiple appropriate tests for the prediction of ventilation and intubation difficulties, for both elective and urgency preoperative assessment (Level D), but it is still uncertain whether true prediction is possible and which variables are the best ones in some specific patients, such as critical ones. Few references can be found comparing elective preoperative patients with critical care patients, whereas the particular clinical context (including specific risks such as trauma and C-Spine injuries-instability, full stomach, shock, etc.) and the mandatory consequent precautions, might require specific guidelines [4, 5].

In order to evaluate the evidence supporting an airway assessment method the actual endpoints of airway management in critical care and their effect on mortality and brain death need to be borne in mind [6]. Unfortunately, the links with adverse respiratory events and even more the definition of how much DAM can effect patient outcome is a challenging task for the critical care arena, and Emergency Department (ED), ICU or In-hospital Rapid Response System (RRS). The assessment of difficult oxygenation remains the primary concern, and we should never forget that patients die of “failure to oxygenate, not failure to ventilate” [7, 8].

The Complexity of the Airway Approach in Critical Care

The assumption that three quarters of difficulties are judged predictable by an accurate patient assessment may be considered not fully applicable to critical care procedures, for which the complexity of the airway approach is worsened by the crossing influence of different components:

- a) **Patients** (case mix): medical or surgical ICUs offer a case mix significantly different from trauma or paediatric ICU. Moreover, the airways themselves might not be anatomically difficult, but they might be physiologically difficult airways. Respiratory distress and the underlying pathology of the patient limit choice (drugs and techniques) [2]. In contrast to healthy individuals, critically ill patients will not only tolerate apnoea less well, but may also prove to be difficult to be properly preoxygenated. In this sense ventilability evaluation itself should take into account not only conventional physical parameters, but also FiO₂ or PEEP level dependence, dramatically modifying the concept of the “cannot intubate-cannot ventilate” (CICV) scenario. For these reasons, evaluation before taking action is crucial, even though in the ED nearly 70% of patients undergoing rapid sequence intubation (RSI) have either altered mental status or cervical spine collars in place, which prevent the assessment of DAM predictive factors [8].
- b) **Team**: the competencies and skills are different between the different health care systems and countries. First rescuers in the emergency chain often are not the best experts in airway management while emergency guidelines emphasize the role of the anesthesiologist as a highly skilled expert [7]. Even though safety and clinical risk management can be considered one of the best competences in anaesthesia [9], residents are not formally trained to manage airways outside the OR and airway crisis resource management should be considered a future teaching goal [10].
- a) **Setting**: ICU, ED and RRS offer different levels of equipment organization, and attention to airway problems can be considered suboptimal. Differences in teams influence clinical procedures: critical care and RRS in Europe are often (always, in Italy) on call for specialists in Anaesthesia and Intensive Care [4, 11, 12]; it is not the same for EDs. Published results underline the need for ICUs to develop strategies for emergency airway management. In the United States very few anaesthesiologists are involved in the outside-the-OR/hospital airways, but they are often consulted for airway management in the ICU. This is a missed opportunity to learn and progress [13, 14].
- b) **Time**: the time limitation for decision making and additional tests or consultations makes it virtually impossible to assess the airways as recommended for preoperative patients. If time is available for a patient examination in the critical care setting, this assessment should be “multileveled” [5]. Moreover, there is very little time and opportunity to evaluate and train with alternative techniques in a real life situation of critical illness [15].

Evaluation of these risk factors must be included in the assessment of risks prior to other airway specific evaluation.

Possible Scenarios

When planning for airway management, intensivists must answer several questions, including whether endotracheal intubation is necessary, whether extralaryngeal ventilation, via mask or laryngeal mask airway can be achieved, whether the patient is at risk of aspiration, and finally whether the patient can tolerate apnoea for any duration. Based on the answers to these questions, the practitioner should not choose endotracheal intubation using laryngoscopy but rather choose an alternate approach to airway management. Intensivists need to be aware (and probably are not) of data regarding complications that might occur with multiple attempts at laryngoscopy [2].

Some of the possible scenarios:

- Intubation may be the chosen strategy for a patient still on spontaneous ventilation, to be performed in the best setting by an advanced team with the wider choice of devices and techniques (pharmacological alternatives included). In this situation the prediction strategy must be the same recommended for the preoperative assessment [2, 4, 8].
- An RSI is necessary: available time is the first recognized limit for any accurate assessment, the patient (cooperation, known and unrecognized risks) is another [8].
- An expert rescuer might be asked for In-Hospital emergency in the ED or ward: CICV can be more frequent if he is not the first to perform laryngoscopy or due to limitation of resources (humans and devices) [5, 7].
- Extubation in critical care is a challenge and should be planned in the safest way. In the ICU reintubation is a well known risk factor, but not always the possibility of a DAM is considered and avoided by applying safe extubation strategies. Extubation or decannulation strategies are needed: both in recognized DAM and a well known patient, or in unpredicted difficulties, risk assessment is the best method for avoiding the nightmare of CICV. Obviously “alert systems” for patients recognized as DAM (i.e. in postoperative intensive care) could help to prevent complications; unfortunately, even though recommended, this is limited in daily practice [2].

In this perspective, data regarding airway assessment must always be considered crucial, as the negative predictive value of the assessment tests are high and can reassure practitioners.

The intensivist needs to be familiar with simple and quick assessment strategies, as well as with alternative and rescue techniques (at least one), including the capacity to achieve an emergency airway: a focused and brief examination of the patient’s airways might substantially influence the strategy for airway management and the success of the procedure [2, 4, 8, 16].

All airways should be analyzed for each individual patient [5]:

- need for invasive or noninvasive ventilatory support;
- difficult mask ventilation (DMV);
- possibility of extraglottic device (EGD) ventilation;
- direct laryngoscopy and intubation difficulties (DI);

- difficulty of intubation by other techniques (fiberoptic bronchoscope, retrograde intubation, ILMA®) or by combined techniques;
- aspiration risk and patients subjective tolerance to apnoea;
- extubation and reintubation difficulties and risks;
- never forgetting:
- time - setting - resources (team and technologies).

Airway Assessment Strategies

Despite the large amount of literature, the application of evidence based medicine analysis to airway assessment could be felt as a critical learning ritual, worthless for prediction [6, 17]. Nevertheless, the SIAARTI Difficult Airway Task Force recommendations point out that only the association of different predictors might be useful for DAM prediction, particularly in borderline difficulty situations [4].

Preoperative elective assessment tests should have high sensitivity, specificity and accuracy, results that might be achieved only by the combination of tests, despite conflicting results [6, 18-21]. Unfortunately the clinical value of airway assessment tests still presents specificity and sensibility limitations for difficult laryngoscopy, difficult intubation (DI), and, even more, DMV prediction [4, 17].

- DI – This has been attributed to several unfavourable anatomical factors such as a receding mandible, protruding upper incisors and long maxilla, limited temporomandibular joint mobility, small atlanto-occipital gap, reduced submandibular tissue compliance, restricted pharyngeal space, high Mallampati test, with and without phonation [22, 23]. For better results, preoperative assessment should be carried out by the same anaesthesiologist who will manage the patient, a visionary hypothesis in daily practice [19], as the personal approach of single operators increases the risk for interobserver variability, as demonstrated by the wide data variations reported by different studies [24, 25]. The reasonable solution recommended by the SIAARTI Guidelines [4] is that before starting any procedure, the charged anaesthetist should personally verify, confirm or even modify the previous recordings, informing the patient of any alternative safe strategy.
- DMV - Independent risk factors for DMV in the elective setting include age 55 years, body mass index $>26 \text{ kg/m}^2$, lack of teeth, male gender, Mallampati class 4 airway, the presence of a beard, and a history of snoring [2].

A quick mnemonic system suggested to identify this risk of DMV in emergency (i.e. in traumatized patients) is summarized by “**MOANS**” (Mask seal poor - Obesity - Aged - No teeth - Stiff, i.e. resistance to ventilation as in COPD or asthma) [3].

To stratify the risk of DI in the Emergency Department, Murphy and Walls have introduced the “**LEMON**” (Look – [e] – Mallampati class – Obstruction – Neck mobility) airway assessment method. Furthermore, Reed et al were able to demonstrate that patients with large incisors, a reduced mouth opening, and a reduced thyroid-to-floor-of-mouth distance are more likely to have a poor airway grade during laryngoscopy [3, 26].

Models developed by multivariate analysis have incorporated multiple clinical factors to derive highly accurate predictive models (sensitivity, 86.8%; specificity, 96.0%) to identify difficult intubations among patients undergoing elective intubations in the OR. Because the incidences of both difficult laryngoscopy (1.5 to 8.0%) and failed intubation (0.1 to 0.3%) are low in the OR, with expert anaesthesiologists working with patients from the healthy population, these models have a high negative predictive value (99.7%) but a low positive predictive value (30.7%). Their routine use in the OR, therefore, has a questionable cost-effectiveness ratio. Moreover, although the incidence of difficult intubations is higher in the ICU, these multivariate predictive models have not been tested in that setting [8].

Despite the absence of validation studies to demonstrate the utility of airway assessment techniques to identify patients who will experience DAM in the ICU, a teaching method must be applied. We wonder how to ensure this non-technical but psychomotor skill...

Our Anaesthesia and Intensive Care Teaching Departments have been keeping DAM under systematic observation since 2003, applying an Airway Management Assessment Form (AMAF), and carrying out the largest Italian prospective observational study on DAM. The study was approved and supported by University Research and Human Investigation local Committees. The AMAF, also approved by ASA/SAM experts [22, 27], includes multiple examinations for DAM prediction and can be easily and quickly performed at the bedside and completed in OR.

AMAF was recorded for all elective patients scheduled to receive general anaesthesia requiring endotracheal intubation; preoperative assessment was systematically performed by residents and reports submitted to a board-certified senior anaesthesiologist. Patients less than 18 years of age, emergency-urgency, instable cervical spine, gross anatomical abnormalities or recent surgery involving head or neck, locoregional procedures and Caesarean section, were excluded and 944 cases were analysed of the 2,000 collected [27]. Statistical analysis was performed using SPSS software version 13.0. Positive predictive values and negative predictive values were calculated based on a prevalence of DI of 6.88%. Patient data (age, weight, height, sex, thyromental distance, Mallampati score, interincisive gap, etc) were also subjected to a binary logistic regression model, in order to identify predictors of DI/DAM. Receiver Operating Characteristic (ROC) curves were used to describe the discrimination ability and to explore trade-offs between sensitivity and specificity of the different indices.

Previous data demonstrated the poor predictive power for DI of the Mallampati test [6]; preliminary data by the same group (750 patients) show that phonation seems to decrease sensitivity (from 55.9% to 25.4%) while increasing specificity (78.7 to 95.1%) when correlated to the modified Cormack and Lehane classification (6 grades). On the other hand, DMV does not appear to be related to higher Mallampati class score [in press].

Preliminary results predicted DMV in 18 patients (1.9%) and found real difficulty in 25 patients (2.65%) [27]. Anticipation of DMV by the trainees was accurate in almost all cases: only 7 patients (0.93%) were wrongly evaluated and for two of them an EGD was effective as a rescue. The main errors were all made by 1st-2nd

year trainees and were discussed in teaching audit. DI was predicted in 298 patients (31.56%) corresponding to real difficulty during induction in only 87 patients (9.2%) (SIAARTI definitions adopted) [4]. The tutor's help was asked by trainees to intubate in 149 cases (15.8%); in 5 patients the problem was solved with a call for senior physician assistance. No CICV occurred.

The ideal model for DAM prediction should have perfect sensitivity and specificity. The proposed Assessment Form has a good sensitivity (82%) for DMV prediction, with a specificity of 84%, a positive predictive value of 99% and a negative one of 11%. On the other hand, DI sensitivity was 71%, with a specificity of 60%, a positive predictive value of 94% and a negative one of 17%.

The result of this experience is that airway assessment tests reach poor to moderate discriminative power [17, 19, 21], their performance is subjective and the need for systematic training is a crucial mission for a teaching Department [22, 27, 28].

Conclusions

Teaching is essential to achieve good clinical performance in airway management. The learning curve is subjective and largely dependent on daily clinical experiences, even more for non-technical skills, such as risk management. Guidelines should devise a framework to predict hindrance in providing oxygenation before embarking on any course of action (in emergency too, i.e. for RSI). The most important benefit for encouraging an airway assessment ritual is that it forces decision making and preformed strategies as a proactive tool in a risk-management program [10, 25].

In every clinical setting, a correct DAM strategy provides an answer to patient expectations in terms of safety and quality of care. In such a perspective, the definition and implementation of protocols to be adopted in case of DAM should be a mandatory task for all Anaesthesia and Intensive Care Departments. An assessment check-list can help the team in planning solutions and works as a teaching tool, without fearing the "Hawthorne effect" [18]. The application of AMAF is useful for internal audits and the retrospective analysis of outcomes [29].

Despite suggestions of published recommendations, patients are not sufficiently informed postoperatively, thereby hampering future care [30]: the adoption of a special DAM report is another useful advantage (alert system), for clinical safety and quality improvement [4, 31]. A simple algorithm for airway management is needed in the ED, ICU and RRS for hospital emergencies; this should include risk assessment strategies, DAM identification and prediction. An advantage for the Italian healthcare system could be the high level of specialization of critical care teams. Anaesthesiologists must be considered airway experts, even if the residents are not formally trained to manage airways outside the OR [13].

A re-evaluation of the SIAARTI recommendations, including new DAM definitions for emergencies, will probably influence outcome, improving decision making and helping to avoid human errors. The risk assessment for DAM must be inscribed inside proactive methods for risk management and teaching in critical care.

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Out-Of-Hospital Airway Management: Knowledge and Equipment

S. RUSSO, C. EICH, A. TIMMERMANN

The 2005 European Resuscitation Council Guidelines for Adult Advanced Life Support state that the tracheal tube remains the gold standard for securing the airways during cardiopulmonary resuscitation (CPR), when placed by experienced personnel [1]. It provides a patent airway, protection from the aspiration of gastric contents or blood from the oropharynx, the ability to provide an adequate tidal volume during chest compressions, the ability to aspirate tracheal secretions, a route for administering drugs, and the ability to deliver positive pressure ventilation [2].

The Challenge of Endotracheal Intubation in the Emergency Setting

However, out-of-hospital airway management is a critical skill, demanding expert knowledge and experience. Failure to secure the airways in critically ill emergency patients can drastically increase the likelihood of a poor or fatal outcome. In the emergency setting, the presence of debris, secretions, blood, vomitus, subcutaneous emphysema, anatomical derangement, dental damage, or the application of cervical spine immobilization devices and in-line axial stabilization can further reduce the ability to use direct or indirect laryngeal visualization techniques and face mask ventilation [3]. Additionally, difficult out-of-hospital airway management is mostly unanticipated, airway equipment is limited, respiratory dysfunction and hypoxia are often present, and the position of the patient can make access to the head difficult. Other issues complicating the airway management of the emergency patient include CPR or other medical procedures being performed simultaneously, altered and varying levels of patient consciousness, and lack of professional help [4-6].

Several studies have documented out-of-hospital tracheal intubation success rates from 98 to 100% in non-trauma or mixed patient groups when the rescuer is experienced in airway management [4-8], but these results are derived from self-reported data and are subject to potential reporting bias. Even when tracheal intubation was performed by experienced anaesthesiologists, a significantly increased incidence of difficult laryngoscopy, number of intubation attempts and the use of extraglottic airway devices in the out-of-hospital arena was demonstrated, as compared to data obtained in the operating theatre [6].

Unrecognized Oesophageal and Endobronchial Intubation

While the potential benefits of successful prehospital tracheal intubation remain controversial, the harm caused by unrecognized oesophageal intubation is indisputable.

When the position of prehospital placed tracheal tubes was re-examined by independent observers, either on arrival in the emergency department or in the field, unrecognized oesophageal intubation was recorded in 6% to 25% of patients [9-13]. The 24 h mortality rate of patients whose trachea were intubated correctly in the field was reported as 10%. This rate increased dramatically to 70-80% for those with misplaced tubes [12]. If we extrapolate this data to the whole of Germany with approximately 100,000 out-of-hospital tracheal intubations per year, a rate of 7% undetected oesophageal intubations [12], and only 30% of the rescue ambulances equipped with end-tidal CO₂ monitoring [14, 15], will cause annually a high number of deaths due to complications of airway management.

Interestingly, Silvestri et al demonstrated a dramatic decrease in unrecognized oesophageal intubation from 23% to 0% for those emergency medical service (EMS) teams who confirmed tracheal tube placement with capnography [11]. Therefore, the use of end-tidal CO₂ monitoring has to be compulsory for all types of airway management, especially for the out-of-hospital setting.

Laryngoscopic Guided Endotracheal Intubation for Novice Medical Personnel

Successful airway management particularly depends on the skill level provided by the medical personnel who are in charge of patient care. Whereas experienced anaesthesiologists with a wide range of expertise in many different aspects of advanced airway management skills are available in the operating room, this level of experience can hardly be achieved by EMS personnel. Johnston et al reported only an average of 6-10 endotracheal intubations (ETI) performed by paramedics during their airway management training in the operating room [16]. Timmermann et al reported that 20% of non-anaesthesia trained German EMS physicians had performed less than 20 ETI prior to their assignment to the rescue ambulances [15]. About 50-60 intubations in patients with normal airways seem to be necessary to achieve adequate proficiency [17]. Therefore, success rates as low as 50% have been noted for providers who do not frequently perform tracheal intubation [18], even under the optimal conditions in the operation room and in patients without anticipated difficult airway management. Taking into account the fact that the median ETI frequency is one per paramedic per year [19] and 0.5-1.5 ETI per month when German EMS physicians performed out-of-hospital ETI [20], there is no ongoing practice of ETI for healthcare providers working in the preclinical setting. Furthermore, proficiency deteriorates over time if airway management skills are not regularly practised. Tiah et al and Weksler et al demonstrated that the retention skills of medical students are more accentuated with the classic laryngeal mask airway (LMA) and the oesophageal-tracheal Combitube (Tyco-Healthcare-Kendall, Pleasanton, California) than with an endotracheal tube [21, 22].

Alternative Airway Management Devices

Consequently, all providers of prehospital emergency medical care need to be particularly proficient not only in ETI, but also in the use of alternative instruments such as LMA, the intubating laryngeal mask airway™, the Laryngeal Tube™ or Combitube and in the performance of cricothyrotomy.

Oesophageal Obturators

Oesophageal-Tracheal Combitube

The oesophageal-tracheal Combitube (Tyco-Healthcare-Kendall, Pleasanton, California) is an alternative airway device recommended for airway management in patients following failed tracheal intubation in the hospital and especially in the field. It has two lumina, one of which resembles a conventional endotracheal tube while the other seals off the oesophagus with an oropharyngeal balloon. The Combitube can be inserted blindly through the mouth and is more likely to pass into the oesophagus (95%) than into the trachea (<5%). Combitube insertion is easy to learn. It is feasible from the front and with head and neck in the neutral position (cervical spine injury). Furthermore, only minimal mouth opening is required. However, continued training is necessary to retain skills [23]. Successful Combitube ventilation has been reported in 95% of patients who could not be intubated by direct laryngoscopy [24]. Conversely, Calkins et al reported a failure rate of 28% when inserted by paramedics, which was higher than that of failed endotracheal tube placement (16%) with the same group of paramedics [25]. The most common reason for ventilation failure with this device is placement of the device too deeply, so that the perforated pharyngeal section has entirely entered the oesophagus. Pulling the Combitube back 3-4 cm usually resolves the problem. However, it is not well tolerated in patients with a persistent strong gag reflex after resuscitation and should be exchanged with an alternative airway as soon as possible [26].

Laryngeal Tube

The laryngeal tube (LT) (VBM Medizintechnik GmbH, Sulz, Germany) consists of a single-lumen reusable or disposable tube with a pharyngeal and oesophageal cuff which seals the pharyngeal airway and the oesophageal inlet, and a ventilation outlet in between [27]. It is available in all sizes from newborns to tall adults. The simple-to-handle LT may be the appropriate device when basic ventilatory life support has to be performed by health-care professionals untrained in emergency airway management. Kette et al described the successful use of the LT by minimally trained nurses during 30 out-of-hospital resuscitations [28]. Insertion was successful within two attempts in 90% of patients, and ventilation was adequate in 80% of cases. This device may be a valuable choice to replace the bag mask ventilation (BMV) system in the future.

Laryngeal Mask Airways

Many studies have reported that laryngeal mask airway (LMA) devices are more successful for ventilation as compared to laryngoscopic-guided tracheal intubation [29]. A comparison of laryngoscopic-guided tracheal intubation with laryngoscope-guided, gum elastic bougie-guided LMA insertion was performed by Hohlrieder et al [30]. At the start of their training, first year anaesthesia residents were able to insert the LMA successfully in 100% of cases, compared to 65% of tracheal intubations.

Intubating Laryngeal Mask Airway

Kurola et al compared three different extraglottic devices for ventilation in the OR [31]. Clinically inexperienced paramedical students successfully used the intubating LMA (ILMA) (LMA Fastrach™, North America Inc., San Diego, California), the LT and the CopraPLA (Engineered Medical Systems, Indianapolis, IN, USA) in 75%, 44% and 22% of cases, respectively. The ILMA is recommended as an ideal device for inexperienced medical personnel as it supports both ventilation and intubation [3, 32, 33]. Recent studies have reported the successful use of the ILMA in out-of-hospital areas [34, 35] and particularly in patients with difficult to manage airways [36]. Conventional bag mask ventilation and laryngoscopic-guided tracheal intubation has been compared with ILMA-guided ventilation and intubation by medical personnel who were novices in airway management [37, 38]. Both studies demonstrated that medical students were more successful and faster with ILMA-guided ventilation and intubation than with conventional techniques. Furthermore, ILMA-guided ETI was successful in patients in whom laryngoscopic guided ETI had failed.

An unpublished survey of the use of the CTrach (LMA-Company, North America Inc., San Diego, California) showed a 100% success rate for both ventilation and tracheal intubation (data by Russo et al). The CTrach contains an integrated fibreoptic system for visualization of the laryngeal structures. In contrast to in-hospital data, which report a sufficient view of the larynx in 85-100% of cases [39, 40], in the preclinical setting a good view was achievable only in 70% of cases due to the emergency setting with blood and vomitus in the oral cavity. However, in the remaining 30% intubation was always blindly possible.

Surgical Airways

The 'surgical airway' is definitively a technique of last resort. It is indicated if oxygenation cannot be achieved by endotracheal intubation or by alternative techniques (Extraglottic airway devices, EGA, or BMV). A surgical airway can be life-saving, especially in patients with massive oropharyngeal swelling caused by tumour, insect bite, profuse bleeding after injury to the facial skeleton, or airway obstruction by a non-extractable foreign body. As a rule, a surgical airway is established

by cricothyrotomy (coniotomy) in adults and by ‘transtracheal ventilation’ in children up to 10 years. Transtracheal jet ventilation, both for children and adults, can be supported by mobile jet ventilator devices like the Manujet™ (VBM Medizintechnik GmbH, Sulz, Germany). Depending on the available equipment and skills of the personnel, in a prehospital setting a surgical airway has to be established in up to 15% of cases [41-46]. The availability of alternative airway devices and highly trained personnel may significantly lower the incidence of this very invasive measure.

Difficult Airway Management Algorithm for the Out-of-Hospital Setting

Due to the personnel and logistical limitations of the difficult airway management in the out-of-hospital setting, Dorges proposed an algorithm adapted to these restrictions (Fig. 1) [26]. This algorithm describes the sequences of the various procedures: If the first intubation attempt fails, it should be discontinued after 40 seconds at most in order to oxygenate the patient by BMV. If BMV is also unsuccessful, a ‘cannot intubate, cannot ventilate’ situation is present which requires an immediate switch to an alternative approach – generally a supraglottic procedure.

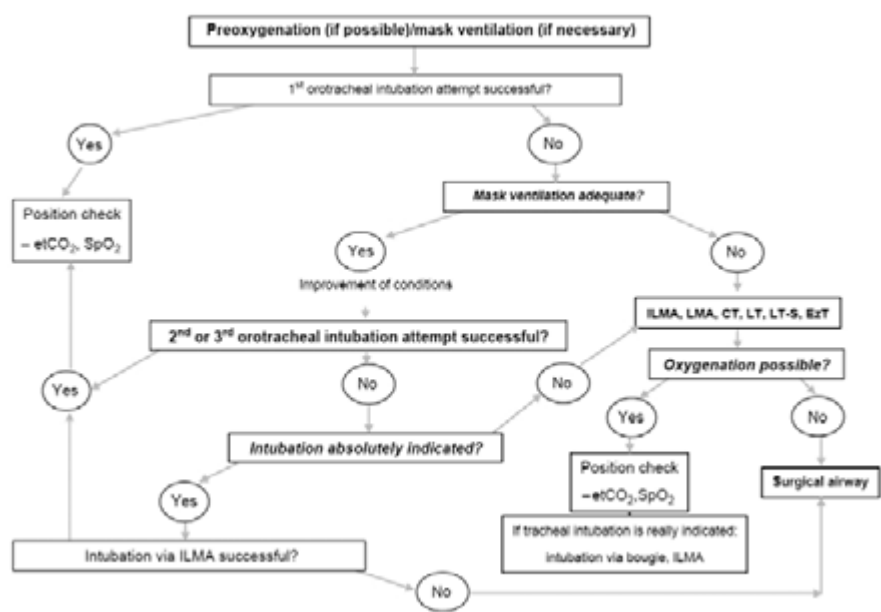


Fig. 1. Emergency airway management algorithm as proposed by Dorges [26]. Abbreviations: etCO₂, end-tidal carbon dioxide; SpO₂, oxygen saturation; ILMA, intubating laryngeal mask airway; LMA, laryngeal mask airway; ETC, oesophageal tracheal Combitube; LT, laryngeal tube; LTS, laryngeal tube with suction port; EzT, Easytube

Failed intubation manoeuvres should be discontinued after the third attempt at the latest and alternative procedures applied in order to maintain oxygenation and avoid further airway deterioration. If these alternatives also fail, surgical access should be established without any further delay. A position check is mandatory after placement of every endotracheal tube or any alternative device. The entire duration of the procedure leading to a patent airway in patients requiring immediate intubation should not exceed the hypoxic tolerance of the individual, even when complications arise. An algorithm should be adapted to the airway devices available and the skills of the health care professionals. However, the medical teams must be aware of all emergency procedure and should be trained in situations without difficult-to-manage-airways and in simulated scenarios.

Simulation for Airway Management Training and Education

Simulation is an exciting tool in medical education. It has been applied creatively to teaching clinical, technical, and cognitive tasks. Training programmes focus on cognitive skills, and have been found to be an effective way of teaching trainees methods of team building as well as giving them increased exposure to airway emergencies [47]. Several studies have shown that advanced clinical experience and simulator training have improved airway management skills for both physicians and paramedics [48, 49]. An educational course consisting of lectures, skill station and simulated difficult airway management scenarios demonstrated a significant impact on self-reported accuracy and confidence in evaluation of airways, use of alternative airway devices, and changes in the practitioner's clinical practice towards difficult airway situations [50]. This kind of continued training is of particular importance for those clinicians whose duties include prehospital airway management and who do not perform airway management techniques on a regular basis.

Conclusions

In conclusion, in the out-of-hospital setting, the endotracheal tube remains the gold standard. Extraglottic devices should be considered by emergency medical personnel who are novices in laryngoscopic-guided tracheal intubation. Furthermore, all medical emergency teams should be provided with end-tidal CO₂ monitoring or oesophageal detector devices in order to identify the tracheal tube position. Furthermore, should regularly attendance at courses on airway management, which include the use of specialized airway simulators and clinically difficult airway management scenarios should be considered.

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Practical Aspects for Managing Extubation of the Difficult Airway

M. SORBELLO, A. GUARINO, G. MORELLO

Every beginning, calls an end.
Chinese proverb

Difficult airway management (DAM) is one of the most fascinating tasks for anaesthesiologists, in a certain sense a continuous challenge which requires solutions for potentially life-threatening problems.

A large amount of literature confirms that DAM-related problems are the first cause of severe anaesthesia-related accidents [1] and that difficulties and fatal accidents are increased in the emergency setting [2-4]. Conversely, few studies have explored the role of extubation in both normal and difficult airways, while all agree that many critical situations and fatal accidents occur during this phase of anaesthesia.

Interestingly enough, the recently published American Society of Anesthesiologists (ASA) Closed Claims Analysis [5] compared data regarding airway accidents during the ten years before and after the introduction of 1993 ASA guidelines [6]. While fatal accidents (death or brain damage) occurring mainly during anaesthesia induction (the incidence in this phase being twice that of the intraoperative, extubation and postanaesthesia phases) after the introduction of the guidelines the incidence of fatal accidents was reduced by half for this phase, while it remained unchanged for all other phases. In other words, this suggests that many things are yet to be done to increase the safety of extubation and the postanaesthesia course.

Extubation, no less than intubation, is a critical moment in general anaesthesia. To our knowledge there are no algorithms or ordered sequences of steps for extubation, although the Italian Society of Anaesthesia, Analgesia, Reanimation and Intensive Care (SIAARTI) Difficult Airways Study Group is currently working on the publication of ICU Difficult Airways Guidelines, including notes on extubation management.

According to the few data available, and taking into account the “near misses phenomenon” [7], difficult extubation is probably a main concern in the post-anaesthesia care unit (PACU) or the intensive general care unit (ICU), with a lower occurrence in the operating room (OR), as generally difficult-to-intubate patients are cautiously extubated in protected settings and difficult to extubate patients are currently made up of patients receiving lengthy or peculiar surgery.

The current approach when expecting a difficult extubation, at least theoretically, is to closely observe the patient in a setting equipped with monitors, material for managing the difficult airway, and staffed by experienced personnel who should be able to establish an airway access immediately, provide oxygen, and facilitate gas exchange, keeping the airway open and safeguarding it in case of a failed extubation attempt [8].

In the following paragraphs some practical aspects for managing difficult extubation will be discussed, after the analysis of factors influencing extubation and of data regarding incidence of this phenomenon.

What Makes an Extubation Difficult?

Although relatively common, intubation is not an atraumatic procedure, especially whenever it is not performed correctly [9]. The literature confirms that different degrees of trauma might occur during the procedure [10] and that the more difficult the intubation is, the higher the possibility of developing oropharyngeal (19%), temporomandibular joint (10%), oesophageal (18%), tracheal (15%) and laryngeal (87.3%) trauma [11], including vocal cord palsy, which has been demonstrated to be more frequent in elderly, hypertensive and diabetic patients [12]. Much more importantly, unexpected or misdiagnosed minor laryngeal trauma might occur in up to 80% of “normal” and “easy” intubations [11].

With these data in mind, the first practical recommendation might include the need to consider factors of potential difficult extubation (such as pre-existing oral, pharyngeal or laryngeal pathology), comorbidities (severe diabetes, severe hypertension, severe pulmonary pathology such as asthma or severe COPD, or obstructive sleep apnoea syndrome [13]) and to consider that a difficult intubation always provides traumatic consequences in proportion to the number and quality of attempts.

Even when correctly performed, translaryngeal intubation is known to generate complications such as mechanical or biochemical lesions [14]; the first signs of laryngeal lesion can be seen 3 h after intubation; transient laryngeal injury or chronic stenosis have been described to appear 6 days after intubation (5%), rising to 12% after 11 days [15]. Acute upper airway obstruction secondary to laryngeal oedema is one of the primary causes of respiratory distress after extubation (2-16% of cases), and it can be a dramatic event requiring emergency reintubation in rather difficult circumstances. Unfortunately, no pharmacological strategies seem to be currently available to prevent or treat this occurrence [16], nor does a reliable method for identifying patients at risk of laryngeal oedema before extubation exist, although great hopes seem to be placed in the measurement of *cuff leak test* to avoid this eventuality [15, 17].

These last considerations are more appropriate for the ICU setting rather than the OR, where only lengthy surgery or the use of particularly invasive devices such as double-lumen tubes seem responsible for acute complications at extubation [18].

These findings make the role of extra-glottic devices (EGDs) critical for rescue

ventilation and oxygenation in this setting. Over the past decade novel options for DAM have evolved, and a myriad of new devices, particularly EGDs, have been introduced to facilitate failed airway rescue [19]. Unfortunately, whenever an extra-glottic factor occurs preventing proper flow passage, all these devices become partially or completely useless. In such cases it becomes mandatory to extend the already known limitations of these devices to the possibility of difficult or impossible EGD ventilation because of upper airways obstruction [20].

With these data in mind, the second practical recommendation might include the need to consider as difficult any extubation performed after a lengthy intubation, or whenever particularly invasive devices were used for airway control.

What is the Incidence of Difficult Extubation?

Very little data is available regarding the incidence of difficult extubation. Interesting data might be drawn from ICU reports, although they undoubtedly underestimate the dimension of the problem because of both “near misses” and because of reticence due to teamwork in the PACU or ICU [7].

Errors and adverse events occur more frequently in the ICU for different reasons: patients frequently have severe, multiple-system illnesses, thus presenting greater complexity and requiring caregivers to do more testing and make more decisions than in other settings. Furthermore, the use of numerous medications increases the potential for error, and, generally, the more problems encountered in a patient, and the more testing, monitoring and treatment needed, the greater is the risk of committing errors [7]. Indeed, all modern ICUs can be considered what psychologists term a “cognitively complex environment”, that is, an environment where the number of pieces of information required by a single operator to make a correct decision often exceeds the five that can be held simultaneously in a conscious working memory [21].

The incidence of fatal accidents in the ICU ranges from 20 to 50% of patients [22]. In this regard, a study by Bracco [23] interestingly found that the amount of human errors (31%) were evenly distributed among planning (n=75), execution (n=88), and surveillance (n=78), respiratory accidents accounted for more than 20% of total errors.

A recent study [24] conducted on 60 patients over a 12-month period reported an incidence of 763 non-airway events and 78 airway events, more than half of which were considered preventable, including one death. Accidental extubation (AE) is a typical airway accident, its incidence being reported in 1-14% of episodes of mechanical ventilation [24], in 9% of intubated or tracheostomized patients [25]. In a series of 96 patients over one year, 101 episodes of AE were observed (85% self-extubations and 15% accidental) and difficulty with reintubation was common [26].

The non-reassuring finding is that throughout the literature 22 to 51% of all errors and incidents were rated as serious and greater than 80% were considered potentially preventable [24].

Besides accidental or unpredicted extubation, there are at least two other

settings in which extubation might be considered difficult: extubation failure during mechanical ventilation weaning and discontinuation, and tracheostomized patients.

Postextubation respiratory failure is a common event after discontinuation of mechanical ventilation, re-intubation being needed in about 10% of patients [27]: in this particular setting, although findings have been contradictory [28, 29] and the technique is yet to be defined [30], great advantages might derive from noninvasive ventilation (NIV) use in the ICU, including a “prophylactic role” in certain circumstances [31]. Currently available data show that postextubation NIV is of interest only to prevent postextubation respiratory failure, yet this acquisition would mean earning time for strategy planning and oxygenation if reintubation is needed [32]. In all cases, postextubation NIV must never delay (re)intubation time, providing that acquired experience with this technique is one of the main predictive factors of success [31].

Tracheostomized patients requiring cannula removal or exchange might be an important, though peculiar, aspect of difficult extubation, especially as a consequence of widespread diffusion of percutaneous techniques for tracheostomy. A tracheostomic cannula might have to be changed because of secretions, bleeding or cuff rupture; it is advisable to wait several days after a percutaneous tracheostomy for the stomal route to stabilize enough to leave the stoma temporarily patent despite the absence of the cannula. It should be borne in mind that in all procedures with a tight adhesion between cannula and tissues, such as many percutaneous techniques, at least 5-7 days or even more are necessary to stabilize the stomal route. The advantage of such adhesion is the low infection rate and the low incidence of bleeding, the most important disadvantage being the risk of airway loss in the event of accidental decannulation in the non-ICU setting.

While the surgical technique grants the stoma patency thanks to stitches at the sides of the stoma or the suture to the skin of a cartilaginous window, which makes reinsertion of the cannula relatively easy, the same manoeuvre in the case of percutaneous tracheostomy might be more difficult and require a protected procedure [33].

With these data in mind, practical recommendations might include the need to consider accidental extubation the most common ICU accident, and that reintubation is always more difficult than the first intubation because of the setting, the patient and the urgency.

NIV ventilation could be of great help both for managing extubation or for earning time while planning new intubation, never delaying the latter when needed.

Similar risks and precautions for tracheostomized patients need to be considered, including the possibility of urgent intubation or surgical airway performance, especially in cases of percutaneous tracheostomic techniques.

Practical Aspect for Managing Difficult Extubation: Operating Room

As the above suggests, the first way to anticipate a potentially difficult extubation

is to think of it in the presence of risk factors or after a difficult intubation. If the surgical procedure required a dedicated airway (such as laser endotracheal tubes or double-lumen tubes) and a tube exchange is required, the best way to proceed is to maintain the anaesthesia plan deep enough to perform tracheal tube exchange with dedicated devices.

Any attempt at tube exchange should be preceded by generous preoxygenation ($\text{FiO}_2=100\%$ for some minutes before the procedure) and by the preparation of a dedicated cart in case of airway loss, including laryngoscope, tubes (same and lower inner diameter), any EGD for which enough skill has been developed by the operator and all the necessary equipment for performing a rapid tracheal access. It is advisable to provide tube exchange after careful suctioning and generous lubrication of the tube exchanger, the diameter and length of which should be in-line with the tube size [34]. Lastly, any tube exchange procedure should be performed under direct vision, using either conventional or new video laryngoscopes such as Glidescope®. After tube exchange, tube position control must be rigorous and complete (auscultation, exhaled CO_2 and fiberoptic monitoring where required), as suggested by recent Italian guidelines [35]. The devices available on the market are typically characterized by long introducers or, better, by dedicated tube exchange catheters, offering the advantage of being hollow (possibility of providing jet ventilation and exhaled CO_2 detection) and attachable to common oxygenation, jet ventilation or standard 22 mm hubs (airway exchange catheters, Cook Critical Care, Bloomington, IN, USA).

An interesting alternative is provided by the Aintree™ catheter (Cook Critical Care, Bloomington, IN, USA), whose diameter allows the introduction of a 3.7 mm diameter fiberoptic bronchoscope to assess the correct positioning of the tube exchanger before removal of the endotracheal tube. The catheter might be used in combination with a laryngeal mask to provide ventilation during any tube exchange procedure or in the event of DAM [35, 36]. Note that in comparison to conventional tube exchangers, the Aintree™ catheter is shorter and with a larger inner diameter.

A tube exchanger might also be used to provide an oral-to-nasal passage [37] or vice versa [38] in already intubated patients. It could also be considered a possible strategy of “protected extubation”, as a safeguard to grant quick intubation by simply railroading tubes over a lubricated and local anaesthetic topicalized small diameter tube exchanger left in situ [39–41]. This second option requires good compliance by the patient, who could be informed the during preoperative consultation of this possibility, and requires satisfactory local anaesthesia of the lower airway and of the tracheal cords, which could be performed as “spray as you go (away)” during extubation within the tracheal tube.

Some authors report the use of small diameter (styletted) nasogastric tubes. In the absence of other devices this could be permissible, but it should be avoided because of the higher risk of “hang on” or impingement of the tracheal tube in the event of urgent reintubation.

Conceptually, all these behaviours should also take into account the “classical” rules for high-risk extubations, such as the traditional practice of extubating in the

head-down, left lateral position after a rapid sequence induction or in the case of full stomach risk.

In any case, a difficult extubation should always be performed by carefully observing the patient in a setting equipped with monitors, materials for managing the difficult airway, and experienced staff able to cooperate promptly and readily.

Practical Aspects for Managing Difficult Extubation: PACU and ICU

The same consideration expressed for OR can be extended to the ICU or PACU. What is different is that in this setting the cutting edge for defining difficulty shifts to lower values, because of pathophysiological changes occurring in long-term intubated ICU patients.

By definition, ICU patients will have disordered physiology which will either have an adverse impact on airway management or will be adversely affected by airway management. Therefore, wherever the airway itself might not be anatomically difficult, it will invariably be a physiologically difficult airway.

A typical ICU patient will hardly tolerate apnoea, unlike a typical preoxygenated and denitrogenated OR patient. ICU patients will not only tolerate apnoea less well, but may also prove to be difficult to properly preoxygenate because of oxygen consumption/oxygen reserve impairment and V/Q mismatch, as proposed recently in a milestone paper by Mort [42], who demonstrated that ICU patients have little reserve for tolerating the interruption of oxygen delivery, with preoxygenation resulting only marginally effective in providing an effective safeguard against hypoxaemia during emergency intubation.

Generally speaking, the major challenge in DAM for ICU patients remains the impact of the chosen strategy on the underlying pathophysiology. Notable examples include acidosis, haemodynamic instability, hypotension and myocardial depression or tachycardia and increased sympathetic response in ischaemic heart disease, neck manipulation in the presence of cervical spine injury, increasing intracranial pressure by coughing, laryngoscopy and drugs. Lastly, in the event of intubation failure, ICU patients present a high frequency of comorbid conditions and underlying vascular disease that may further increase the risk of complications when intubation attempts are prolonged [43]. Last but not least, in anticipating intubation failure, the concept of ventilability itself should take into account not only conventional physical parameters, but also the patient's FiO_2 or PEEP level dependence, which dramatically modify the "cannot intubate-cannot ventilate" scenario concept.

Several drugs are available to aid endotracheal intubation, and rapid sequence intubation might be useful in selected ICU patients. Nevertheless, according to the patient's conditions, "atypical" pharmacological strategies (e.g. sedatives alone, without muscle relaxants) could be chosen, with a preferential route for spontaneous breathing maintenance [43].

Intubation itself could be considered different in the ICU. The underlying pathophysiology of the patient enhances intubation-related risks, especially in

cases of difficulties and in emergency conditions [44, 45]. Furthermore, as previously discussed, in already long-term intubated patients, reintubation can be extremely difficult, both because of unplanned high FiO_2 and/or ventilatory support discontinuation and because of deep anatomical and pathophysiological changes to the upper airways.

In any case all OR suggestions regarding tube exchange procedures and protected extubation can be extended to the ICU, but the abovementioned differences need to be taken into account.

Important practical aspects might include drug administration and the “cuff-leak test”. Intravenous administrations of antiinflammatory drugs such as methylprednisolone has been demonstrated to be a valid approach to reduce tissue oedema all around the cuff, thus resulting in a reduction in postextubation stridor [16]. The author suggested a 4-dose regimen/24 hours, and while questionable according to some [46], this is currently the best available evidence.

Similarly, aerosol therapy or the administration of helium-oxygen mixtures are also considered useful postextubation strategies for reducing secretions, stridor, oedema and work of breathing [47].

There is currently no good method for identifying patients at risk for laryngeal oedema before extubation. Flow-volume curves and their derivatives [48] are reliable, but while on the one hand they are difficult to perform in poorly cooperative critically ill patients, on the other they should be performed after extubation, thus losing any predictive role they might play.

Computed tomography scan or magnetic resonance imaging might enable the visualization of upper airway oedema, but they cannot be used routinely and present several technical limitations [49]. Ultrasonographic techniques for upper airway examination in ICU patients have been poorly studied [50], and video bronchoscopy – the “gold standard” for upper airway examination – requires hazardous manoeuvres such as the partial removal of the tracheal tube [51].

Therefore, some authors have developed a cuff leak test for the indirect estimation of tissue oedema all around the tube’s cuff and to screen for the presence of upper airway obstruction before extubation [17, 52]. This test consists of deflating the balloon cuff of the endotracheal tube to assess the air leak around the tube, thus establishing an indirect evaluation of upper airway patency.

Other authors, however, (referring to paediatric patients) have reported that the air-leak test does not predict an increased risk for postextubation adverse events and reintubation [53], and this might be partially true as the measurement fails to take into account other factors such as respiratory and cardiac function, oedema of the airways, and the level of sedation and analgesia, all of which may affect the successful weaning process and extubation.

Therefore, an important concept in the ICU setting might be extubation prediction: recent papers suggest that extubation outcome can be accurately predicted by putting together various components of the capacity to protect the airway and to sustain oxygenation [54-57]. This means that when planning extubation we should have instruments either to determine its failure or success and to give provisional help to the patient, particularly resorting to NIV. The key concept is

that this should lead neither to excessive faith in NIV (resulting in delay of unavoidable intubations) nor to excessive fear in extubation (resulting in keeping patients intubated when they need not be), and in any case a fully equipped emergency airway cart should always be at hand, in order to choose the best solution from among those that should always be pre-planned.

In any case a precautionary approach is always better than a permissive one, the risk being urgent reintubation with its related difficulties.

Practical Aspect for Managing Difficult Extubation: Tracheostomized Patients

Tracheostomized patients present all the features of the ICU patients previously discussed, with the only difference being the implications of the presence of a tracheostomic cannula. While these patients reach the possibility of weaning from ventilatory support slowly, so extubation, or rather decannulation, can be safely planned and performed. The real risk lies in accidental decannulation and cannula exchange procedures.

Because of the previously described characteristics of the stoma and differences between standard surgical and percutaneous dilational techniques, a different approach must be considered. Usually surgical tracheostomy, while fixing the passage between the trachea and superficial plane, does not offer problems of stomal patency and of cannula exchange. In contrast, percutaneous techniques, especially during the first 48 hours after performance, and generally in the first week, cause the stoma a certain tendency to collapse, which might make difficult or even impossible any procedure involving tracheal stoma [58].

For these reasons, if accidental decannulation occurs, especially in the absence of specific skills or in high risk situations (night-time, acute oxygen desaturation, etc.) a safe choice could be cannula reinsertion delay and performance of traditional translaryngeal or trans-stomal intubation.

Whenever cannula exchange is needed (secretions, clots, bleeding, cuff rupture, etc.) the use of modified (shortened) tube exchangers for cannula exchange procedures is strongly recommended; as an alternative a small-size uncuffed endotracheal tube, a suction catheter, a rectal probe, a dedicated cannula-exchanger or a fiberscope-AintreeTM (Cook Critical Care, Bloomington, IN, USA) [59] might be used to remove the old cannula and to railroad the new one into the correct position (with preference for any device which might allow periprocedural oxygenation).

Difficulties in cannula exchange procedures might last even longer in chronically ill homebound patients, without any possibility of prompt medical intervention. For these reasons, standard surgical tracheostomy remains an advisable procedure in this kind of patient, or in extremely obese patients, in small children and generally in all anatomically difficult situations, whenever dedicated skills and experience are missing. Loss of airway, in the event of failure of the above mentioned techniques, might require urgent tracheal access followed by the creation of a (new) tracheostomy.

Conclusions

Unfortunately, despite the evidence of a higher incidence during tracheal extubation of complications such as desaturation, laryngospasm, airway obstruction and vomiting than during intubation [60], recent papers have shown that competencies for tracheal extubation do not exist and trainees are not formally assessed [61].

The challenge of DAM starts with difficult intubation, and only apparently ends there. Extubation and the immediate postoperative period are high-risk situations in all cases of difficult intubation, and are even more dangerous as the unexpected occurs when tension has vanished, reflexes are slower, attention is low and the airway cart is far from where it is urgently needed. The ICU might be a lower risk setting because of the environment, but it is made more difficult by the underlying pathophysiology of the patient.

So the message is clear: the patient is (relatively) safe only when they return home, and it is the ethical, moral and legal duty of physicians involved in airway management to give them maximum attention and expertise; this will happen only if physicians are aware of risks, that is, only if they have good knowledge and good sense.

Si vis pacem, para bellum!

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TRAUMA

Head Injury Treatment in 2007

M.G. ABATE, F. SALA, G. CITERIO

Incidence of Traumatic Brain Injury

Head trauma accounts for the majority of trauma deaths [1] with an incidence of 150–300 per 100,000 each year. The variation in its incidence could be partially explained by differences in the criteria used to define traumatic brain injury (TBI) or to identify patients [2]. TBI is the leading cause of morbidity and mortality in individuals under the age of 45 in the world [3]. Injuries are the leading cause of death between the ages of 15 and 44 throughout Europe [4]. In Southern Europe, road traffic accidents account for the vast majority of cases, while falls, mainly related to alcohol consumption, are the leading cause of trauma in Northern Europe [5]. In the United States alone, 2–3 million people per year on average sustain a TBI [6].

A systematic review of brain injury epidemiology in Europe has reported an aggregate hospitalized plus fatal TBI incidence rate of about 235 per 100,000, an average mortality rate of about 15 per 100,000 and a case fatality rate of about 11 per 100 [2]. The mean incidence rate of hospitalized and fatal TBI for Europe is similar to the average rate of Australia [8] (226 per 100,000), but considerably higher than that reported for the U.S. [6] and India [9] (103 and 160 per 100,000, respectively). In Europe the TBI severity ratio of hospitalized patients is about 22:1.5:1 for mild vs. moderate vs. severe cases, respectively. The percentages of TBI from external causes varies considerably and several studies have reported an association between alcohol use with TBI [2].

In Italy the most accurate data on incidence of TBI exist for two regions Trentino and Romagna, which report 314 per 100,000 and 294 per 100,000, respectively [7].

Cerebral Ischaemia as Therapeutic Target in Traumatic Brain Injury

The current management of head injury generally focuses on the prevention or attenuation of cerebral ischaemia. Cerebral ischaemia occurs in the early setting of TBI, even in patients who achieve the suggested target of intracranial pressure (ICP) and cerebral perfusion pressure (CPP) control, with the ischaemic burden not always being detected by the bedside monitors [10].

Although nothing except prevention can alter the extent of primary injury,

secondary neuronal injury is a major, modifiable determinant of outcome. The inability of the brain to store metabolic substrates, in the face of high oxygen and glucose requirements, makes it very susceptible to ischaemic damage. Secondary insults encompass a wide range of ischaemic, ionic, neurochemical and immunological insults imposed on a susceptible brain, leading to the additional cerebral injury [11]. These secondary insults are related to derangements in cerebral physiology, they prevent sufficient oxygen and nutrients from reaching the injured brain and lead to cerebral ischaemia and neuronal death. Thus in the context of a traumatized brain, after the primary insult, secondary disturbances in cerebral blood flow (CBF) and metabolism may have deleterious effects on potentially viable neurons in a variety of postulated scenarios, and in the end produce energetic and metabolic disturbances [12].

Systemic and regional disturbances, such as the arterial hypoxia, severe anaemia and critical reductions in global CPP are recognized as being responsible and linked in this setting. The latter can occur as a result of low arterial blood pressure (ABP) or elevated ICP.

Management of intracranial hypertension is one of the main challenges in the treatment of patients who have suffered from a TBI and will be the focus of this review.

3rd Edition of the Guidelines for the Management of Severe Traumatic Brain Injury

In May 2007 the Journal of Neurotrauma published a special issue dedicated to the updated edition of the: Guidelines for the Management of Severe Traumatic Brain Injury [13]. Under the sponsorship of the Brain Trauma Foundation (BTF), these guidelines were first published in 1995, and the 2nd revised edition was published in 2000. This 3rd edition comprises six new topics and an updated critical appraisal of the literature. The guidelines reflect only what is published in the existing human-based literature. They do not report information from animal studies, neither in vitro nor mathematical modelling studies.

The aim of the paper is to review some of the current strategies for monitoring and treating intracranial hypertension. We would focus on the latest evidence in our understanding of cerebral derangements underlying intracranial hypertension and on the existing tools available in ICP assessment and treatment. In addition, we will highlight some of the latest recommendations made in the 3rd revised edition of the BTF guidelines [13] on ICP monitoring and its treatment, particularly hyperosmolar therapy, CPP thresholds and hyperventilation.

ICP significance in TBI

The control of ICP is one of the mainstays of treatment in the management of severe head injury as elevated ICP has been confirmed as the most powerful predictor of neurological deterioration after severe TBI [14].

In a recent paper, Czosnyka et al infer that ICP, the most frequently monitored brain parameter in neurocritical care, is more than a number [15]. To date there has been no randomized controlled trial in which the influence of ICP monitoring on overall outcome following head injury has been examined, but a recent study has demonstrated an almost twofold lower mortality rate in neurosurgical centres, where ICP is usually monitored, compared with general intensive care units, where it is not monitored [16]. As Czosnyka suggests the analysis of the ICP waveform provides important information about the nature of cerebrospinal pathophysiology. CBF autoregulation and cerebrospinal system compliance are both expressed in the ICP waveform. Understanding of ICP and CPP are useful both for obtaining functional information and for guiding the treatment of patients [15].

Moreover, the ICP value in head injury depends on a close connection between monitoring and therapy. For example, CPP-oriented protocols [17] and osmotic therapy [18] cannot be conducted correctly without ICP guidance. Furthermore, a decision about decompressive craniotomy ought to be supported by the close inspection of the ICP trend and, possibly, by information derived from its waveform. To date none of these aforementioned “ICP-approaches” has been proven to be *per se* harmful or beneficial.

Clearly, the goal of the Guidelines is to summarize the best available clinical evidence, and this has led to the scrupulous selection criteria applied to update the Guidelines [13]. A Level I Recommendation infers that in 2007 a high degree of clinical certainty is available for some treatments, but other treatments are still on cerebral pathophysiology. For example, we might mention (and understand) the lack of Class I evidence for blood pressure and arterial oxygenation management. Although clinical common judgment suggests that hypotension and hypoxia are detrimental and harmful, clinical studies have failed to produce Class I evidence supporting this data. It is worth mentioning how numerous excellent imaging and clinical studies have clearly shown derangements in cerebral physiology due to cerebral hypoperfusion or hypoxia [10].

This might be the reason why the Guidelines state: “*As in all areas of clinical medicine, the optimal plan of management for an individual patient may not fall exactly within the recommendations of these guidelines. This is because all patients, and in particular, neurotrauma patients, have heterogeneous injuries, and optimal management depends on a synthesis of the established knowledge based upon Guidelines, and then applied to the clinical findings in the individual patient, and refined by the clinical judgment of the treating physician*”.

Thus, the topics we would like to focus on in this review are still objects of controversy.

ICP Assessment

In patients who receive ICP monitoring, a ventricular catheter device connected to an external strain gauge transducer is still the most accurate and cost effective method of monitoring ICP [13].

Current data support 20–25 mmHg as an upper threshold above which treat-

ment to lower ICP should generally be initiated [18] with no substantial differences in outcome between ICP thresholds of 20 or 25 mmHg [19].

As stated in the guidelines, *“the critical value of ICP and its interaction with CPP and other measures (e.g., SjO_2 , $PbtO_2$ and CBF) is a major unanswered question”*. The ICP threshold value might be most closely related to the risk of herniation. This risk varies between and within patients and, to date, no method has been developed to estimate “herniation” pressure [13].

When considering monitoring ICP, recent studies demonstrate that when a detailed monitoring of ICP in individual cases is desirable a digital system with proper filtering appears more accurate. Although the end-hour ICP manually recorded by experienced nurses is reliable and provides a robust description of the general ICP trend, a number of episodes of high ICP (HICP), some of long duration, may be missed, with the risk of underestimating the severity of a patient’s injury and the intensity of treatment required. To properly capture HICP episodes and to effectively grade the severity of intracranial hypertension, continuous computerized ICP monitoring has shown clinical advantages over manual recording [20].

HICP Therapy Strategies

Hyperosmolar Therapy

Hyperosmolar therapy is a key intervention for the management of cerebral oedema and raised ICP after TBI [21]. Cerebral oedema contributes to increased intracranial pressure, hypoperfusion, cerebral ischaemia, and poor functional outcome from traumatic brain injury. Hyperosmolar agents currently in clinical use are mannitol and hypertonic saline. To date, as stated in the Guidelines, there is insufficient data to support a Level I recommendation for this topic and debate is still ongoing as to whether solutions that alter oncotic pressure or osmolarity contribute to a better outcome following TBI.

Mannitol

Mannitol is a cell-impermeable and non-toxic polyalcohol which acts as an osmotic diuretic with a plasma-expanding effect. It improves blood rheology because it reduces blood viscosity by reducing haematocrit and increasing erythrocyte deformability [22]. Mannitol establishes an osmotic gradient between plasma and brain cells and reduces cerebral oedema by removing extravascular water across areas of intact blood-brain barrier (BBB) into the vascular compartment. As a volume expander, mannitol improves perfusion pressure, CBF and cerebral oxygen delivery [23]. These effects may explain why mannitol reduces ICP within a few minutes of its administration, and why its effect on ICP is most marked in patients with low CPP and with preserved autoregulation [24].

Furthermore, the osmotic effect of mannitol is delayed for 15–30 min while gradients are established between plasma and cells. Its effects persist for a variable

period of 90 min to 6 h or more, depending upon the clinical conditions [25]. $T_{1/2}$ elimination is about 30 to 60 min. Although several issues need to be clarified, the conclusion in the 3rd edition of the Guidelines is that mannitol is effective in reducing ICP in the management of traumatic intracranial hypertension at doses of 0.25 gm/kg to 1 g/kg body weight [13]. Previous studies have been published suggesting that administration of high doses of mannitol (1.4 g/Kg) is associated with improved outcome compared with normal dose, after TBI. Serious questions have been raised about the conduct of these studies [28]. These cited studies were in fact mentioned as Class II evidence in the 2000 edition but they are now supported at Class III. (See Appendix A, Changes in Quality Ratings from the 2nd Edition to the 3rd Edition) [13].

Mannitol has been used as a long-lasting therapy for raised ICP but there is still a lack of evidence to recommend repeated and regular administration of mannitol over several days. There are few human studies that validate different regimens of mannitol administration [13]. Repeated administration of mannitol may increase serum osmolality and lead to renal impairment, hypotension, hyperkalaemia and possibly rebound in high ICP [21]. Indeed, the latest edition of these guidelines provided a Level III recommendation that intermittent boluses may be more effective than continuous infusion. [26]. In addition, some studies support evidence that in prolonged administration mannitol could pass from the blood into the brain, where it might worsen increased intracranial pressure [27].

From this statement it might be argued that the effectiveness of mannitol may be impaired when the BBB is open. For these reasons, drug administration timing and the control of the effects requires strict and continuous ICP guidance.

The 3rd Edition of the Guidelines for the Management of Severe Traumatic Brain Injury conclusions on this topic state that there are still many unanswered issues regarding the optimal use of mannitol following TBI. The extensive current uses of mannitol, and the lack of clarity regarding its optimal administration, represent an opportunity for conducting randomized controlled trials.

Hypertonic Saline

As stated in the Guidelines: *“Current evidence is not strong enough to make recommendations on the use, concentration and method of administration of hypertonic saline for the treatment of traumatic intracranial hypertension (...) Research is needed to determine the optimal administration and concentration for hypertonic saline”*

Hypertonic saline (HS) is increasingly used as an alternative to mannitol. Some studies have proven its efficacy in controlling ICP in patients with HICP refractory to Mannitol [32]. HS is available in a range of concentrations from 1.7% to 29.2%, with 1.7% to 7% being the most commonly found in the clinical setting. Numerous regimens have been described and this makes it difficult to reach conclusions about the optimal dose or concentrations required to control ICP [21]. HS produces a reduction in cerebral oedema by moving water out of the cells of non-traumatized brain tissue, and improves blood rheology by decreasing endothelial cell volume.

It reduces cerebral water content [29] and tissue pressure with a consequential decrease in ICP [30]. HS increases the diameter of the capillary lumen and reduces erythrocyte size due to the osmotic mobilisation of water across the intact BBB. The effects on the microcirculation may also play an important role. Indeed, HS dehydrates endothelial cells and erythrocytes which increases the diameter of the vessels and erythrocyte deformability and leads to plasma volume expansion with improved blood flow [31].

However, in 2007 the debate whether solutions that alter oncotic pressure or osmolarity may contribute to a better end result following traumatic brain injury is still sustained. A recent animal study on non-haemorrhagic traumatic brain injury induced by a controlled cortical impact (CCI) investigated whether the composition of hypertonic fluid and the time of administration might have an impact on injury volume and oedema following traumatic brain injury in the absence of haemorrhagic complications [33].

The study hypothesizes that in addition to a direct effect on fluid movement hypertonic and hyperoncotic solutions may influence tissue damage from traumatic brain injury through immunomodulation. Indeed, the inflammatory response has been observed to influence cerebral oedema, intracranial pressure, cerebral blood flow, brain ischaemia, and cell death following traumatic brain injury [34]. In fact, inflammation may contribute to secondary damage following tissue trauma and hypertonic saline administration can contribute to a number of changes in the post-traumatic brain. One of the changes that has received significant attention is the effect on vascular permeability. In a study by Suarez JJ and coll. [33], blood brain barrier permeability was assessed to identify a mechanism for fluid treatment effectiveness. Indeed, previous reports support that the permeability of the BBB is greater immediately after injury compared to later time points after 1 h [33, 35]. Therefore, hypertonic saline may aggravate tissue damage and oedema when given immediately after CCI injury when the BBB is more permeable and has had insufficient time for repair. The results of this investigation support that hypertonic saline does not accentuate tissue damage nor cerebral oedema when administered at 6 h as it does with the immediate fluid treatment after CCI injury. These findings suggest that the permeability of the BBB plays a major role in the efficacy of hypertonic solutions in reducing injury volume and oedema following CCI injury. As the conclusions of this study suggest, the presence of colloid in solutions used to treat traumatic brain injury and the timing of treatment have a significant impact on tissue damage and oedema.

When considering bolus administration for the treatment of intracranial hypertension, four case series are reported in the Guidelines which evaluate bolus infusion of between 7.2% and 10% saline in patients after TBI. Bolus infusion of HS reliably decreased ICP in all studies. HS effectively lowered ICP in patients that were refractory to mannitol. Repeated administration of HS in the same patient was always followed by a reduction in ICP and a rebound phenomenon was not observed [36-38]. In a pilot randomized controlled trial, HS bolus infusion was compared to mannitol, and it was found superior for ICP reduction [39]. Given these reports, the Guidelines state that “*HS as a bolus infusion may be an effective*

adjuvant or alternative to mannitol in the treatment of intracranial hypertension. However, the case series design, and the small sample of the trial, do not allow for conclusions”.

Despite this encouraging evidence, the conclusion is that: *“To date no randomized controlled trials (RCT) have determined the relative benefit of hypertonic saline versus mannitol (...) The use of a single high dose of mannitol needs to be validated, preferably in a multicenter trial, as well as for the entire severe TBI population. Studies are required to determine the efficacy of prolonged hypertonic therapy for raised ICP, especially with respect to the effect of this therapy in relation to outcome”*

In this setting it must be recalled how HS is advocated in fluid resuscitation in trauma patients. In fact it significantly increases blood pressure and decreases overall fluid requirements [13].

CPP

CPP is a major determinant of cerebral perfusion in the injured brain.

Cerebral ischaemia is the single second-most important factor that affects outcome following TBI, after high ICP. As stated above, the identification and treatment of secondary ischaemic damage is the main therapeutic target in the management of TBI and, to this the end maintenance of CPP has become central to the management of patients suffering from head injury. CPP can be calculated from the relationship: $CPP = MAP - ICP$, where MAP is the mean arterial pressure.

Current therapies used for ICP control may tolerate the risk of further reducing perfusion to the brain either by lowering blood pressure and CPP or by causing cerebral vasoconstriction (hyperventilation). The ideal therapeutic intervention should effectively reduce ICP while preserving or improving CBF. With the first BTF guidelines published in 1998, the target of a CPP of 70 mmHg was adopted. CPP and ICP can be controlled in a number of ways, including reduction of metabolic requirements with sedation, induced hyperventilation, hyperosmolar therapy, and surgical adjunctions. As stated in the guidelines: *“There are insufficient data to support a Level I recommendation for this topic”.*

Maintaining CPP to increase oxygen delivery to the brain has an obvious rationale but it might be harmful. In many patients experiencing head injury, mostly the more severe, loss of cerebral autoregulation may occur. Increasing pressure in a passive vascular bed may increase blood volume and therefore ICP. The increased hydrostatic pressure can lead to vasogenic oedema. Indeed, as Class II evidence, the Guidelines conclude that: *“Aggressive attempts to maintain cerebral perfusion pressure (CPP) above 70 mmHg with fluids and pressors should be avoided because of the risk of adult respiratory distress syndrome”.*

Several recent studies have attempted to provide data on optimal CPP targets within the context of protocols for the intensive care management of severe traumatic brain injury. Robertson et al [40] compared in a randomized controlled trial the effects of two acute-care management strategies on the frequency of jugular venous desaturation and refractory intracranial hypertension and on long-term

neurological outcome in patients with severe head injury. Patients were randomly assigned to either CBF-targeted or ICP-targeted management protocols. In the CBF-targeted protocol, CPP was kept at >70 mmHg. In the ICP-targeted protocol, CPP was kept at >50 mmHg. The CBF-targeted protocol reduced the frequency of jugular desaturation from 50.6% to 30%, and the risk of cerebral ischaemia was 2.4-fold greater with the ICP-targeted protocol. Despite the reduction in secondary ischaemic insults, there was no difference in neurological outcome. Failure to alter long-term neurological outcome was probably attributable to two major factors. Low jugular venous oxygen saturation was treated in both groups, minimizing the injury that occurred in the ICP-targeted group (in which CPP was maintained above 50 mmHg). In the CBF-targeted protocol (aimed at maintaining CPP above 70 mmHg), a five-fold increase in the frequency of hypoxia was observed. A recent commentary by Robertson [41] made a credible case for targeting a CPP of 60 mmHg in traumatic brain injury protocols. These results provide useful guidance on optimal CPP levels across patient populations.

The guidelines provide the following level III recommendations : “*CPP of <50 mmHg should be avoided. The CPP value to target lies within the range of 50–70 mmHg. Patients with intact pressure autoregulation tolerate higher CPP values. Ancillary monitoring of cerebral parameters that include blood flow, oxygenation, or metabolism facilitates CPP management*”.

In 2007, we might infer that the heterogeneity between or within patients is still an issue. Some patients, or some areas in the injured brain, might benefit from a higher (or lower) CPP. There is growing evidence of pathophysiological heterogeneity between and within patients following head injury. Indeed, in TBI, widespread oxygen and glucose metabolism derangements have provided support for the concept of a *traumatic penumbra*, defined in a pathophysiological rather than anatomical way. The challenge is to find ways to identify such penumbral tissue, to define management approaches in individual patients, and to find sensitive measures that can determine whether such individualized therapy produces improvements in neurocognitive outcome. As stated in a interesting editorial: “*We need to try to move away from attitudes that try to shoehorn patients into a single range of CPP values*” [42]

CPP Assessment and Autoregulatory Failure

After head injury, impaired cerebrovascular autoregulation has been associated with abnormally high or low CBF. However, we also need to take into consideration that cerebral metabolic rate of oxygen (CMRO_2) may be abnormal, therefore in our patients the relevance of CBF level is difficult to asses.

There is a close relation between dysautoregulation and abnormal cerebral metabolism, but not blood flow [43]. The mechanisms that lead to cerebrovascular post traumatic dysautoregulation are not entirely understood.

Decision making regarding treatment in patients with impaired autoregulation would be facilitated by an understanding of the physiological context in which autoregulation impairment is observed, thus leading to different therapeutic strategies.

Steiner et al [44] have tested the hypothesis that after head injury disturbed autoregulation is related to disturbed oxygen metabolism. Their study obtained quantification of autoregulatory efficiency by using the PRx index.

This study demonstrated that in a substantial proportion of patients dysautoregulation was associated with primary metabolic impairment, characterized by CMRO₂ reductions which cannot be attributed to ischaemia. The study concluded that further discussion is required to determine whether metabolic dysfunction is the cause of or the result of disturbed pressure reactivity [44]. Manipulating cerebral blood flow or shifting the patient to a more favourable part of autoregulatory curve, might improve cerebral metabolism.

This evidence would support the development of an autoregulation- oriented treatment strategy based on optimizing CPP according to an evaluation of autoregulation or pressure reactivity. Thus, this potentially useful method may be used in an attempt to refine CPP-oriented therapy, as both too low (ischaemia) and too high CPP (hyperaemia and secondary increase in ICP) are detrimental. The CPP should be optimized to maintain cerebral perfusion in the most favourable state. There is also early evidence that brain tissue oxygenation increases with increasing CPP but only until the level of the optimal CPP [15].

In fact, the dynamics of ICP, its waveform, and the derived indices reveal useful information about brain homeostasis. There is evidence that this information can be used to modify and optimize patient treatment. Secondary variables, such as pulse amplitude and the magnitude of slow waves, index of compensatory reserve, and pressure-reactivity index (PRx), look promising in clinical practice.

Czosnyka et al have described the cerebrovascular pressure-reactivity index (PRx) [45] by observing the response of ICP to spontaneous changes in ABP. PRx is derived continuously by analysing the transmission of the heart pulse from the ABP to the ICP wave form [46] and it is determined by calculating the correlation coefficient between 40 consecutive, time-averaged data points of ICP and ABP. The correlation coefficient has a standardized value (range from -1 to +1). A positive PRx means a positive gradient of the regression line between the slow components of ABP and ICP that may be associated with passive behaviour of a non-reactive vascular bed. A negative PRx reflects a normally reactive vascular bed, as blood pressure waves provoke inversely correlated waves in ICP. A positive PRx has been correlated with lower admission Glasgow coma scale, poorer outcome, greater ICP and disturbed transcranial-doppler-derived index of autoregulation. Autoregulation has been proven to be a powerful protective mechanism. Moreover the PRx has a standardized value (from -1 to +1), and may be a convenient index suitable for comparison between patients. This index may be analysed as a time-dependent variable, responding to dynamic events such as ICP plateau waves or incidents of arterial hypo- and hypertension. Indeed, in the damaged brain, CPP driven therapy needs to take into account that frequently there is failure to observe an increase in cerebral perfusion despite an increase in CPP and the hyperaemic brain may suffer from an increase of cerebral oedema which, by increasing tissue pressure, reduces perfusion at the capillary level. The optimal CPP derived using the PRx is a new concept that may help to avoid excessive use of vasopressors in CPP-oriented

therapy. Despite the fact that relevance of secondary ICP indices remains to be confirmed in clinical trials, several studies have already addressed the usefulness of this approach.

CPP should be optimized to maintain cerebral perfusion in the most favourable state.

As stated in the Guidelines, *“Minimally invasive, efficient, and accurate methods of determining and following the relationships between CPP and autoregulation and between CPP and ischemia in individual patients are needed. There is a need for randomized trials of the influence on outcome of basing optimal CPP on ischemia monitoring (e.g., jugular venous saturation or PtiO₂) or on the quantitative indices of pressure autoregulation”*.

Howells et al have applied PRx in two series of brain trauma patients [47]. The aim of this study was to retrospectively evaluate the effects of two CPP therapies on physiological features and outcome in patients with TBI. The authors aimed to compare the effects of two different treatment protocols on physiological characteristics and outcome in patients with head injury. In one group the management was mainly directed toward ICP less than 20 mmHg and on maintaining CPP at approximately 60 mmHg. Another series of 64 patients were treated aiming at maintaining CPP greater than 70 mmHg and, secondarily, ICP less than 25 mmHg. The ICP and CPP insults were assessed as the percentage of monitoring time that ICP was greater than or equal to 20 mmHg and CPP less than 60 mmHg, respectively, for the first 24 h and 30 mmHg subsequently. Outcome was analysed at 6 months according to the Glasgow outcome scale.

Pressure reactivity in each patient was assessed based on the slope of the regression line relating mean arterial blood pressure (MABP) to ICP.

The study concludes that patients who are pressure active or pressure stable, with a slope less than 0.13, respond best to hypertensive CPP-oriented therapy. Pressure-passive patients, whose regression lines have slopes greater than 0.13, have a better outcome when ICP-oriented therapy has been employed. Authors data analysis indicates that this combined approach will result in significantly better overall patient outcome than either protocol separately. What might be inferred from this study is that different approaches may lead to different results, depending on whether the autoregulation is impaired or not. The variability of pressure reactivity provides a mean of identifying the appropriate treatment strategy for a given patient.

We might argue that this result is the pragmatic example of the fact that the same treatment does not fit all and that an anti-Procrustean approach is needed [42].

Hyperventilation

In the Guidelines, prophylactic (i.e. without intracranial hypertension) hyperventilation (PaCO₂ of 25 mmHg or less) is not recommended (Level II). As for other therapeutic strategies, the application timing and the control of the effects requires strict and continuous ICP guidance (and not the application of prophylactic strategies).

Moreover, a level III recommendation states that therapeutic “[h]yperventilation is recommended as a temporizing measure for the reduction of elevated intracranial pressure (ICP). Hyperventilation should be avoided during the first 24 hours after injury when cerebral blood flow (CBF) is often critically reduced. If hyperventilation is used, jugular venous oxygen saturation (SjO_2) or brain tissue oxygen tension ($PbrO_2$) measurements are recommended to monitor oxygen delivery”.

Cerebral vessel calibre is mainly determined by the partial arterial pressure of carbon dioxide ($PaCO_2$). Hypercarbia has long been known to increase cerebral blood volume (CBV) and CBF, by cerebral vasodilatation. This phenomenon leads to increased ICP, and hence reduction of cerebral perfusion.

Reduction in $PaCO_2$ causes cerebral vasoconstriction, reducing CBV and ICP. In an early traumatized brain, there is a lack of *a priori* knowledge of the “CBF status”. A depressed level of consciousness, therapeutic sedation and trauma induced mitochondrial dysfunction [12] can reduce $CMRO_2$ and consequentially may impair the coupled perfusion. This occurrence might reduce the critical CBF threshold for ischaemia [48, 49]. Particularly, in the first 24 h after TBI, CBF is reduced.

The long-lasting debate on hyperventilation is still open. A recent study [50] reported no reduction in mean $CMRO_2$ with hyperventilation, even in regions of interest (ROIs) where CBF was reduced to 10 ml/100 g. However, these data come from averaging values across ROIs and cannot exclude that critical ischaemia may result in a significant subpopulation of ROIs. McLaughlin et al [51] have investigated CBF and vasoresponsivity around and within cerebral contusions in patients suffering from head injury. They concluded that a relative hypoperfusion was present in this setting, and that a hypersensitivity to $PaCO_2$ of the injured brain was possible. Given this evidence, the lesions were particularly vulnerable to secondary injury such as those caused by hyperventilation.

While the issue remains controversial, some theoretical caveats have been postulated as Level II and III recommendations. Indeed, the Guidelines state that *“In the absence of trials that evaluate the direct effect of hyperventilation on patient outcomes, we have constructed a causal pathway to link hyperventilation with intermediate endpoints known to be associated with outcome. Independent of hyperventilation, CBF can drop dangerously low in the first hours following severe TBI. The introduction of hyperventilation could further decrease CBF, contributing to the likelihood of ischemia.”*

Thus it is clear that pathophysiological derangements in a traumatized brain are far from being a simple picture.

Although some clinical studies have proposed thresholds of moderate hyperventilation to a target $PaCO_2$ of 4.0 kPa in patients with intractable intracranial hypertension [52], in the management of TBI in 2007 these questions still need to be answered: *How does short-term hyperventilation affect outcome? What is the effect of moderate hyperventilation in specific subgroups of patients? Which are the critical levels of $PaCO_2$ /CBF and outcome?*

Decompressive Craniectomy

Decompressive craniectomy (DC) is a surgical procedure, based upon overturning the Monro-Kellie dogma, in which a large part of the skull vault is removed and the dura opened to allow the brain to expand out of the confines of a rigid skull. The procedure has had a controversial history, with advocates and opponents and equivocal patient outcomes [53]. Decompression provides immediate relief of intracranial hypertension. But of greater importance is whether surgery has a beneficial effect on patient outcome. The literature provides several reports of improvement in both patient outcome and independent predictors of outcome, following DC [54]. In 2007 DC is a last resort that could be used in patients when other techniques have failed. Though the operation is being increasingly used, current opinion is still divided regarding its overall benefits and, despite the fact that the procedure has been used for decades many questions must still be answered. To date there are no results from randomized trials to confirm or refute the effectiveness of DC in adults suffering TBI, subarachnoid haemorrhage or stroke. However, the results of controlled trials with historical controls involving adults suggest that DC may be a useful option when maximal medical treatment has failed to control ICP. The real question that must be solved before decompression is when does energy failure become irreversible. No single monitoring system is able to answer the key question, i.e. to operate or not. A combination of monitoring system and clinical evaluation helps the clinician to identify patients that would not reasonably improve after the procedure. Monitoring and clinical elements help to identify exclusion criteria and assist in avoiding futile procedures. This process unfortunately has neither been formalized nor standardized [54].

The main challenge is knowing when this decision should be undertaken. The clinicians facing this decision have to take account of having appropriately used all the conventional weapons against intracranial hypertension and the absence of data indicating an already negative outcome. The selection of the patient to decompress is based, in the current uncertainty, on a probability evaluation of offering a better outcome.

Currently the RESCUEicp study is examining DC vs. barbiturate coma for raised refractory intracranial hypertension [54].

Conclusions

Major progress has been made in the last 20 years in understanding the mechanism and pathophysiology of secondary insults following TBI. In different clinical areas, many studies have shown lower overall mortality rates for patients enrolled in clinical trials than in those not enrolled [55].

Several recent publications attest the efficacy of protocol-driven neurocritical care in improving outcome in patients suffering brain disease [49]. Patel et al [56] have demonstrated how an evidence based head injury management algorithm resulted in outcome improvement. In 2007, good quality intensive care does

improve outcome and the actual trend in head injury management is directed in optimizing the cerebrovascular physiology in a more integrated fashion [49].

Improved outcome occurs when secondary delayed insults to the injured brain are prevented or respond to treatment. Indeed, this evidence is reflected in the progressive and significant reduction in severe TBI mortality, from 50% to 35% to 25% and lowers over the last 30 years, even when adjusted for injury severity, age and other admission prognostic parameters [42]. This trend in reduced mortality and improved outcomes from TBI has been subsequent to the use of evidence-based protocols that emphasize monitoring and maintaining adequate cerebral perfusion [57]. Moreover, since the first Guidelines for Management of Traumatic Brain Injury were published in 1995, there have been several studies clearly demonstrating that TBI management in accordance with the Guidelines can achieve substantially better outcomes. In the United States, surveys conducted in 1995, 2000, and 2006 have shown that increasing numbers of severe TBI patients are being managed in accordance with the *Guidelines*, with ICP monitoring, for example, rising from 32% in 1995 to 78% in 2005.

The derangements in cerebral physiology following head injury are dynamic and so is our increasing understanding in this fascinating field. To date several remarkable caveats have been reached. The strategies we are using to do the best for our patients are definitely promising but still need to be improved. It is worth concluding that: *“In order to continue to improve outcomes for TBI patients, it is necessary to generate strong research capable of answering key questions, and to assess, synthesize, and disseminate the findings of that research so that practitioners have access to evidence-based information. Therefore, this document should not only be used as a roadmap to improve treatment, but also as a template from which to generate high quality research for future use. The primary marker of the success of the 3rd edition of these Guidelines will be a sufficient body of Class I and II studies for Level I and II recommendations in the 4th edition”* as it is honestly stated in the 3rd Edition of the *Guidelines for the Management of Severe Traumatic Brain Injury*.

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Penetrating Injuries to the Neck: Operation, Observation or Angiointervention

J. DuBOSE, D. DEMETRIADES

Penetrating neck injuries (PNI) are notoriously difficult to evaluate and manage because of the complex anatomy and the dense concentration of numerous vital structures in a small anatomical area. The clinical evaluation can challenge the skills of the less experienced physicians and significant injuries may easily be missed. The radiological evaluation of these injuries has undergone major changes in the last few years and shifted from invasive diagnostic procedures to noninvasive methods, but the selection of the most appropriate investigation remains a controversial issue. New advances in interventional radiology have revolutionized the management of some complex vascular injuries. The concept of selective nonoperative management in selected patients has gained considerable acceptance. This chapter discusses these issues in detail and provides practical guidelines and algorithms for the safe evaluation and initial management of PNI.

Epidemiology

Firearms are responsible for about 43%, stab wounds for about 40%, shotguns for about 4% and other weapons for about 12% of all PNI in urban trauma centres in the United States [1]. Overall, about 35% of all gunshot wounds (GSW) and 20% of stab wounds to the neck are associated with significant injuries to vital structures, but only 16.5% of GSW and 10.1% of stab wounds require a therapeutic operation. Transcervical GSW are associated with significant injuries to vital structures in 73% of victims, although only 21% require a therapeutic operation [2]. Shotgun injuries account for about 4% of civilian PNI, often cause injuries to multiple structures and pose major evaluation and management problems. The mechanism of war injuries is significantly different from civilian trauma. In a study of 117 patients with penetrating neck injuries during the 1991-1992 war in Croatia, the wounds were mostly inflicted by shell or bomb fragments and only about 25% were due to GSW [3]. Overall, in penetrating trauma the most commonly injured structures in the neck are the vessels, followed by the spinal cord, the aerodigestive tracts, and nerves [1]. The incidence of injury to the various neck structures according to mechanism of injury is shown in Table 1.

Table 1. Incidence and type of injuries according to mechanism of injury (N=223 patients) [1]

Injury	All mechanisms	GSW	SW
Vascular	21.5%	26.8%	14.6%
Aerodigestive	6.3%	7.2%	3.4%
Spinal cord	6.7%	13.4%	1.1 %
Peripheral or cranial nerves or sympathetic	9.0%	12.4%	0.5%
Haemo or pneumothorax	17.9%	15.5%	13.5%

GSW = gunshot wounds; SW= stab wounds

Anatomy

The anatomy of the neck is characterized by a very dense concentration of vital structures, enveloped in tight fascia compartments in a small anatomical area. This anatomy predisposes to significant injuries of vital structures and potentially lethal complications following penetrating trauma. Thorough knowledge of the local anatomy is essential for the management of PNI. The fascial planes of the neck play an important role in the clinical presentation and complications following penetrating trauma. In penetrating trauma the neck is divided into three anatomical zones for evaluation and therapeutic strategy purposes (Fig. 1): Zone I comprises the area between the clavicle and the cricoid cartilage. This zone includes the innominate vessels, the origin of the common carotid artery, the subclavian vessels and the vertebral artery, the brachial plexus, the trachea, the oesophagus, the apex of the lung, and the thoracic duct. The surgical exposure of the vascular structures in Zone I is difficult because of the presence of the clavicle. Zone II comprises the

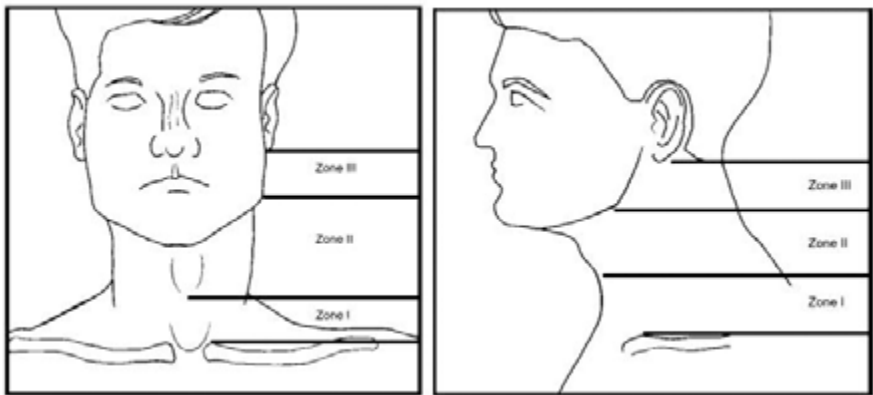


Fig. 1. Surgical zones of the neck: zone 1 is between the clavicle and cricoid, zone 2 is between the cricoid and angle of mandible, and zone 3 is between the angle of mandible and the base of skull.

area between the cricoid cartilage and the angle of the mandible and contains the carotid and vertebral arteries, the internal jugular vein, trachea and oesophagus. This zone is more accessible to clinical examination and surgical exploration than the other zones. Zone III extends between the angle of the mandible and the base of the skull and includes the distal carotid and vertebral arteries and the pharynx. Zone III is not amenable to easy physical examination or surgical exploration.

Overall, Zone II is the most commonly injured area (47%), followed by zone III (19%) and I (18%). In 16% of cases there is involvement of more than one zone [1]. The incidence of vascular and aerodigestive injuries according to zone, in a prospective study of 223 patients with PNI [1], is shown in Table 2. In series with predominantly stab wounds, zone I is the most commonly injured area (44%), followed by zone II (29%) and zone III (27%) [4]. Most stab wounds involve the left side of the neck (74% of cases), presumably due to the predominance of right-handed assailants [4].

Table 2. Incidence of vascular and aerodigestive injury according to zone (223 patients) [1]

Zone	No. of patients	No. of patients with aerodigestive or vascular injury	No. of patients with therapeutic operation
I	41	14.6%	12.2%
II	105	22.9%	14.3%
III	42	23.8%	4.8%
Multiple	35	31.4%	20.0%

Emergency Room Management

The initial evaluation and management should follow the Advanced Trauma Life Support (ATLS) protocols. During the primary survey the following life-threatening conditions from the neck should be identified and treated as soon as possible:

1. Airway obstruction due to laryngotracheal trauma or external compression by a large haematoma.
2. Tension pneumothorax.
3. Major active bleeding, externally or in the thoracic cavity.
4. Spinal cord injury or ischaemic brain damage due to carotid artery occlusion.

During the secondary survey the following neck injuries should be identified:

1. Occult vascular injuries.
2. Occult laryngotracheal injuries.
3. Pharyngoesophageal injuries.
4. Cranial or peripheral nerve injuries.
5. Small pneumothoraces.

Airway Management

Airway management is the first and most challenging priority in the management of severe PNI. Approximately 8 to 10% of patients with PNI present with airway compromise [5-7]. In patients with laryngotracheal injuries about 30% require emergency room airway establishment because of threatened airway loss [7]. Airway problems may be due to direct trauma or severe oedema to the larynx or trachea, or from external compression by a large haematoma. Small penetrating injuries to the airway tract by knife or low-velocity bullets rarely cause respiratory problems. However, major laryngotracheal transections or high-velocity gunshot wounds often cause respiratory problems. In a prospective study of 223 patients with PNI about 3% had major direct laryngotracheal trauma and about 13% had a large neck haematoma [1]. GSWs were significantly more likely to result in large haematomas than knife wounds (20.6% versus 6.7%) [1].

Air bubbling through a neck wound is pathognomonic of laryngotracheal injury. Firm manual compression over the wound reduces the air leak and usually improves oxygenation. Orotracheal intubation in these cases may be dangerous because of the risk of further damage to the larynx or trachea or misplacement of the tip of the tube into the paratracheal tissues. Emergency room endotracheal intubation should be considered only in patients who fail to improve after firm occlusion of the wound with the air leak.

In general, orotracheal intubation in the emergency room should be performed only in patients with severe respiratory distress or imminent cardiac arrest. The airway management of these patients should be undertaken by the most experienced physician and a surgeon should always be present in case a surgical airway is needed. The technique of endotracheal intubation in the presence of a large, expanding haematoma or major air leaks from the wound should be individualized, taking into account many factors: (a) the severity of respiratory distress; (b) the haemodynamic condition of the victim; and (c) the nature of the local neck pathology (size and site of any haematoma and presence of an open wound with air bubbling), and d) the experience of the trauma team.

In patients with large neck haematomas who are not in respiratory distress, fiberoptic intubation is the safest approach. However, this procedure requires experience and skill, it can only be performed semi-electively and the reported failure rate is about 25% [7]. The presence of severe respiratory distress or apnoea are absolute contraindications for fiberoptic intubation.

Orotracheal intubation, with or without neuromuscular paralysis, is the most common method of airway management and it is used in about 80% of patients requiring emergency endotracheal intubation for PNI [7]. With appropriate selection of patients and experience, the success rate is very high [7, 8]. The use of neuromuscular paralysis during orotracheal intubation in the emergency room in cases with PNI is controversial and has major advantages and disadvantages. Orotracheal intubation without neuromuscular paralysis is difficult and any coughing or gagging may worsen bleeding and increase the size of the haematoma. On the other hand, pharmacological paralysis may be dangerous if the cords cannot

be visualized because of distorted anatomy due to a compressing haematoma or significant local oedema. It has been suggested that abolishment of the muscle tone after pharmacological paralysis results in further displacement of the airway, leading to total obstruction [9]. Orotracheal intubation, with or without pharmacological paralysis, should be performed by the most experienced physician present and with a surgeon ready to intervene and perform a surgical airway. In a review of 76 patients with laryngotracheal trauma in Los Angeles, 16 cases (21%) required emergency room airway establishment. Although rapid sequence induction was successful in most cases, in 12% the orotracheal intubation failed and a cricothyroidotomy was performed [8].

Blind nasotracheal intubation without the use of pharmacological paralysis has been occasionally used in cases with neck haematomas. This approach should rarely be used because of the reasons mentioned above, the reported high failure rate and the potentially lethal consequences associated with failed attempts [10]. In rare occasions with visible large laryngotracheal wounds the endotracheal tube can be inserted under direct view into the distal transected segment through the neck wound. The distal larynx or trachea should be grasped and secured with a tissue forceps before insertion of the tube in order to avoid complete transection or retraction into the mediastinum.

Cricothyroidotomy in the emergency room may be necessary in about 6% of all penetrating neck injuries [10] or about 12% of laryngotracheal injuries [7]. In the presence of large midline haematomas the procedure is difficult and may be associated with severe bleeding.

In summary, the airway management of PNI should be individualized according to the condition of the patient, the nature of the injury and the experience of the trauma team. Alternative approaches should be planned in advance and be immediately available in case the initial attempt is not successful.

Bleeding Control

In the presence of active bleeding the patient should be placed in the Trendelenburg position in order to reduce the risk of air embolism in cases with venous injuries. Intravenous lines should be avoided in the arm on the side of the neck wound. External bleeding can successfully be controlled by direct pressure in most cases. However, bleeding from the vessels behind the clavicle or near the base of the skull or the vertebral artery is often difficult to control by external pressure. In these cases digital compression with a gloved index finger through the wound should be attempted. For these situations, we have successfully used balloon tamponade [6, 11, 12]. The technique involves insertion of a Foley catheter into the wound and advancement as far as it can go. The balloon is then inflated with water until the bleeding stops or moderate resistance is felt. If the bleeding continues after this manoeuvre, the balloon is deflated and the catheter is slightly withdrawn and reinflated. Significant bleeding through the catheter is suggestive of bleeding distal to the balloon and repositioning should be attempted. In periclavicular injuries the bleeding may occur in both, the intrathoracic cavity and externally. In these cases

a Foley catheter is advanced into the chest cavity through the neck wound, the balloon is then inflated, and the catheter is pulled back until some resistance is felt. In this position the balloon compresses the bleeding vessels against the first rib or the clavicle. The traction is maintained by application of a Kelly forceps on the catheter, just above the skin. If external bleeding continues, a second Foley is inserted and inflated in the wound tract [11]. Blind clamping of suspected bleeding should be avoided because it is rarely effective and the risk of further vascular or nerve damage is very high.

Many patients with major injuries to the neck vessels reach the hospital in cardiac arrest or imminent cardiac arrest. These patients may benefit from a resuscitative thoracotomy. Bleeding from the left subclavian vessels can be controlled with a vascular clamp applied under direct view through the thoracotomy. Besides the usual resuscitation measures, the right ventricle should be aspirated for air embolism. In our experience, survival following resuscitative thoracotomy for PNI is very poor [13].

Clinical Examination

Physical examination, preferably according to a written protocol, remains the most reliable diagnostic tool. The physical examination should be systematic and specifically directed to look for signs or symptoms of injuries to the airway tract, the vessels, pharyngoesophageal tract, spinal cord, nerves, and the lungs. The clinical signs are classified into “hard” signs, which are pathognomonic of injury, and “soft” signs, which are suspicious but not diagnostic of significant injury [1, 14]. The incidence of the various signs and symptoms is influenced by the mechanism of injury. In GSWs, the most common clinical sign is a moderate or large haematoma (20.6%), and in stab wounds painful swallowing (14.3%) and haemo/pneumo- thorax (13.5%) [1]. Table 3 shows the incidence of the various signs and

Table 3. Clinical findings on admission according to mechanism of injury (N=223) [1]

	Overall	GSW	SW
Severe/moderate bleeding	5.8%	4.1%	6.7%
Large/moderate haematoma	13.0%	20.6%	6.7%
Shock	9.9%	13.4%	7.9%
Diminished peripheral pulse	4.9%	8.2%	3.4%
Pain on swallowing	15.7%	15.8%	14.3%
Hoarseness	8.3%	10.5%	8.3%
Subcutaneous emphysema	6.9%	9.5%	5.9%
Air bubbling through wound	2.8%	4.2%	2.4%
No signs of vascular injury	71.7%	64.9%	80.9%
No signs of aerodigestive injury	70.4%	64.2%	77.4%
Spinal cord injury	6.7%	13.4%	1.1%
Nerve injury	9.0%	12.4%	4.5%
Haemo/pneumothorax17.	9.0%	15.5%	13.5%

GSW= Gunshot wounds; SW = stab wounds

symptoms according to mechanism of injury in a prospective study of 223 patients with PNI.

Evaluation for Laryngotracheal Injuries

“Hard” signs highly diagnostic of significant laryngotracheal trauma include respiratory distress, air bubbling through the neck wound, and major haemoptysis. In the presence of any of these findings an operation is indicated without any specific diagnostic studies.

“Soft” signs are present in about 18% of PNI [1], and include subcutaneous emphysema, hoarseness and minor haemoptysis. These patients need further diagnostic evaluation to identify those with significant injuries requiring surgical repair. Only about 15% of patients with soft signs have a significant laryngotracheal injury.

Subcutaneous emphysema is the most common soft sign and is found in about 7% of PNI [1]. It may be secondary to laryngotracheal or oesophageal injury or an associated pneumothorax. In about 15% of cases there is no obvious source explaining the subcutaneous emphysema and it is assumed that the air comes from outside, through the wound.

Evaluation for Vascular Injuries

“Hard” signs of significant vascular trauma include severe active bleeding, large expanding haematoma, absent or diminished peripheral pulse, bruise on auscultation, and unexplained hypotension. This group of patients warrants emergent operative intervention. In one published series of 29 patients with hard signs of vascular injury, 28 (97%) had significant injuries [1].

“Soft” signs of vascular trauma include stable, small to moderate size haematomas, minor bleeding, mild hypotension responding well to fluid resuscitation, and proximity wounds. Patients with soft signs need further investigation because only about 3% require a therapeutic operation. In a prospective study, which included 34 patients with soft signs who underwent angiographic evaluation, 8 (23.5%) had an angiographically detected abnormality but only 1 (3%) needed an operation [1].

Evaluation for Pharyngoesophageal Tract Injuries

There are no hard signs diagnostic of pharyngoesophageal injuries. Soft signs which require evaluation of the pharynx and oesophagus include painful swallowing, subcutaneous emphysema, and haematemesis. These symptoms are present in about 23% of patients with PNI and they are not specific. Only about 18% of patients with these findings have pharyngoesophageal trauma [1].

Evaluation for Nervous System Injuries

The clinical examination should include assessment of the Glasgow Coma Scale (GCS) score, localizing signs, pupils, cranial nerves (VII, IX-XII), spinal cord, brachial plexus (median, ulnar, radial, axillary, musculocutaneous nerves), the phrenic nerve and the sympathetic chain (Horner's syndrome). The GCS may be abnormal due to ischaemia secondary to a carotid injury or due to an associated intracranial missile injury.

The clinical examination should ideally be performed according to a written protocol. Failure to follow this recommendation, especially by the less experienced surgeon, may result in missing significant signs and symptoms. Figure 2 shows the written examination protocol which has been in use at the Los Angeles County and University of Southern California Trauma Center for many years. The protocol has been tested in large prospective studies of 223 patients in Los Angeles [1] and 335 patients in Johannesburg, South Africa [4]. Clinical examination according to this protocol reliably diagnoses or highly suspects all significant injuries. The absence of any clinical signs or symptoms suggestive of vascular or aerodigestive injury reliably exclude significant injuries to these structures requiring therapeutic inter-

PROTOCOL FOR CLINICAL EXAMINATION IN PENETRATING INJURIES OF THE NECK

A. SYSTEMIC EXAMINATION

- 1 Dyspnoea: "yes" "no"
- 2 Blood pressure:
- 3 Pulse:

B. LOCAL EXAMINATION

VESSELS

- 1 Active bleeding: "minor" "severe" "no bleeding"
- 2 Haematoma: "small" "large" "no bleeding" "expanding"
- 3 Pulsatile haematoma: "yes" "no"
- 4 Peripheral pulses (compare with normal side)
"normal" "diminished" "absent"
- 5 Bruit: "yes" "no"
- 6 Ankle-Brachial Index (ABI):

LARYNX-TRACHEA-ESOPHAGUS

- 1 Haemoptysis: "yes" "no"
- 2 Air bubbling through wound (ask the patient to cough): "yes" "no"
- 3 Subcutaneous emphysema: "yes" "no"
- 4 Pain on swallowing sputum: "yes" "no"

NERVOUS SYSTEM

- 1 Glasgow Coma Scale (GCS):
- 2 Localizing signs (describe):
- 3 Cranial nerve injury:
 - Facial nerve: "yes" "no"
 - Glossopharyngeal nerve: "yes" "no"
 - Recurrent laryngeal nerve: "yes" "no"
 - Accessory nerve: "yes" "no"
- 4 Spinal cord: "normal" "abnormal (describe):"
- 5 Brachial plexus injury:
 - Median nerve: "yes" "no"
 - Ulnar nerve: "yes" "no"
 - Radial nerve: "yes" "no"
 - Musculocutaneous nerve: "yes" "no"
 - Axillary nerve: "yes" "no"
- 6 Horner's syndrome: "yes" "no"

Fig. 2. The LAC+USC Trauma Center Protocol for local examination in penetrating injuries of the neck.

vention. In a prospective study of 335 patients predominantly with stab wounds to the neck, 269 (80%) had no symptoms or signs suggestive of vascular or aerodigestive injuries and were selected for nonoperative management. Only two of the observed patients (0.7%) required semielective operation for vascular injuries. In both cases a bruit was detected the day after admission and angiography demonstrated an arteriovenous fistula [4]. In another prospective study of 223 patients with PNI, predominantly with GSWs, 160 of them (71.7%) had no clinical signs suggestive of vascular trauma. None of these patients required surgery or another form of treatment (negative predictive value [NPV] 100%). Angiography was performed on 127 asymptomatic patients and revealed 11 vascular injuries (8.3%), none of which required treatment. The most common angiographically detected abnormality was occlusion of a vertebral artery (4 cases) [1]. In the same study there were 152 patients with no signs or symptoms of aerodigestive injuries and none of these asymptomatic patients had a significant injury requiring operation (NPV 100%).

Investigations

The mechanism of injury and clinical examination should determine the need and type of specific investigations in the evaluation of PNI. Patients with hard signs of major vascular or laryngotracheal injuries should undergo an operation without any delay for definitive investigations. If time permits, chest and neck films may be helpful in locating foreign bodies or diagnosing an associated haemopneumothorax which requires treatment. There is good evidence from large prospective studies that patients with no signs or symptoms of vascular or aerodigestive injuries do not have significant injuries requiring treatment and they are very unlikely to benefit from routine angiography or oesophageal studies.

Plain Chest and Neck Films

Chest films should be obtained in all fairly stable patients with penetrating injuries in zone I or any other wounds which could have violated the chest cavity. About 16% of GSWs and 14% of stab wounds to the neck are associated with a haemo/pneumothorax [1]. Other important radiological findings include a widened upper mediastinum which is suspicious of a thoracic inlet vascular injury, subcutaneous emphysema, fractures, and missiles.

Angiography

Angiographic evaluation of the neck vessels following PNI remained a standard practice in many centres for many years [15-17]. Since then, numerous publications have suggested that routine angiography in asymptomatic patients is unnecessary, has a low yield, and does not offer any benefit over physical examination and other noninvasive investigations [1, 4, 6, 18-20]. In a prospective study from Los Angeles

127 asymptomatic patients examined according to a written protocol were evaluated angiographically at a cost of \$254,000 and 11 vascular injuries not requiring any form of treatment were identified. Clinical examination alone would not have missed any significant injury requiring treatment. The combination of clinical examination and Colour Flow Doppler (CFD) diagnosed all vascular injuries [1]. In another prospective study of 335 patients with PNI, 269 (80%) were selected for nonoperative management. Angiography was performed on only 7 cases. There were no deaths or significant complications in this group of patients. Early follow up (mean 16 days) of 192 patients or late follow up (mean 48 days) of 111 patients did not identify any significant missed vascular injuries [4].

Clinical examination alone may miss minor injuries to the neck vessels not requiring treatment [1, 20]. Many studies have suggested that clinically occult, angiographically detected injuries have a benign prognosis and do not require treatment [21, 22]. However, there is concern that minor carotid injuries may be different from extremity minor vascular injuries and it might be prudent to monitor them until complete healing. In order to address this concern we suggest that asymptomatic patients are evaluated with a combination of clinical examination according to a written protocol and CFD [1].

Although the absence of clinical signs suggestive of vascular trauma reliably excludes significant injuries requiring treatment (NPV 100%) [1, 20], the presence of soft clinical signs do not reliably identify patients who will require an operation. In a subgroup of 34 patients with soft signs of vascular injury, angiography diagnosed injuries in 8 (23.5%) but only 1 (3%) needed an operation [1]. It is obvious that angiography in this group of patients has a low yield. However, clinical examination according to a written protocol combined with CFD studies reliably diagnosed all vascular injuries [1, 20].

Some surgeons suggested a policy of routine angiography only for injuries in zones I and III, irrespective of clinical findings [23]. Such policy still has a very low yield at considerable costs and patient discomfort. Only 5% of 148 zone I and 13% of 92 zone III injuries require treatment for vascular injuries [4].

In summary, angiography for PNI should be reserved only for selected cases with specific diagnostic or therapeutic indications (Table 4).

Table 4. Indications for Conventional Angiography

Diagnostic Indications

- Inconclusive CFD or CT angiogram
- Shotgun injuries
- Gunshot wounds involving the transverse foreman of the spine
- Widened upper mediastinum in zone I injuries

Therapeutic Indications (Possible stenting or embolization)

- Bruit on auscultation
- Diminished upper extremity pulse
- Persistent slow bleeding from suspected vertebral artery injury or external carotid branches

Colour Flow Doppler

CFD has been suggested as a reliable alternative to angiography in the evaluation of PNI [1, 6, 12, 20, 24-28]. In a prospective study from Los Angeles, 82 haemodynamically stable patients were clinically examined according to a written protocol and subsequently had angiographic and CFD evaluation. CFD diagnosed 10 of the 11 angiographically detected injuries and missed one small intimal tear which did not require treatment [20]. The study concluded that the combination of a careful clinical examination and CFD imaging is a safe and cost-effective alternative to routine angiography. In another prospective study with 25 patients with PNI who were evaluated by angiography and CFD, Corr et al [25] reached similar conclusions.

CFD has the disadvantage of being operator-dependent and has some limitations in the visualization of the proximal left subclavian artery, especially in obese patients, the internal carotid artery near the base of the skull, and the segments of the vertebral artery under the bony part of the vertebral canal [12, 26].

Computed Tomography

Computed tomography has become a very useful tool in the evaluation of PNI, especially in GSWs. At our centre it has become the first-line investigation in all haemodynamically stable patients with GSWs to the neck. The entry and exit of the bullet should be marked with radioopaque markers and 3 mm CT slices should be obtained between the markers or between the entry and the retained bullet. Identification of the bullet trajectory is very helpful in determining the need for further invasive investigations, such as angiography or endoscopy. Patients with trajectories away from the major vessels or the aerodigestive structures do not need further evaluation [12]. Gracias et al [29] in a study of 19 patients with PNI found that in 13 cases (68%) the CT scan showed trajectories away from vital structures and no further evaluation was required. In addition to the missile trajectory, the CT may provide information about the site and nature of any spinal fractures, involvement of the spinal cord, the presence of fragments in the spinal canal and the presence of any haematomas compressing the cord [12].

Helical CT angiography has been used in the last few years for the evaluation of the major neck vessels following PNI. The reported results are very encouraging and CT angiography has become an excellent initial investigation for suspected vascular injuries [30-32]. Munera et al [30] in a prospective study of 60 patients with PNI compared conventional angiography and helical CT angiography. The performance of CT angiography was very good, with a sensitivity of 90%, specificity 100%, PPV 100% and NPV 98%. In another study of 175 patients, Munera reported excellent results with CT angiography and suggested that it is a valuable investigation for the evaluation of suspected arterial injuries of the neck [31]. The study may have some limitations due to artefacts from metallic fragments or excessive air in the soft tissues [32]. In these cases conventional angiography may be necessary for accurate evaluation.

A brain CT scan is indicated in patients with PNI and unexplained central neurological deficits in order to evaluate for a possible anaemic infarction secondary to a carotid artery injury or an associated direct brain injury due to a missile fragment [12].

Oesophageal Studies

Oesophageal studies are recommended in stable patients with suspicious clinical signs, such as painful swallowing, haematemesis or subcutaneous emphysema and in cases with a CT scan bullet trajectory towards the oesophagus. Contrast oesophagography is the most commonly used study for the evaluation of the oesophagus following PNI. It is used in about 82% of suspected oesophageal injuries while oesophagoscopy is used in about 18% of cases [1]. There has been some concern that oesophagography may miss small oesophageal injuries. In a retrospective review of 23 cervical oesophageal injuries, Armstrong et al [33] reported that contrast oesophagography diagnosed only 62% of perforations, compared to 100% with rigid oesophagoscopy. This is not our experience and at our trauma centre, which is one of the busiest in the United States, we have not seen any missed oesophageal injuries by oesophagography in the last 13 years. The technique of oesophagography is important in avoiding false negative studies. The study is first performed with a water-soluble contrast, such as gastrographin. If no leak is identified the study is repeated with thin barium. Gastrographin alone may miss small injuries [34].

Oesophagoscopy, if performed by an experienced endoscopist, may be a useful investigation in the evaluation of the cervical oesophagus. Flexible endoscopy has been shown to have a negative predictive value of 100% but a positive predictive value of up to 33% [35, 36]. We reserve flexible endoscopy only for patients who cannot undergo oesophagogram because of a depressed level of consciousness or intraoperatively.

Rigid oesophagoscopy may be superior to flexible endoscopy in the evaluation of the upper oesophagus and is the investigation of choice of some authors after oesophagography [37]. However, rigid oesophagoscopy can be performed only under general anaesthesia and many surgeons are not experienced with the technique. We reserve this procedure only for intraoperative evaluation of the oesophagus.

Studies for Laryngotracheal Evaluation

Indications for laryngotracheal evaluation include proximity injury with soft clinical signs suspicious of airway injuries (minor haemoptysis, hoarseness, subcutaneous emphysema) or CT scan findings showing a bullet tract near the larynx or trachea.

Flexible fiberoptic endoscopy is the investigation of choice and it can be performed in the emergency room. The most common abnormal findings are blood or oedema in the laryngotracheal tract and vocal cord dyskinesia [1]. GSWs are

significantly more likely to be associated with abnormal endoscopic findings than knife injuries (24.6% versus 8.5%). However, only 20% of patients with abnormal findings require an operation [1, 37]. The Los Angeles County and University of Southern California trauma centre algorithm for the evaluation of penetrating injuries of the neck is shown in Figure 3.

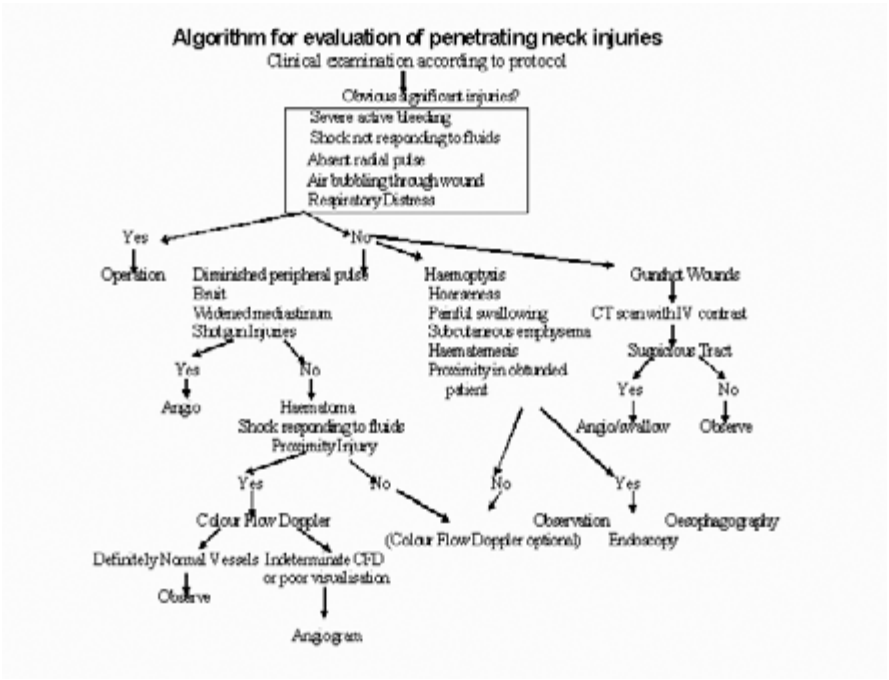


Fig. 3. Algorithm for the evaluation of penetrating injuries to the neck.

Operative versus Nonoperative Management

For many years mandatory operation for all patients with penetrating injuries of the neck which violated the platysma remained the standard of care. However, this policy was associated with an unacceptably high incidence of unnecessary operations, ranging from 30% to 89% [38, 39]. The rationale for routine operation is that clinical examination is often not reliable and may miss significant injuries. In addition, it has been suggested that routine operation avoids expensive investigations and does not prolong hospital stay [39]. This policy has now been abandoned by most trauma centres and has been replaced by a policy of selective nonoperative management. There is strong evidence that clinical examination is very reliable in identifying or highly suspecting significant injuries requiring treatment [1, 2, 4, 19-21, 40-42]. As discussed under epidemiology, only about 17% of GSWs and 10%

of stab wounds to the neck require a therapeutic operation. Subjecting the remaining 83 to 90 percent of patients to an unnecessary operation is not an acceptable practice.

The selection of patients for operation or observation is based on clinical examination and appropriate investigations. The indication and selection of the most appropriate investigation varies from centre to centre and is still a controversial issue. It is essential that clinical examination is performed systematically, preferably according to a written protocol (Figure 2) and investigations are selected with the help of an algorithm which takes into account the experience and resources of the individual trauma centre. Figure 3 shows the algorithm which has been in use at the Los Angeles County and University of Southern California trauma centre for more than 10 years. Failure to follow written protocols and algorithms, especially in low-volume trauma centres or by an inexperienced surgeon, may result in missing of significant injuries or performing unnecessary operations.

GSWs are associated with a higher incidence of significant injuries requiring operative management than stab wounds. For this reason, it has been suggested that mandatory operation may be appropriate for gunshot wounds [43]. However, more than 80% of gunshot wounds to the neck do not require an operation and there is strong evidence that these patients can safely be identified and spared an unnecessary operation, on the basis of clinical examination and appropriate investigations [1, 2, 6, 20, 44, 45].

Transcervical GSWs are associated with a much higher incidence of significant injuries than GSWs that have not crossed the midline (73% versus 31%) [2]. For this reason, it has been suggested that all patients with transcervical GSW should undergo an operation irrespective of clinical examination [46]. However, many of these severe injuries, such as spinal cord or nerve injuries, do not require an operation. In a prospective study of 33 cases with transcervical GSW from Los Angeles, although 73% had injuries to vital neck structures, only 21% needed a therapeutic operation [5]. It has been our practice for many years to evaluate and manage these injuries like any other penetrating injury of the neck. In our experience, thin-slice CT angiography can reliably identify those patients who do not need further investigation or those who might benefit from specific studies by determining the bullet trajectory [15, 32-35].

Angiographic Interventions

Catheter-based endovascular techniques have revolutionized the management of selected haemodynamically stable patients with complex vascular neck injuries. Persistent, slow bleeding from facial branches of the external carotid artery or from the vertebral artery are difficult to control surgically because of the difficult exposure. These patients can successfully be managed with angioembolization. A more recent and very promising development is the use of endovascular stent/grafts in patients with post-traumatic false aneurysms or arteriovenous fistulae or arterial stenosis. This approach is useful in patients with stable vascular

lesions in areas that are difficult to assess and intervene via a surgical approach, such as zone I or III vascular injuries. This approach has been successful in the management of high internal carotid artery, subclavian artery and vertebral artery injuries.

Further experience with the use of interventional radiology for arterial injury will help clarify the optimal indications, timing, techniques, and outcomes.

Conclusions

The evaluation and initial management of PNI have undergone many major changes in the last few years. Invasive diagnostic procedures have been replaced by noninvasive methods. New advances in interventional radiology have revolutionized the management of some complex vascular injuries. The concept of selective nonoperative management in selected patients has become the standard of care. Tested clinical protocols and algorithms can help the physician in the selection of the most appropriate investigation and therapeutic modality.

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OBSTETRICS

Clinical Decision Making in Obstetric Patients

R. ALEXANDER, A. PARATORE

Risk Management in Obstetric Patients

Risk management was defined by Clemens [1] “as the aim is to reduce the frequency of adverse events and harm to patients”.

More extensively, the Royal College of Obstetricians and Gynaecologists defines risk management as “methods for the early identification of adverse events, using either staff reports or systematic screening of records... it is an approach to improving the quality of care which places special emphasis on care episodes with unexpected outcomes” [2].

Conceptually, the process of risk management should follow specific steps:

- Risk identification (identify risk and potential for risk)
- Risk analysis
- Risk control (once the risk has been identified and analysed, we can consider how it might be avoided, reduced, transferred or eliminated by using protocols and guidelines, environmental changes, cultural and attitudes changes)
- Risk funding

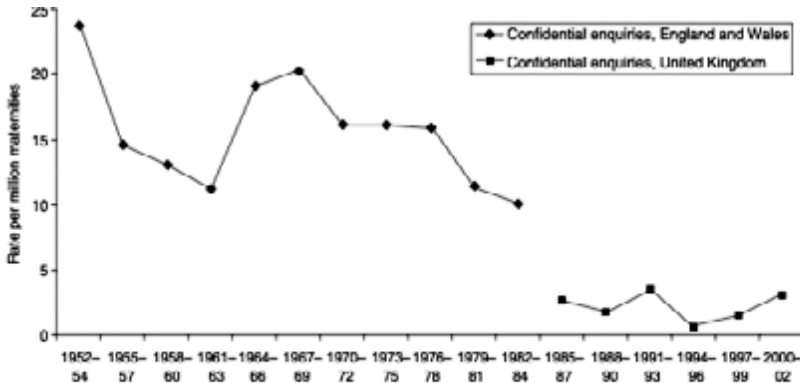
Risk rating and assessment framework for obstetrics [3]

Risk rating and assessment framework for obstetric anaesthesia

Likelihood	5 Insignificant	4 Minor	3 Moderate	2 Major	1 Extreme
A – Almost certain	Venipuncture bruise	Post GA nausea	Post GA vomiting		
B – Likely		Post GA headache Post GA sore throat Inadequate pre-anaesthetic assessment	Spinal headache Severe postop pain		
C – Occasionally			Failed spinal/epidural Difficult intubation Oral damage Inadequate spinal/epidural	Failed intubation Inadequate resuscitation	Failed intubation with failed ventilation
D – Unlikely			Respiratory difficult in Recovery Hypothermia in Recovery Wrong drug/dose	Aspiration pneumonitis	Incompatible transfusion Anaphylaxis
E – Very unlikely				Awareness Air embolism Total spinal Malignant hyperthermia	Maternal death Fetal death Permanent neural damage

Maternal Mortality: Anaesthetic Implications

Clearly, anaesthesia-related maternal mortality rates are improving, with a dramatic reduction in the proportion of anaesthesia-related deaths [4], declining from 11% in the first 9-year time period to around 3% in the most recent [5].



Maternal death rates from anaesthesia for all obstetric or maternity procedures; England and Wales 1952-1984, United Kingdom 1985-2002.

Problems of General Anaesthesia in Obstetrics Related to Physiological Changes in Pregnancy

Maternal dangers linked to general anaesthesia (GA) in obstetrics are typically represented by pulmonary aspiration of gastric contents (known as Mendelson's syndrome), hypoxaemia related to difficult or failed intubation and magnified by physiological changes of pregnancy, multifactorial hypotension (aortocaval compression and regional anaesthesia, possible obstetric haemorrhage, uterine relaxation due to inhalation agents), and awareness [6].

Problems of aspiration of gastric contents and control of gastric acidity and volume

Problems of treating shock in obstetric patients (physiological changes relating pregnancy)

Problems of treating massive blood loss (haemorrhage)

Disseminated intravascular coagulopathy

Preeclampsia and eclampsia (invasive haemodynamic monitoring for severely preeclamptic patients)

Amniotic fluid embolism

Complication of epidural anaesthesia (hypotension, total spinal block, haematoma, infection, postdural puncture headache, prolonged neural block, haematoma, infection)

Cardiorespiratory disease

Respiratory – Importance for Anaesthesia

There is capillary engorgement of the mucous membranes throughout the respiratory tract, causing swelling and may lead to difficulty in visualization of the vocal cords, or to haemorrhage following manipulation of the airway.

- a. intubation
 - mucosal bleeding
 - difficult intubation
- b. respiratory reserve
 - rapid onset of hypoxia*
 - high MRO_2 / low $\text{FRC} \pm$ low PaO_2
- c. rapid gaseous induction
 - $\downarrow$ MAC: $\sim 25\%$ halothane; $\sim 40\%$ isoflurane
 - $\downarrow$ FRC $\rightarrow$ less dilution
 - $\uparrow$ MV $\rightarrow$ rapid increase in depth of anaesthesia
- d. foetal effects
 - maternal respiratory alkalosis and hypoventilation between contraction
 - umbilical/uterine vasoconstriction
- e. $\uparrow$ maternal HbO_2 affinity (relative not absolute, $\uparrow$ DPG & right shifted curve)

Cardiovascular – Importance for Anaesthesia

Patients undergoing spinal or epidural anaesthesia should

- a. be maintained in a lateral tilt position, with left uterine displacement
 - b. be adequately volume preloaded
- Distension of the peridural venous plexus leads to
- a. decreased epidural space volume & local anaesthetic (LA) requirements
 - b. increased risk of intravascular injection or catheter insertion, and subsequent LA toxicity
 - c. increased epidural space pressure, rendering the “hanging drop” technique unreliable.

Regional anaesthesia also attenuates some of the CVS changes which normally accompany labour, excepting those in the third stage which are not due to circulating catecholamines. Thus, epidural anaesthesia is recommended for any patient in whom an increase in myocardial work is undesirable.

Blood Constituents

There is a slight decrease in $[\text{Na}^+]$, $[\text{K}^+]$ and $[\text{Cl}^-]$ albumin, globulins and total protein increase, but their plasma concentrations decrease the normal albumin/globulin ratio of $\sim 1.6/1 \rightarrow 1/1$ at term.

Colloid osmotic pressure progressively decreases, together with the fall in serum albumin. Further decreases in COP occur in the postpartum period, irrespective of the mode of delivery or type of anaesthesia used. Thus, the preeclamptic patient, or those on tocolytic therapy are prone to the development of pulmonary

oedema, despite near normal pulmonary artery occlusion pressure. Changes in plasma protein binding may lead to drug toxicity, due to an increase in the unbound fraction.

Pregnancy leads to a hypercoagulable state, due to

- a. ↑ factors VII, VIII, X, XII (? IX)
 - b. ↑ fibrinogen (I) and FDPs
 - c. ↓ fibrinolytic activity - ↓ levels of plasminogen activators
 - d. ↓ antithrombin III
- increased risk of thromboembolic disease

Aspiration Pneumonia

Several factors increase the risk of aspiration in these patients.

Pregnancy is unique among the risk factors for aspiration as the risk is multifactorial

1. delayed gastric emptying – opioids administered during labour will further delay gastric emptying
2. increased gastric acidity – placental gastrin secretion
3. lower oesophageal sphincter tone is reduced during pregnancy, decreased LOS tone – anticholinergics (atropine, glycopyrrolate) – narcotics
4. increased intragastric pressure – mechanical effects of the uterus (some research have found an increase in the first trimester)

Prevention

1. nil orally – some would argue this increases gastric volume/acidity – prevention of prolonged fasting with regular fluid intake
2. nonparticulate antacids
3. H₂-blocking agents
4. anticholinergic agents – however, these reduce tone of the LOS
5. head-up position
7. avoidance general anaesthesia
8. rapid sequence induction of anaesthesia
10. endotracheal intubation with a cuffed tracheal tube
11. awake extubation
12. alert, well trained recovery room staff

Failed Endotracheal Intubation

This was the leading cause of anaesthetic related maternal mortality.

The result of failure to intubate and ventilate is hypoxaemia, which may eventually lead to brain damage or death.

The incidence of failed intubation in a general surgical population is approximately 1: 2,303 ~ 0.04% and in an obstetric population 1: 300 ~ 0.33%.

Reasons for this include a broad spectrum of anatomical and physiological changes which occur in women during pregnancy such as

- a. the presence of full dentition
- b. increased airway oedema especially in preeclamptic patients
- c. enlargement of the breasts may impact on the ability to place a laryngoscope blade into the mouth due to increased difficulty in navigating the blade handle
- d. failure to allow adequate time for paralysis with suxamethonium
- e. incorrectly applied, or overenthusiastic cricoid pressure may distort the larynx.

There is an increased incidence of difficult/failed intubation during general anaesthesia in the obstetric patient population compared with the general surgical population [7]. Recognition of this fact has led to a decreased incidence of maternal deaths.

Decision Making

Airway Assessment

Assessment of the airway is made using several scoring systems such as Mallampati, clinical assessment: restriction in mouth opening, short neck and receding mandible, prominent teeth and neck mobility. Investigations may include laryngoscopy, X-ray and CT scan.

1. When difficult intubation is suspected in airway management, if feasible under these circumstances, the procedure should be performed under regional anaesthesia.
2. Appropriate airway management equipment should always be available.
3. Management depends on whether surgery is elective or urgent and whether a difficult airway is predicted. Furthermore, the condition of the foetus (distressed or not) may influence the anaesthetic approach.

Obstetric Haemorrhage

Delay in dealing with pelvic haemorrhage only accentuates the problem. Hoping that haemorrhage will spontaneously cease is futile and steps should be taken immediately.

Peripartum haemorrhage includes a wide range of pathophysiological events having more than one aetiology for haemorrhage.

Unexpected obstetric haemorrhage is a major challenge to the obstetric anaesthesiologist. A bleeding parturient is difficult to manage because of inadequacy in assessing blood loss and coagulation status in the fast-changing scenario, complicated by supine hypotensive syndrome in term patients and an increased risk for pulmonary aspiration of gastric contents.

Obstetric haemorrhage is a leading cause of maternal and foetal morbidity and mortality worldwide. It is the major cause of maternal mortality, significant bleeding occurs in ~ 3% of all pregnancies [8]

Because approximately 600-700 ml blood flows through the placental intervillous spaces each minute, obstetric haemorrhage can rapidly result in severe signs of shock.

Precaution in peripartum haemorrhage

Anticipation of peripartum haemorrhage is vital in the management of high-risk parturients.

1. The blood bank should be informed.
2. Haemoglobin, platelet count, platelet volume, PT, aPTT, and baseline fibrinogen level should be tested and measured in such patients.
3. Provision and preparation for invasive monitoring of the circulation should be done in advance.

Initial resuscitative measures for the bleeding parturient:

1. Establish two venous access sites using large-bore cannulae (e.g. 6 to 8.5 French) with emergency infusion devices, or peripheral intravenous catheters (larger than 16G).
2. Administer appropriate fluids.
3. Place the patient in the lateral decubitus position, or provide left uterine displacement using a right pelvic wedge.
4. Administer oxygen by face mask.

The general approach to anaesthesia is the same, regardless of the cause of bleeding. The patient should be quickly assessed for cardiovascular and respiratory compromise and initial resuscitation commenced. The choice between general and regional anaesthesia will then depend on a balance of risks involving the degree of cardiovascular stability, consciousness level and coagulation status of the patient, and the clinical urgency of the situation.

Steps in management of obstetrics haemorrhage:

1. restoration of circulating blood volume
2. correction of impaired blood coagulation
3. treating the causes of haemorrhage

Guideline update

These guidelines summarize current opinions regarding the management of massive blood loss and update previous recommendations.

Therapeutic goals:

1. Maintenance of tissue perfusion and oxygenation by restoration of blood volume and haemoglobin
2. Arrest of bleeding by
 - treating any traumatic, surgical or obstetric source
 - judicious use of blood component therapy to correct coagulopathy

Pregnancy-Induced Hypertension

Management of the Preeclamptic Patient

The anaesthetist has a crucial role to play in the management of the preeclamptic parturient [9].

The chief role of the anaesthetist is to provide safe labour analgesia and anaesthesia for caesarean section. Anaesthetists also play a key role in resuscitation and intensive care management, including provision of invasive monitoring and limitation of cardiorespiratory, cerebral and renal complications.

The therapy of choice includes the use of magnesium for prevention of seizures and antihypertensive medications to decrease severe hypertension.

Regional anaesthesia is the mainstay of therapy both in labour and for caesarean section, in the absence of contraindications. The value of a regional approach to the analgesic and anaesthetic management of preeclamptic patients, after appropriate attention to possible effects of the disease on the coagulation system, has only grown stronger; the appreciation of the airway narrowing, the concern for the increased systemic and cerebral pressures accompanied with intubation and extubation, and the benefit of assessing an awake, nonsedated patient to evaluate the severity of the disease all serve to augment the benefit of regional techniques in this patient population.

Management of the preeclamptic parturient includes adequate foetal monitoring, management of hypertension, prevention of seizures, active management of labour, maintenance of uteroplacental perfusion, and provision of adequate analgesia for labour and safe anaesthesia for operative delivery. Initial laboratory investigations should include a platelet count, liver function tests, a urine test for proteinuria, serum blood urea nitrogen, and creatinine.

Conclusion

Fifty years ago...

The preface of the first Report of the Confidential Enquiries 50 years ago drew attention to the fact that anaesthesia was a major primary or associated factor in maternal death. The predominant cause of anaesthetic death used to be related to airway management. One of the key ways of avoiding airway management problems has been the increased use of regional anaesthesia.

Other causes of death:

- lack of multidisciplinary cooperation
- lack of appreciation of the severity of the illness
- lack of perioperative care
- the management of haemorrhage

Anaesthesia: Key Recommendations

Invasive monitoring via appropriate routes should be used, particularly when the cardiovascular system is compromised by haemorrhage or disease. Invasive central venous and arterial pressure measurement can provide vital information about the cardiovascular system. Samples for arterial blood gas estimation should be taken early and any metabolic acidosis should be taken seriously. Intensive care beds may not be available in an emergency.

Practice Guidelines for Obstetric Anaesthesia

Guidelines are recommendations that assist the anaesthetist in making decision about anaesthetic management of pregnant patients during labour, nonoperative delivery, operative delivery and selected aspects of postpartum care and analgesia [10].

Because the availability of anaesthesia resources may vary, members are responsible for interpreting and establishing the guidelines for their own institutions and practices. Anaesthesiology groups should adapt the guidelines to their own particular situation and write policies they believe are appropriate for their setting.

Perianaesthetic Evaluation

History and Physical Examination

The anaesthesiologist should conduct a focused history and physical examination before providing anaesthesia care. This should include, but is not limited to, a maternal health and anaesthetic history, a relevant obstetric history, a baseline blood pressure measurement, and airway, heart, and lung examined, recognition of significant anaesthetic or obstetric risk factors and when a neuraxial anaesthetic is planned or placed, the patient's back should be examined. The literature reports certain patient or clinical characteristics that may be associated with obstetric complications; these characteristics include, but are not limited to, preeclampsia, pregnancy-related hypertensive disorders, HELLP syndrome, obesity and diabetes.

Platelet Count

A specific platelet count predictive of neuraxial anaesthetic complications has not been determined. The literature suggests that a platelet count is clinically useful for parturients with suspected pregnancy related hypertensive disorders and a platelet count reduces maternal anaesthetic complications for patients with suspected coagulopathy and for other disorders associated with coagulopathy.

Blood Type and Screen

The decision whether to order or require a blood type and screen, or a crossmatch, should be based on maternal history, anticipated haemorrhagic complications (placenta accreta in a patient with placenta praevia and previous uterine surgery). Good blood pressure control in proteinuric hypertension is required to avoid cerebral haemorrhage.

Perianaesthetic recording of the foetal heart rate

The foetal heart rate should be monitored before and after administration of neuraxial analgesia because anaesthetic and analgesic agents may influence foetal heart rate pattern.

Aspiration Prevention

Clear Liquids

The oral intake of modest amounts of clear liquids may be allowed for uncomplicated labouring patients (up to 2 h before induction of anaesthesia). However, patients with additional risk factors for aspiration (e.g. morbid obesity diabetes, difficult airway) or patients at increased risk for operative delivery may have further restrictions of oral intake.

Solids

Solid foods should be avoided in labouring patients. The patient undergoing elective surgery should undergo a fasting period for solids of 6-8 h depending on the type of food ingested because of the oral intake of solids increases maternal complications.

Antacids, H₂ Receptor Antagonists, and Metoclopramide

Before surgical procedures (i.e. Caesarean delivery) the timely administration of nonparticulate antacids, H₂ receptor antagonists, and Metoclopramide is clinically useful for aspiration prophylaxis.

Because of the relationship between reduced gastric acidity and the frequency of emesis, pulmonary aspiration, morbidity or mortality in obstetric patients who have aspirated gastric contents, the literature suggest that H₂ receptor antagonists are effective in decreasing gastric acidity in obstetric patients and supports the efficacy of preoperative nonparticulate antacids (e.g. sodium citrate, sodium bicarbonate) in decreasing gastric acidity during the peripartum period and the efficacy of Metoclopramide in reducing peripartum nausea and vomiting.

American Society of Anaesthesiologists Obstetric Anaesthesia Guidelines

The 10 guidelines are as follows [11]:

1. Regional anaesthesia should be initiated and maintained only in locations in which appropriate resuscitation equipment and drugs are immediately available to manage procedurally related problems.
2. Regional anaesthesia should be initiated by a physician with appropriate privileges and maintained by or under the medical direction of such an individual.
3. Regional anaesthesia should not be administered until (1) the patient has been examined by a qualified individual and (2) maternal and foetal status and progress of labour have been evaluated by a physician with privileges in obstetrics who is readily available to supervise labour and manage obstetric complications.
4. Intravenous infusion established before the initiation of regional anaesthesia and maintained throughout the duration of the regional anaesthetic.
5. Regional anaesthesia for labour and/or vaginal delivery requires that the parturient's vital signs and the foetal heart rate be monitored and documented by a qualified individual. Additional monitoring appropriate to the clinical condition of the parturient and the fetus should be employed when indicated. When extensive regional blockade is administered for complicated vaginal delivery, the standards for basic anaesthetic monitoring should be applied.
6. Regional anaesthesia for Caesarean delivery requires that the standards for basic anaesthetic monitoring be applied and that a physician with privileges in obstetrics be immediately available.
7. Qualified personnel, other than the anaesthesiologist attending the mother, should be immediately available to assume responsibility for resuscitation of the newborn.
8. A physician with the appropriate privileges should remain readily available during the regional anaesthetic to manage anaesthetic complications until the patient's post-anaesthesia condition is satisfactory and stable.
9. All patients recovering from regional anaesthesia should receive appropriate postanaesthesia care. After Caesarean delivery and/or extensive regional blockade, the standards for postanaesthesia care should be applied.
10. There should be a policy to assure the availability in the facility of a physician to manage complications and to provide cardiopulmonary resuscitation for patients receiving postanaesthesia care: trays and drugs.

Case reports

Case report 1

A 30 year old parturient was admitted in labour to the delivery suite in labour at 37 weeks. She had had a normal pregnancy with no complications or medical history.

13:00. She was reviewed for vaginal bleeding and her cardiotocograph showed signs of foetal distress. She received a spinal anaesthetic and surgery was uneventful. She had a healthy baby boy.

20:00 The patient had a seizure which resolved before any medication was administered. She was somnolent, tachypnoeic with a respiratory rate of 15 breaths per minute, tachycardic (heart rate of 100 bpm) and normotensive. Oxygen was administered via a facemask at 4L/min. Her blood results showed her to have a normal blood (11.7 g/dl) and platelet count (217,000 mm³). Her fibrinogen level was 800mg/dl, D-dimer 3572 mcg/l and antithrombin III 104%. The obstetricians decided to withhold initiating the protocol for preeclampsia as the fit resolved. There was no evidence of bleeding despite the tachycardia, arterial blood gases were not taken as her oxygen saturation was 99% on 4 l/min.

22:00 She had a second seizure which was controlled with administration of diazepam 5mg iv and an infusion of magnesium sulphate and phenytoin was started following loading doses. A repeat blood count revealed a fall in platelet count to 150. She was normotensive and had a regular heart rate.

24:00 The patient had a third seizure in spite of her medial therapy and remained normotensive.

A differential diagnosis of the following conditions was made:

Hypo- or hyperglycaemia, hyponatraemia, hypokalaemia, pheochromocytoma, haemolytic uraemic syndrome in pregnancy, meningitis or encephalitis, intracranial haemorrhage, stroke or eclampsia.

A neurological examination revealed clonus and upward plantar reflexes with brisk reflexes in her lower limbs. Further blood tests excluded abnormal urea and electrolytes and her laboratory-measured blood sugar was normal. She was sent for a computer tomography of the head, which was normal. She became rousable over the next few hours and no more fits occurred.

Over the next 2 days her blood results showed a picture of anaemia, elevated liver enzymes and low platelets (HELLP syndrome). Her haemoglobin count fell to 8.0 g/dl and her platelets to 60. Her serum lactate dehydrogenase rose to 1009 and her ALT to 356 and AST to 145. By day three postoperative her platelet count had returned to normal and her liver enzymes fell to normal levels. She was weaned of the magnesium and phenytoin and no more fits occurred. A diagnosis of eclampsia and HELLP syndrome was made and she made an uneventful recovery and was discharged 6 days after her admission.

Fulminant eclampsia and HELLP syndrome have been described up to 7 days post delivery. Every obstetric department should have robust protocols for the treatment of preeclampsia, which should preferably be based on the national guidelines. Clinical risk drills should be conducted regularly so all the medical and

midwifery staff are up to date with the current hospital drug doses and administration as well as advanced life support. This patient made a complete recovery thanks to the prompt response of the staff.

Case Report 2

A 25-year-old woman had a caesarean section under general anaesthesia for failure to progress and gave birth to a healthy baby boy at 23:30. She was fit and healthy but complained of having a cough for a few days before admission. The anaesthetist was asked to review her the next morning at 08:30 because the midwife was worried with her condition and was unable to have the obstetric resident review her during the night due to the busy shift.

On entering the room it was clearly obvious this woman was not well. She was somnolent only being aroused when stimulated and had a respiratory rate of approximately 43 breaths per minute and her chest expansion was shallow. Examination showed equal chest movements with no tracheal shift. Percussion was dull over the right middle and lower lobes of her chest and she had bronchial breathing over that area. Her saturation was 87% on air. She was receiving no oxygen therapy. She had a sinus tachycardia and was normotensive but had a capillary refill time of 5 seconds with cool peripheries. Her abdomen was soft and there was no vaginal evidence of bleeding. Her arterial blood gas analysis on $O_2 10$ l/min showed severe hypoxia and a respiratory alkalosis. Her pH was 7.31 pO_2 7.6 kPa, PCO_2 3.6 kPa, HCO_3 21.6 kPa and a base deficit of 5.

Arrangements were immediately made to transfer her to the intensive care unit where she was intubated and ventilated following a short period of continuous positive airway pressure with no improvement.

A differential diagnosis was made of pulmonary embolism or collapse and consolidation secondary to chest infection. A ventilation perfusion scan was negative and chest X-ray confirmed basal collapse on the right side and shadowing on the left lower lobe.

For the next three days she required up to 60% O_2 and PEEP at 10cms H_2O to maintain her pO_2 above 10 kPa. Her oxygenation improved with physiotherapy and antibiotics sensitive to staphylococcus which was grown from a sputum sample. She required 5 litres of crystalloid directed by oesophageal noninvasive cardiac output monitoring indicating her state of hypovolaemia on admission to the ICU but then just required maintenance fluids to produce an adequate urine output and a normal pH and base excess.

She was extubated on day 4 postoperatively and discharged back to the delivery suite for high dependency monitoring still requiring O_2 at 4-6 l/min. By day 6 she was on room air and eventually made a full recovery to be discharged 10 days after her caesarean section.

This case report highlights just how quickly parturients can deteriorate and this is one of the reasons for the drive in the UK to centre obstetric units in hospitals with on-site ICU or HDU facilities. Where this is not possible then robust procedure and protocols must be in place for early transfer with good communication. The

use of early warning scoring systems, of which many are published, is vital for non-medical staff to be able to detect sick patients and appropriate referrals to be made especially in busy units where there is greater dependency on the midwifery staff to look after patients postoperatively.

This patient should have been reviewed during the night and the anaesthetic resident involved in her care much earlier.

Conclusions

Significant changes have been witnessed in the obstetric and anaesthetic care of pregnant patients, foetuses, and newborns, particularly in the realms of preeclampsia and peripartum haemorrhage.

Pregnancy and anaesthesia for delivery has never been safer than it is today. Maternal mortality has decreased thanks to increased use of regional anaesthesia and decreased use of GA, improved aids for difficult intubation, more precise respiratory and cardiovascular monitoring. However, if it is possible, we must do better. Even a few hundred deaths a year are tragic, in that they occur in young women with many years of life ahead of them and families dependent on their presence. We may never reduce maternal mortality to zero because some women develop severe, often life-threatening, illnesses that are pregnancy related. But anaesthetic mortality is rarely disease related. It occurs because of lapses in vigilance, technique, or judgment. It would be wonderful if the next survey showed that although some women tragically lost their lives because of a decision to have a child, none of these deaths were the result of anaesthesia. We still have work to do.

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Organization of Obstetric Services

R. ALEXANDER, A. SAXENA

Aims

The aims of the obstetric anaesthetic service are:

- To provide the highest quality analgesia and anaesthesia to mothers before, during and after the delivery of their baby.
- To support and advise mothers, midwives and obstetricians antenatally and to contribute to the planning of care for high risk cases.
- To assist with the management of mothers requiring urgent medical treatment including resuscitation and high dependency and intensive care and to arrange for transfer of very sick patients with special needs to an appropriate centre.

According to the latest maternity statistics, 647,847 babies were born in the UK last year. Of these around 24% were born by Caesarean section (CS). The main reasons for increase in Caesarean section rates (CSR) are previous CS and maternal requests. The estimates for France suggest rates comparable to England and Scotland up to 1995. In Italy, CSR were comparable in 1980 at 11% but rose dramatically to 22% in 1995. These numbers support the need for a more robust approach to the management of anaesthetic services.

Clinical Services

- The anaesthesia team is based in the labour ward and theatre area and provides input in all areas of the delivery suite.
- There should be a named senior anaesthetist with responsibility for organizing and auditing obstetric services in hospitals providing these services who should be allocated sessions for the administrative work involved.
- Consultant obstetric units are expected to provide a 24-hour service for the analgesic, anaesthetic and resuscitation requirements of women admitted from the community or other hospitals with conditions associated with child-birth.
- There should be induction programmes for all new members of staff including locums. Locums should be assessed and vetted prior to undertaking unsupervised work.
- A trained Resuscitation Team should be available.
- There should be a system for multidisciplinary critical incident reporting in

the maternity unit that should involve the obstetric anaesthetic team.

- There should be a named senior anaesthetist with responsibility for each scheduled section lists.
- A resident anaesthetist should be provided for all consultant units. Where a resident anaesthetist is not provided in smaller consultant units, a non-resident anaesthetist should be available within thirty minutes between a decision to operate and provision of anaesthesia for an instrumental or operative procedure. Where an epidural analgesic service is provided an anaesthetist of adequate experience should be immediately available to the obstetric service throughout the 24 hours.

It is important to acknowledge and deal with problems associated with the provision of anaesthetic services on multiple sites within a hospital or exceptional and unpredictable changes in workload.

Efforts should be made to have effective communication between staff within the maternity hospital or other regional centres and to avoid failure to recognize the relevance of medical disease, poor data collection in the antenatal period or lack of organized route of access to an anaesthetic opinion antenatally.

This can be achieved with guidelines available to obstetricians and midwives on conditions requiring antenatal referral to the anaesthetist and a system to ensure that such women are seen and assessed by a senior anaesthetist within a suitable time frame.

This preanaesthetic clinic is aimed at pre-planning for labour and delivery and reviewing women during the antenatal period who may have clinical conditions with possible anaesthetic implications.

While these recommendations may be achieved in larger district general and teaching hospitals with over 3,500 deliveries a year the problem arises with the provision of service in the smaller community hospitals. In European countries these small units thrive and local populations demand such a local service. However, the clinical risks for this patient population still exist and therefore robust protocols and auditing must be in place to identify which women should be transferred to larger units with resident anaesthetic cover. The political health scene in the UK is rapidly changing with the government announcing in September that there should be a centralization of specialized skills in larger centres and local community hospitals dealing with just minor-to-intermediate surgery and medical admissions.

Anaesthetic Clinical Services

- General and regional anaesthesia for emergency and planned obstetric procedures are probably the most important among the services provided.

Although 24-h consultant cover and resident anaesthetist presence are quite important, of vital importance are other members in the paramedic team. A suitably-trained senior member of either nursing, midwifery or operating department staff with overall responsibility for the safe running of obstetric theatres

ensures that current standards in all aspects of theatre work are met. This operating room manager should be responsible for maintaining communication with staff groups, and ensuring competent staffing and suitable equipping of all theatres.

Urgency of CS should be categorized by a system agreed locally by obstetricians, anaesthetists, theatre staff and midwives, and the anaesthetist should be informed about the category of CS. British national guidelines recommend that the time from decision to delivery at CS with foetal compromise should not exceed 30 min. Life threatening maternal emergencies such as massive blood loss require a prompt response time.

As assigned to the four categories of urgency, the proportion of CS procedures in the UK were:

1. an immediate threat to the life of the mother or foetus (16%)
2. maternal or foetal compromise that was not immediately life threatening (32%)
3. the mother needed early delivery but there was no maternal or foetal compromise (18%)
4. delivery was timed to suit the mother and the staff (31%)

Clinical features thought to be consistent with category 1 above were placental abruption, cord prolapse, uterine rupture, active bleeding, placenta praevia, intra-partum haemorrhage or presumed foetal compromise.

In the UK where a 24-h epidural service is offered, the time from the anaesthetist being informed about an epidural until being able to attend the mother should not normally exceed 30 min, and must be within 1 h except in exceptional circumstances. It is also mandatory to have a trained midwife for monitoring the progress of the mother and foetus during the period of labour analgesia. In addition, epidural analgesia should not be used unless a trained obstetric team is immediately available in the same hospital to treat emergencies. The provision of a 24-h epidural analgesia service in Italy is not universally available. These recommendations may then not apply in these circumstances as an anaesthetist may not be available to provide such a service.

In the busier units (i.e. one or more of the following: 5000 deliveries/year, epidural rate >35%, CSR >25%, tertiary referral centres / high proportion of high risk cases) it may be necessary to provide extra anaesthetic cover during periods of heavy workload in addition to the supervising consultant. Women who require CS should take preference over those who request epidural analgesia for labour.

A comprehensive obstetric analgesic service needs to be provided in larger hospitals. Smaller units not offering a comprehensive service must state the level of service provided.

- Antenatal education is of prime importance. There should be a detailed unbiased explanation about pain relief and operations under regional and general anaesthesia. This allows explanation of key facts in a low-stress environment. It is still necessary to give the patient an explanation at the time of the proposed procedure with appropriate documentation of the same.

Information about obstetric anaesthesia and analgesia is of utmost importance to enable women to make informed decisions about their care. They require access

to evidence-based information to enable them to make these decisions. For consent to be morally and legally valid, the patient must receive sufficient information to make an informed decision. Changing legal and public expectations demand that we adapt our current practice and improve the accuracy and timing of information provided.

Reasons for failure could be non-attendance at antenatal classes, inadequate availability of patient information leaflets, inadequate availability of patient information leaflets in foreign languages, inadequate availability of patient information in other media forms or insufficient or non-availability of interpreter services.

- The anaesthetist is responsible for ongoing regional analgesia in labour and must be able to assess the mother as required.
- Often an obstetric anaesthetist is involved in teaching midwives the art and science of postoperative and recovery skills, risk factors associated with women who have medical problems and care of the critically ill mother in HDU/ITU. The midwife must be trained to an agreed standard in regional analgesia and be aware of potential complications and their management as well as able to assess and document sensory block height. Learning difficult intravenous cannulations, management of epidurals and the latest resuscitation skills form an important part of their continuation of professional development and training.
- Active involvement in resuscitation of pregnant and post partum women, and of neonates if the neonatal paediatric service is unable to attend, is imperative. Emergency resuscitation equipment and a cardiac arrest procedure must exist for obstetric patients and be known to all staff. In a recent British survey 23% of hospitals provide neonatal intensive care facilities. The median CSR in these hospitals was 21% compared with 18% in units without such facilities.
- Multidisciplinary advice and care for patients requiring intensive care management as in major organ failure, clotting disorders and severe haemorrhage should be available.
- Pre- and post-procedure visiting of patients for assessment and explanation, early detection of complications and audit of quality and satisfaction is required.
- Written notes and records of all visits and clinical procedures should be undertaken. These should be legible, contemporaneous to every possible extent, complete and retrievable.
- Consenting the patient for any procedure or treatment requires:
 - 1) Provision of adequate information and its understanding by the patient.
 - 2) Capacity and competence to weigh up consequences and alternatives and come to a decision.
 - 3) Allowing adequate time for the process.
 - 4) Voluntariness i.e. without any coercion.

There is no difference between verbal and written consent except that the latter provides concrete evidence in case a dispute arises, specially if taken in the presence of a third party, e.g. midwife.

When applied to informed consent, each patient should be given the informa-

tion that she herself would want and not what the doctor thinks she needs.

The laws may differ from country to country but a recent judgment in the House of Lords in the UK suggested that a doctor may now be found negligent with respect to provision of adequate information to the patient even if this failure had no effect on the patient's decision to undergo treatment.

Obtaining consent in obstetrics has special considerations due to the following facts:

- Even though not all women end up having regional analgesia or anaesthesia for labour or delivery, they should be informed well ahead about these options as during the labour they are exhausted, in pain or under the effect of analgesic drugs which incapacitates the decision making process.
- Even though the risks and benefits of any procedure to the foetus are explained, they should not interfere with the patient's right to make an autonomous decision about her own care, even at the expense of her unborn child.
- The views of the partner / a relative are to be given due importance even though the consent is ultimately given by the woman in question.
- Patients with other spoken languages have as much right to information and consenting as any local patients. It is best to have an official interpreter although the partner may act as a translator in an emergency.
- Involvement as a part of multidisciplinary team in the making and updating of local management protocols and guidelines is another important service as not only do they serve as an efficient method of risk management and maintaining good practice, they also ensure uniformity in adherence to best practice and are used for teaching or training of staff.

Protocols should be based on evidence rather than general consensus of the clinicians to avoid flaws and criticism in the eyes of the law, but as evidence can be far from good or sometimes inapplicable to local conditions, sound judgment and collaborative effort is needed to draw conclusions from it.

As these documents become legal tools, they need to be stored safely even when obsolete. A potential exposure to criticism comes from the facts that they restrict clinical freedom and by their mere existence may indicate any other management as suboptimal, thereby deterring some clinicians from making and following them.

All obstetrics anaesthetic departments should have agreed and regularly updated guidelines on the following topics:

- antenatal referral to the anaesthetist (e.g. maternal cardiac disease, diabetes, severe asthma)
- major haemorrhage
- preeclamptic toxemia
- failed intubation drill
- management for regional anaesthesia including regional blocks for analgesia and regional blocks for surgery
- unintentional dural puncture
- severe hypertension
- total spinal anaesthesia
- admission and discharge criteria from delivery suite to HDU.

Teaching and training responsibilities

- These include well-structured training and assessment of the junior anaesthetists, midwives, other paramedics like operating department practitioners / anaesthetic technicians specially in this era when enforcement of time directives could be decreasing clinical exposure. Regular drills should be conducted for emergencies such as maternal collapse and massive haemorrhage to ensure knowledge of the whereabouts of resuscitation equipment and drugs and that the system works smoothly when needed.

Audits

- There are a number of potentially serious complications that can occur after anaesthetic intervention during pregnancy. It is therefore important to evaluate current practices and implement changes. The national / local guidelines need to be audited for analysis of any shortcomings and reassessment should be done in due course of time to complete the ‘audit loop’.

Risk Management

- The anaesthetic risk could be due to a human error or due to working in a different environment (communication problems between medics and paramedics in theatre / labour ward) or system based where simple preventable errors present mainly due to inherent flaws in the system.

Risk management is all about avoiding risky practices, analyzing adverse outcomes and devising further strategies to prevent them, thereby reducing the negative clinical and financial outcome. A proactive approach using a well designed critical incident reporting system and audits is a more effective means of improving service than the traditional reliance on outcome studies.

Stress Management Services

- It is absolutely essential to have stress management services in this high risk area of medical practice. The very fact that we deal with mother and foetus at a time when they are both physiologically stressed makes obstetric anaesthesia a tough practice at times coupled by the volume of work during busy shifts or miscommunication between different groups of professionals.

Communication with all levels of staff and a non-judgmental approach is essential.

Post-crisis management includes providing counselling through the review of records and the identification of any legal and/or financial treatment to the individual or to the hospital.

Support Services

- Haematology (including coagulation studies) and biochemistry services must be available to provide rapid analysis of blood and other body fluids and to make available blood and blood products for transfusion without delay and in sufficient quantities. A supply of uncrossmatched O Rh-ve blood or screened and group-confirmed blood must always be available in the delivery suite for emergency use. Rapid efficient communication channels must exist to avoid delay in the event of massive haemorrhage. While no delay is acceptable in the provision of packed red cells, arrangements should be in place for the quick availability of other products such as platelets and fresh frozen plasma and cryoprecipitate.
- There must be provision for rapid availability of consultation with other specialists experienced in non-obstetric aspects of pregnancy such as cardiac disease and diabetes. At all times there should be a trained paediatrician available should the need arise.
- There must be rapid availability of imaging services.
- All maternity units must be able to provide high dependency care for patients. This may include facilities for invasive monitoring, transfusion of blood and blood products, foetal monitoring and short term ventilation prior to transfer to an intensive care unit (ICU). This also helps providing intensive care to the sick mother within the maternity unit. Midwifery staff deputed to look after postoperative patients should be specifically trained in monitoring, care of the airway and resuscitative procedures and should be supervised by a defined anaesthetist at all times. Non-availability of appropriate monitoring aids or adequate number or quality of trained staff should necessitate the transfer of the patient to the nearest HDU available.
- Large units and those specializing in the care of the high risk mother should have ICUs for the mother as well as for the neonate on the same site and provision for high dependency care within the obstetric unit. It is anticipated that whilst in the ICU, patients will continue to receive obstetric care from the obstetric team involved.

In smaller and isolated maternity units the requirements for ICU may necessitate transfer of the patient to another hospital. Such maternity units should have well trained anaesthetic staff, paramedics, portable monitors with the facility for invasive monitoring and definitive arrangements with a specific ICU to facilitate the rapid transfer of patients when necessary so that continuity of care is achieved with regard to treatment decisions and information given to relatives. The same applies to the availability of neonatal ICU facilities.

Particular points to be noted are the physiological changes in pregnancy, risks to foetus and need for fetal monitoring, requirements of partner and family, the midwifery care required and associated psychological problems.

The CEMACH (Confidential Enquiry into Maternal and Child Health) reported the direct maternal deaths resulting from obstetric complications to be 27% in 2000-2 and indirect deaths due to previous disease or disease developed during

pregnancy to be 40% of reported maternal deaths. The leading causes were cardiac, thromboembolic and haemorrhagic cases. One needs to ensure the availability of adequate resources to handle complicated cases or refer them to the nearest specialist centre available, in time. Expertise in anaesthesia is needed for patients with conditions like cardiomyopathies who may need specialized care throughout the pregnancy with special procedures like cardiac interventions. Those with morbid obesity may need special beds, surgical and anaesthetic equipment, those with eclampsia/preeclampsia may need specialist drugs, investigations from time to time and emergency delivery. Those with diabetes may need aids for strict control of blood glucose apart from all these cases needing expertise and equipment for difficult intubation, postoperative high dependency facilities as well as neonatal resuscitation for the newborn.

Premises

- There should be a dedicated anaesthetic office on or close to the labour ward with adequate accommodation for consultant and trainee anaesthetists and their support staff.
- A dedicated operating theatre must be available at all times for obstetric anaesthesia.

Where the size of the unit or the nature of the work requires it, a second theatre should be available for concomitant emergencies and control of infection contingencies (e.g. HIV and hepatitis). Theatres should ideally be in close proximity to the delivery suite.

They should be equipped with adequate gas supply, adequate monitoring and operating table for safe conduct of surgery, warming devices, aids for difficult intubation and scavenging for anaesthetic gases and access to resuscitation equipment.

Recognizing the importance of the recovery period, changes related to pregnancy and the requirements for the neonate is vital.

- An appropriately equipped post anaesthetic recovery unit of adequate size and staffing for the work of the unit must be available within or close to the labour ward.

All patients must be observed on a one-to-one basis by an anaesthetist and other appropriately-trained members of staff until they have gained airway control and cardiovascular stability, and are able to communicate. The recommendations by Association of Anaesthetists of Great Britain and Ireland and the Obstetric Anaesthetists' Association for recovery are as follows:

- oxygen outlet and breathing system for 100% oxygen administration, electrical sockets, pulse oximeter, ECG monitor, suction unit, blood pressure measurement for each bed
- easily available disposables (IV cannulas, giving sets, tape, blood test bottles, IV fluid)
- for the area as a whole – defibrillator, emergency drug box, intubation equipment, telephone and/or emergency buzzer

- for all staff in the area – training in recovery care and training in cardiopulmonary resuscitation. Minimum nursing ratio of one-to-one (recovery) and one to two (HDU) at all times, available 24 h
- for all women with a live infant, facilities for breast feeding (or use of breast pump) should be available

Discharge from the recovery area should be in accordance with an agreed protocol. If ICU facilities are not on site, high dependency facilities must be available in the obstetric hospital.

Conclusions

The delivery of a first-class obstetric service depends on the integration and performance of multiple facets of team work. No one specialty has overriding care or duty to the patient. Continuing education and service provision are essential.

Suggested Reading

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PAEDIATRIC ANAESTHESIA

Clinical Decision Making in Paediatric Anaesthesia

P. BUSONI

Decision making is the cognitive process leading to the selection of a course of action among variations. Every decision-making process produces a final choice. Decision making is said to be a psychological construct. This means that although we can never “see” a decision, we can infer from observable behaviour that a decision has been made. Therefore, we conclude that a psychological event that we call “decision making” has occurred. It is a construction that imputes commitment to action: i.e. based on observable actions, we assume that people have made a commitment to perform the action. If the environment is predictable and routine, some decisions and actions can be relegated to an almost automatic level. In contrast, when there is uncertainty, a sustained level of vigilance and attention may be required. At the highest level of cognitive function we can make a decision to monitor our decision-making process: this is meta-cognition [1]. The spectrum of decision-making in medicine runs from simple to complex and is related to the level of uncertainty. There are a variety of tasks with varying degrees of certainty.

In anaesthesiology, there is a variable set due to the variety of settings in which anaesthesiologists work: preoperative clinics, the operating room, recovery room, labour and delivery, the hospital wards, acute and chronic pain clinics, out-patient departments and others. In each setting there are differing levels of uncertainty. Anaesthesiologists often face added uncertainty and task complexity that results from working in more tightly coupled teams, as well as from the influence of external organisation factors.

Decision making in anaesthesiology should teach the resident or relatively inexperienced practitioner to approach clinical problems in a logical, stepwise manner through the use of algorithms, or decision trees. Each algorithm outlines the decision-making process and guides the anaesthesiologist through five major steps: (1) preoperative preparation; (2) preparation for delivering the anaesthetic; (3) induction of anaesthesia; (4) maintenance of anaesthesia, and (5) postoperative management. The cognitive continuum of decision making runs from informal/intuition at one end to calculation/analytical at the other [3].

One thing we do know about decision making is that experienced clinicians perform better than novices, i.e. practice at clinical decision making appears to improve performance [1]. In many circumstances, this is due to intuitive heuristic approaches. In psychology, heuristics are simple and efficient rules which have been hard-coded by evolutionary processes or learned and proposed to explain how people make decisions, come to judgments, and solve problems when facing

complex problems or incomplete information. These rules work well under most circumstances, but in certain cases they lead to systematic cognitive bias. Bias is a prejudice in a general or specific sense, usually in the sense of having a preference for one particular point of view or ideological perspective. Generally, such heuristics are effective, but occasionally they fail. Heuristics may be influenced by a variety of cognitive biases. A cognitive bias is any of a wide range of observer effects identified in cognitive science and social psychology including very basic statistical, social attribution, and memory errors that are common to all human beings. For example, the fixation errors, a form of anchoring bias, have been well described in anaesthesiologists [4].

In paediatric anaesthesia there are often too many variables or unknowns in the clinical situations, too many ethical and financial restrictions, or too many other resource limitations to ever allow a simple quantitative approach to guide each clinical decision [5]. For example, the safety and efficacy of approximately one third of all paediatric medications in use have not been established in children [6]. The phrase “therapeutic orphan” was used to describe children in 1963 by Henry Shirkey [7]. There had been little stimulus for pharmaceutical companies to study drugs in children because of the complexity of such trials and the small financial return. Furthermore, the assumption that children with diseases or conditions similar to adults respond similarly has perpetuated the use of medications approved in adults but which may be hazardous in children, and frequently without the appropriate studies in the paediatric population. The younger the age groups, the more likely the lack of information is. However, where information is incomplete, where prospective, randomized, double-blind, multi-centre clinical trials do not exist, the clinical imperative to diagnose and treat always remains.

Decision making is a critical area in anaesthesia and important in all disciplines in medicine. Besides basic training in formal decision-making we need to ensure that undergraduates and postgraduates have adequate training in critical thinking, problem solving, and a working understanding of the multiple cognitive and affective biases to which they might be vulnerable. What is required is a closer collaborative approach. For example, paediatricians frequently lack adequate information about preoperative management and believe that their participation is neither respected nor appreciated by anaesthesiologists or surgeons [8]. As a result, preoperative evaluation is often regarded as a poorly focused, perfunctory exercise with little impact on the child’s well being. The paediatrician’s frustration is likely to be paralleled by that of an anaesthesiologist, who receives a prescription-pad note simply declaring “clear for surgery”. This reflects a common communications gap between anaesthesiologists and paediatricians about the best way to facilitate the patient’s surgical procedure. Contributing to misunderstanding between the two disciplines is the fact that stable or self-limiting conditions, although requiring no intervention by the paediatrician, may be of special importance to the anaesthesiologist. Examples include asthma in remission, asymptomatic heart murmur, well-compensated haemoglobinopathy, prior exposure to chemotherapy, or mild symptoms of upper respiratory tract infections. Nevertheless, the continuity of care and the knowledge of the family issue make the paediatrician’s contributions important

in preoperative evaluation. Understanding the ramifications of medical problems for anaesthesia not only promotes better patient care but also facilitates appropriate planning for anaesthesia. Paediatricians have specific skills in clinical diagnosis, assessment of perinatal and congenital conditions, and the pathophysiology of unique paediatric conditions. They facilitate continuity of care for children under multidisciplinary care, supplying insights into medical and social issues not easily accessible to others; moreover, they provide a familiar and secure reference point for the family. On the other hand, anaesthesiologists have special expertise in achieving optimal preoperative medical conditions, airway management, haemodynamic control, vascular access, and the diagnosis and management of pain. As avenues and mutual support and cooperation develop between anaesthesiologists and paediatricians, the level of uncertainty should diminish and decision making about anaesthetic management should be facilitated. Clinical care will be enhanced as each uses to advantage the other's expertise. This example illustrates how cooperative functions can reduce the level of uncertainty, thus rendering the decision-making process easier.

Another important issue concerns who participates in the decisions made regarding paediatric anaesthetic care. Traditionally, decisions made regarding patient care and treatment have followed a paternalistic approach in which the axiom "doctor knows best" was considered the norm. However, since the 1980s, this passive approach appears to have been slowly moving toward an environment of greater patient autonomy [9]. Consumer dissatisfaction with the medical system and pressure from patient advocacy groups has led to a change in the traditional doctor-patient relationship. It has been shown that actively involving patients in the decision-making process increases patient satisfaction, compliance with treatment regimens, knowledge, self-esteem and outcome. A relatively recent study [10] has demonstrated that individual preference for involvement in decision-making varied with respect to the different facets of their child's anaesthetic care. In this study, the majority of parents were comfortable with the anaesthetist making decisions regarding intra-operative pain control but requested greater involvement in decisions regarding postoperative pain control. The apparent disparity in preferences for participation with respect to intra-operative and post-operative pain control may reflect a parent's sense of "loss of control" following separation from their child. Once separated, they relinquish decision making control to the anaesthetist, and attempt to resume some sense of control when reunited with their child in the PACU. This theory may also explain the preference parents have for being involved in decisions regarding their presence at induction.

This issue of parental presence at induction has been a source of considerable debate for many years. Some studies suggest that parental presence decreases anxiety and increases child's cooperation, but other studies report that parents were upset following separation from their child after induction and by seeing their child upset before induction [11, 12]. Therefore, the issue of parental presence at induction is still under a certain degree of uncertainty. To allow the presence of parents at induction appears to be a heuristic decision. However, it is clear that parents are becoming increasingly knowledgeable regarding their option for care

and, as such, will undoubtedly present increasing demands for greater decision-making involvement and autonomy.

Two examples both of an analytical and an intuitive approach are reported below. The first implies a systematic cognitive style, while the second proves to be heuristic and rather approximate.

It is well known that in performing central peri-medullar blocks the presence of a bleeding disorder needs to be excluded. Of all the preoperative laboratory screening tests available, none has generated as much controversy as the use of coagulation testing [13]. On the one hand a previously undiagnosed coagulopathy could lead to serious perioperative morbidity. On the other hand, screening tests have a weak predictive value for the risk of surgical bleeding. The bleeding history of the patient and family is the most useful information in selecting patients. However, what question should be addressed? There is strong medical evidence that the following questions are fundamental for avoiding useless, uninformative and costly coagulation screening tests [14]:

- Blood relatives with suspected bleeding diathesis?
- Concurrent medical illness that may promote bleeding (e.g. liver disease, lupus erythematosus, renal disease)?
- Anti-platelet medications within preceding 10 days (non steroid anti-inflammatory drugs)?
- Prolonged bleeding after biting the tongue, cheek, or lip? Hospitalization ever required for nosebleed?
- Spontaneous bruising? Bruising in *more than one region of the body*, particularly if *larger than 4 to 5 cm in diameter*?
- Prolonged bleeding after minor trauma or surgery (e.g. lacerations, circumcision, dental extraction, skin biopsy)?
- Abnormal bleeding (e.g. into a joint, spontaneous haematuria, melena, repetitive or prolonged epistaxis)?

With this approach, the vast majority of patients will have no clinically important bleeding because of a haemostatic defect, if they result negative with these questions. However, it should be borne in mind that even with the most careful history taking, mild form of von Willebrand disease, platelet dysfunction or factor deficiencies (e.g. factor IX) may be missed [15]. However, these questions are a reliable, highly predictive and scientific approach, since the overall cost and difficulty of preoperatively detecting the abovementioned rare bleeding disorders far outweigh the danger of foregoing routine laboratory studies.

The second example is the case of upper respiratory tract infection (URI). This is probably one of the most common preoperative dilemmas: how to manage a child with a new URI who is scheduled for routine elective surgery? Increased airway, mucous plugging, atelectasis, and post-operative arterial hypoxaemia are recognized complications in patients with a recent URI [16]. On the other hand, children with a new or recent URI are anaesthetized regularly with no complications [17]. No definitive predictor for the risk of complications have emerged. Rescheduling surgery could be of relevant discomfort for the child and his/her family. The decision to proceed in the presence of a new or a recent URI is highly individual,

mostly based on experience and emotional valence, i.e. based on an intuitive rather than analytical approach.

In conclusion, the decision-making process in paediatric anaesthesia presents a vast array of variables. This imposes a cognitive approach to the decision-making process in many circumstances, for example guidelines, algorithms, decision trees etc. However, a heuristic approach due to sound experience, in situations with a high degree of uncertainty, still maintains its value.

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Perioperative Care in Paediatrics: Organization

I. SALVO, A. CAMPORESI, E. ZOIA

Anaesthesiology is the discipline that deals with preoperative, intraoperative and postoperative evaluation and treatment of patients who are rendered unconscious and/or insensible to pain and emotional stress during surgical, therapeutic and diagnostic procedures. Anaesthesiologists are called to protect life functions and vital organs under the stress of anaesthesia and surgery a to monitor and maintain normal physiology during the entire perioperative period [1].

As the ASA guidelines on preanaesthesia care state [2], the anaesthesiologist is *“responsible for determining the medical status of the patient, developing a plan for anaesthesia care, delivering safe anaesthesia, ordering appropriate postanaesthesia management including pain therapy and finally discharging the patient home, when this is the case”* [3]. Before surgery, the anaesthesiologist is responsible for

- Reviewing the available medical record
- Interviewing and performing a focused physical examination of the patient to discuss medical history and assess those aspects of the patient’s condition that may affect decisions regarding perioperative risk and management
- Ordering and reviewing pertinent available tests
- Ordering preoperative medications
- Ensuring consent has been obtained for the anaesthesia care
- Documenting in the chart that the above has been obtained

Anaesthesiologists are also responsible, besides the intraoperative anaesthesia with homeostasis maintenance, of the postoperative stay in recovery room, of the discharge from the operating theatre when vital signs are stabilized, and of pain control in the wards.

Paediatric anaesthesia is a subspecialty of anaesthesia which is complicated by the particular characteristics of the patient, different in terms of anatomy, physiology and psychology from the adult patient. It has been repeatedly stated that anaesthesia to children must be administered only by specialized anaesthesiologists in a specialized setting, and this is increasingly important as the age of the patient decreases. What are the minimum requirements to define a paediatric anaesthesiologist? The Federation of the European Associations of Paediatric Anaesthesia (FEAPA) defines paediatric anaesthesiologists as those *“who have had an extra training of at least one year in a specialized centre and who spend at least 50% of their working week, equivalent to two and a half days, caring for children of different ages”* [4]. A recent publication [5] has outlined the inadequacy of the Italian training program under this aspect: even if a minimum training is manda-

tory in almost all the University Schools of Anaesthesia, only 60% of them have a training period that lasts more than three months as required by FEAPA and only 29% of them requires a minimum number of procedures in different age groups to be performed before the anaesthesia board examination.

The Italian Society for Paediatric Anaesthesiologists and Intensivists (Società di Anestesia e Rianimazione Neonatale e Pediatrica Italiana, SARNePI) is now putting emphasis on the necessity of adequate paediatric training during the anaesthesia residency program. In May 2007, the Italian Society of Paediatric Surgery (Società Italiana di Chirurgia Pediatrica, SICP) has accepted the FEAPA guidelines.

Preoperative Evaluation

Patients undergoing surgery and anaesthesia are evaluated preoperatively by the surgeon and the anaesthesiologist in order to define the necessary procedure and assess the child's conditions.

The preoperative assessment takes place, in most cases, shortly before surgery. It is the occasion in which the anaesthesia team meets the child and the family for the first time: an essential moment for the anaesthesiologist, who can acquire a detailed medical history and a precise physical examination of the patient, and essential for the patient who can start interacting with the anaesthesiologist, ask his questions and express his fears, and gain confidence.

In our institution, patients are visited a few days before anaesthesia, so that time remains to perform any adjunctive examination or evaluation which is considered necessary, but there is only little possibility that the patient's medical condition can change significantly.

The perioperative period is often very stressful for the child and sometimes even more for the family, and any additional stress should be avoided.

It is common in paediatric settings to avoid the execution of routine blood tests before surgery, if the child is over one year of age, has had a normal psychosomatic development and presents with no particular health problem. It is commonly accepted, although the literature is considered insufficient on this topic, that the nonselective ordering of preoperative tests leads to higher costs, patient discomfort and even risks, such as those deriving from a large number of false positive results (which causes postponement of surgery while tests are repeated and a further diagnostic assessment is made) and from false negative results, leading to the omission of the usual measures of caution [6, 7]. It is considered important, however, to have children younger than one year undergo blood cell count and coagulation tests in view of the fact that any abnormality could not have been detected yet because of the reduced motility of the child in this age group. Coagulation tests are also performed when regional anaesthesia is scheduled.

Chest X-ray should be performed only in the case of clinical suspicion or presence of risk factors [8].

Electrocardiography, however, is usually requested in all children on a routine basis in order to detect any abnormality that cannot be discovered with a physical

examination. Recent reports have shown the high incidence of congenital long QT syndrome (1:5000) [9] and the possibility that commonly used anaesthetics (sevo-flurane above all) can cause prolongation of the QT [10, 11]. Since electrocardiography is a noninvasive exam that causes no discomfort to the child and whose cost is acceptable, an evaluation of every child at least once under this aspect is suggested, because anaesthetic management can be consequently changed to reduce the possibility of intraoperative arrhythmias.

The preoperative interview should include information starting from gestation and arriving to current diagnoses and treatments, recent vaccinations, allergies, recent laboratory tests and a physical examination aimed at determining possible difficult airway management, cardiovascular problems and respiratory problems. Moreover, the family history can be helpful in identifying a susceptibility to malignant hyperthermia, a high risk of atypical pseudocholinesterase, an unknown bleeding disorder or muscular dystrophy.

Every child should be assessed for a potentially difficult airway; the assessment is quick and easy but requires cooperation from the child. The child should be asked to open the mouth wide and extend the neck. In this way the motility of the temporomandibular articulation and the relationship between tongue and mouth can be assessed. Difficult intubation is mainly described in syndromes involving head and neck malformations, in the presence of infections (retropharyngeal abscess, adenotonsillitis), musculoskeletal problems (ankylosis of jaw or cervical spine, unstable vertebral), or trauma (facial fractures, burns, foreign body aspiration). Unexpected difficult intubation is described in children, although the incidence of the problem is inferior to the incidence in the adult population [12].

The timing of the interview and physical examination varies between centres. It is appropriate to see the child as close to surgery as possible, but preferably not on the same day. This helps to prevent surgery cancellation in case further examinations are required, as stated above, but also gives the parents time enough to consider different anaesthetic options offered and the potential risks involved.

However, if the child has been examined some time before surgery, a new, short evaluation of the child's health must be made on the day of surgery to detect any changes, such as a freshly developed respiratory tract infection. In any case, the child is always re-evaluated at the time of entering the operating theatre, to make sure the appropriate fasting time [13] has been respected or current medications have been administered as prescribed [14].

Preparation of Child and Parents

Surgery and anaesthesia induce considerable emotional stress in children and parents. Because the consequences of this stress occur in the immediate postoperative period [15] and may remain long after the hospital experience [16], one of the tasks of the paediatric anaesthesiologist is to ensure the psychological as well as the physiologic well-being of patients.

Children are threatened by anticipated parental separation, pain or discomfort,

loss of control, uncertainty about “going to sleep” and masked strangers; younger children are more concerned about separation from parents, and older children about the anaesthetic and surgical processes.

It is important to identify children at risk for preoperative anxiety; risk factors for anxiety include children-related risks (age < 5 years, poor previous experience with medical procedures, shy temperament, lack of developmental maturity and social adaptability), parent-related (high anxiety in parents, divorced parents, parents who had multiple surgical procedures) and environment-related risks [17]. Anaesthesiologists can act on the three categories of risk: with children, through psychological preparation programmes, clear explanations, reassurance, premedication and parental presence until induction of anaesthesia; with parents, through clear explanations and reassurance, and preparation videos or leaflets; and on the environment, by making it as comfortable as possible for everybody.

A clear verbal explanation to parents and the child about what will happen should be backed up by written information and clear guidance about preoperative fasting. If communication to children and families is good, premedication can often be avoided. Parental presence at induction can be used to reduce anxiety of both the child and the mother, provided the parents have been correctly informed about what is going to happen and agree with this option.

It is interesting to note that in day-case setting, even minor sequelae of anaesthesia become magnified, so that the least invasive anaesthetic technique is always preferable. The use of laryngeal masks, for instance, has transformed the maintenance of anaesthesia in day care so that tracheal intubation is only needed in emergency or for specific procedures.

Good pain control is essential. In general it is wise to avoid opioids, which are associated with a high rate of postoperative emesis. Local anaesthesia and peripheral blocks are encouraged, as well as caudal blocks, which are, with the use of low concentration anaesthetic, associated with a low degree of motor blockade.

Discharge of the Patient from the Operating Theatre

After surgery patients are allowed to wake up in a recovery room or Post Anaesthesia Care Unit (PACU), and then discharged from the operating theatre when they reach an adequate level of consciousness and cardiorespiratory autonomy, together with good analgesia.

Table 1. Monitoring parameters in the recovery room

Ventilation (spontaneous, assisted, controlled)
Saturation/Respiratory Rate
Arterial Pressure/Heart Rate
Diuresis
Drainages
Complications (nausea, vomiting, shivering etc)

In our institution, discharge from the operation theatre is possible when, together with cardiocirculatory and respiratory stability, good pain control is achieved. Measurement of adequate analgesia is performed with a behavioural scale [18] that can be used in all different age groups. In this scale (see Table 2), a score of zero means optimal pain control and a score of 10 means the opposite; we chose arbitrarily to allow discharge from theatre when the score achieved is less than 4. Pain control must start in the OR and then be monitored throughout the hospital stay.

Table 2. Pain Scale used in the recovery room: FLACC (Face, Legs, Activity, Crying, Consolability) Scale [18]

	SCORING		
Category	0	1	2
Face	No particular expression or smile	Occasional grimace or frown	Frequent or constant quivering chin, clenched jaw
Legs	Normal position or relaxed	Uneasy, restless, tense	Kicking, or legs drawn up
Activity	Lying quietly, normal position, moves easily	Squirming, shifting back and forth, tense	Arched, rigid or tense
Cry	No cry (awake or asleep)	Moans or whimpers; occasional complaints	Crying steadily; screams or sobs, frequent complaints
Consolability	Content, relaxed	Reassured by occasional touching, or hugging, or being talked to	Difficult to console or to comfort

Many parents want to be with their child as soon as the operation is terminated. In ideal settings, recovery rooms or PACU should be large enough to provide place for parents also – at least one for each child. In any case, parents should not have access to the PACU until vital signs have stabilized and airway obstruction is no longer a threat.

Day Surgery in Paediatrics

Paediatric patients gain particular benefit from well planned and well conducted day care because separation from parents is reduced. Day surgery regimens can be used for most surgical or diagnostic procedures that require analgesia or anaesthesia.

The decision whether a surgical procedure should be performed on an inpatient or outpatient basis includes several factors: minimally- or well-controlled physiological alterations, a procedure associated with a low percentage of surgical or

anaesthetic complications, a short duration of anaesthesia and easily controlled postoperative pain [19]. The majority of cases of surgical or diagnostic procedures that require anaesthesia or analgesia in paediatric populations can be performed on an outpatient basis [20].

Table 3. Selection criteria for day care [14]

Peripheral procedures
Not entering a body cavity
Limited duration
Moderate postoperative pain that can be managed orally/rectally
No major physiologic disturbances
No major blood loss
No postoperative fasting necessary
No ex-premature babies (<36 weeks and up to 60 weeks postconceptional age)

Patient selection for day surgery must fulfil different criteria [21]:

Social Criteria for day surgery: the patient (or his parents, in this case) must be able to:

- Understand and accept what is being proposed
- Respect medical prescriptions
- Guarantee the hygienic conditions required
- Be accompanied by a person who assists the child for the first night after surgery
- Spend the first night in a place not far from the hospital (less than one hour)
- Have a phone

Clinical criteria for day surgery:

- Age is not a contraindication, except for the case of ex-premature babies up to the 60 week postconceptional age who are at risk for postoperative apnoea. In our institution, day surgery is performed only above one year of age.
- Health conditions: only ASA I and II subjects are candidate to day surgery. In selected cases, ASA III patients can be enrolled provided the medical conditions are stable and the pathology does not interfere with the scheduled surgery
- Current medications that add a risk of complications (such as antidiabetics or anticoagulants)

There are no contraindications as to the kind of anaesthesia that can be performed on an outpatient basis, except for the obvious observation that they must take into account the short postoperative observation period. All the techniques must be readily reversible, that is, they must allow a quick return to the baseline conditions [22].

The guidelines for ambulatory anaesthesia edited by the American Society for Anesthesiologists in 2003 state minimal patient care should include [23]:

- Discharge of the patient under the physician's responsibility (both surgeon and anaesthesiologist)
- Written postoperative and follow-up care instructions
- Accurate, confidential and current medical records

Discharge Home

Patients can be discharged home when they achieve [21]:

- Complete neurological recovery
- Cardiocirculatory stability
- Recovery of airway protection reflexes
- Absence of respiratory problems
- Spontaneous urination
- No major bleeding
- Good analgesia
- No nausea or vomiting
- Ability to move like before surgery

Before being discharged, patients and their parents should be informed of the possible complications that can occur. They should receive written instructions on how to manage common problems that can appear in the postoperative period and to recognize unpredictable complications that should lead them back to the hospital. We report an example of the written instructions that parents should be given (see Attachment 1).

The hospital should be able to admit patients overnight in case of problems (2% of patients are admitted after a day-case surgery). The commonest problems are postoperative nausea and vomiting, limited pain control or persistence of motor blockade.

Postoperative Instructions

Surgeons and anaesthesiologist should give clear verbal instruction about pain control, wound care, mobilization, and resumption of normal activities. This must be reinforced by written instructions specific for the procedure, which should explain the type of surgery, type of incision, type of sutures and dressing, the pain medication needed, when to resume normal alimentation, restriction on activities, when to allow bathing and washing and what to do if problems arise. Instructions should include a telephone contact to the family doctor or the surgery unit.

Follow-up

Telephone questionnaires are very useful to determine the frequency of post-hospitalization problems. The questionnaire should determine also whether the

parents were satisfied with the care received and, if not, to request suggestions for improvements.

We report an example of postoperative follow-up questionnaire (see Attachment 2).

Anaesthesia and Sedation for Procedures Outside the Operating Room

Providing and delivering anaesthesia outside the operating room can be challenging and hazardous. The environment can be unfriendly because of limited space and equipment, which often consists of operating room leftovers; the inexperience of supporting personnel in anaesthesia care, particularly in cases of emergencies, and unfamiliarity of the anaesthesiologists with the risks associated with the procedures.

Ideally, anaesthesiologists should be involved from the early stage of site design, to ensure that minimum standards for anaesthesia delivery are met and to advocate for adequate space for induction and emergence. Both the anaesthesia cart and the emergency cart should be well organized and regularly checked [25].

Supporting personnel should be properly trained in order to minimize chaos in critical situations. Sedation and anaesthesia should be provided by anaesthesiologists and not by other personnel.

As with all other kinds of anaesthesia, patients should be evaluated not immediately before the procedure. Typical patients for diagnostic and interventional procedures are chronically ill, nutritionally impaired and medically complicated. For all patients, the same rules apply as for surgery patients: careful evaluation of the past history, physical examination, need for further evaluation tests, and finally obtainment of informed consent from parents. Situations that can alert the physician to possible problems in the administrations of anaesthesia are a history of apnoea, the presence of unstable cardiac disease, respiratory compromise, craniofacial defects or history of difficult airway, active gastroesophageal reflux, hypotonia, or prior failed sedation.

The selection of an anaesthetic technique in an extramural location depends on the patient's medical conditions together with the anticipated procedure. Titrated doses of a short-acting intravenous barbiturate (thiopental for instance) are generally chosen because of the reliable pharmacokinetics. When possible, the use of a single agent is preferable, in order to avoid addiction effects.

Recovery criteria and the recovery room environment after procedural sedation or anaesthesia must not be different from the postanesthesia care delivered to children after a surgical procedure [26].

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Attachment 1

Paediatric Home Care Instructions

General Anaesthesia

(from: The Methodist Medical Center of Illinois – Ambulatory SurgiCare)

Activity

Your child might feel a little sleepy for the next 24 hours. This is due to the medicine your child received. Please do not leave the child alone. Children should rest at home, but may be up and about according to the doctor's instruction. Do not let the child ride bikes etc. for 24 hours.

Medications

Your child may have some pain. A prescription for pain may be given to the doctor. This should be given as directed. If it does not help the pain, contact your doctor. If your doctor does not prescribe anything for pain, then you may give your child a non-prescription, non aspirin pain drug such as paracetamol. Please be sure to follow directions on the label. Take all pain medication with some food to prevent upset stomach.

Diet

Progress slowly to a regular diet. Start by giving liquids such as water or carbonated soft drinks. If your child has no nausea try soup and crackers and finally solid foods.

When to call the doctor

If your child develops:

- fever 38.5 orally
- pain not relieved by pain medication
- any bleeding or unexpected drainage from the wound
- extreme redness or swelling around the incision

- croupy cough
- nausea and vomiting that is not getting better

Where to call with questions

Call your doctor. If unable to reach your doctor, call:

- Ambulatory (number 123456)
- At night and on weekends, phone the emergency room (number 7654321)

Next appointment is on day... at....

I have received and understand the above instructions.

Patient Nurse

Attachment 2

Ambulatory Surgery Postoperative Telephone Follow-up

from: The Presbyterian Hospital, NY

- Activities: has patient resumed normal activity?
 - Diet: is patient tolerating liquids/solids/normal diet? Any nausea/vomiting?
 - Pain: does the patient have pain? If so, describe.
 - Was pain medication prescribed? What medication? How effective?
 - Bathing: is patient bathing normally?
 - Wound: is dressing/cast dry and intact?
 - Is there any swelling, redness or drainage? If so, describe.
 - Did patient experience
 - Muscle discomfort
 - Headache
 - Pain at iv injection site
 - Sore throat
 - Voiding difficulties
 - Fever
 - Did the patient need to contact their doctor, the Day Surgery Unit or the Emergency Room?
 - Patient's (family's) comments or concerns
- Additional follow-up necessary?

Techniques and Drugs in Paediatrics: TIVA and TCI

M. ASTUTO, N. DISMA, E. SANALITRO

After the discovery of barbiturates in the 1930s, the intravenous induction of anaesthesia became common and maintenance has become practical in the past decade. In 1977 propofol was introduced into clinical practice, and became the only available intravenous hypnotic agent suitable for induction and maintenance of anaesthesia. Recent advances in the pharmacokinetics and pharmacodynamics of anaesthetic drugs in infants and children, both with technological developments, have increased the routine use of total intravenous anaesthesia in paediatric patients. Intravenous hypnotic agents, short acting opioids and the new muscle relaxant drugs, together with new and sophisticated infusion pumps, have made total intravenous anaesthesia (TIVA) suitable for a large variety of paediatric surgical procedures, from day cases to cardiac surgery. The final challenge for paediatric anaesthetists will be achieving a profound understanding of the real incidence of awareness, particularly during TIVA, in which the only feedback is the predicted plasma concentration in the case of target controlled infusion (TCI) use [1].

Propofol

Propofol is a modern intravenous agent with a rapid onset of action, easily titratable and with a rapid clearance by redistribution and metabolism. The short-acting opioid analgesics such as alfentanil and remifentanil, with a rapid onset and offset of action, are suitable for continuous infusion use, both with propofol. Lastly, recent technological developments such as reliable and accurate intravenous pumps together with advances in understanding of pharmacokinetic principles have enabled the development of the total intravenous techniques.

Propofol, the main feature of the different total intravenous techniques, is indicated in children 1 month old, and the real application of a pure intravenous anaesthesia is widespread for short cases. Growing understanding of the pharmacokinetic and pharmacodynamic principles in the paediatric age is the key to the large popularity of intravenous anaesthesia in recent years.

Pharmacological Principles of Propofol

When propofol is administered, as with other anaesthetics drugs, a concentration at the site of action is necessary to achieve a clinical effect. This is the dose response relationship and it can be divided into three parts:

- Pharmacokinetic phase: dose of the drug and plasma concentration
- Pharmacodynamic phase: site concentration and clinical effect
- Coupling between pharmacokinetic and pharmacodynamic

The inhalational anaesthesia administered using the vaporizer can be measured through the end-tidal concentration, which is a reasonable measure of the blood concentration. In this way, the anaesthetist should mainly be concerned with the pharmacodynamic phase of the drug. A similar facility is not possible using intravenous agents. For each agent, the loading bolus or infusion and the maintenance infusion rates must be calculated and corrected for age, weight, maturity, severity of illness and presence of organ failure. The main problem is the complex relationship between dose and effect-site concentration. Children tend to have a large central compartment volume and rapid clearance of intravenous anaesthetics. The metabolic capacity of infants and young children tends to be very high due to the relatively large proportion of cardiac output perfusing the liver. However, below one year of age the immaturity of hepatic enzyme systems and renal metabolic, concentrating and excretory functions become progressively more important and cause significant impairment in the clearance of intravenous agents and their metabolites in the neonate, especially if preterm.

TIVA in Children

The effector site concentration in the central nervous system is the clinically important value rather than the arterial or venous plasma concentration. The blood-brain barrier is immature in the neonate and in most cases, term and preterm neonates are very sensitive to the central nervous system depressant effects of all intravenous agents. Propofol produces a rapid smooth induction of anaesthesia with dose related cardiovascular and respiratory depression and a reduction in muscle tone. Recommended adult induction doses of $2\text{--}2.5\text{ mg}\cdot\text{kg}^{-1}$ are almost half of the $4.0\text{ mg}\cdot\text{kg}^{-1}$ recommended in children (with the higher dose for unpremedicated patients). It is preferable to inject the induction dose fairly quickly over about ten seconds to minimize involuntary movements and reawakening due to the rapid redistribution of the drug. McFarlan et al described the decreasing exponential dosing. The 10-8-6 rule of propofol infusion in adults was transformed into a 15-13-11-10-9 (where the numerals represent $\text{mg}\cdot\text{kg}^{-1}$ at given time intervals) rule in children to achieve the same target concentration and equivalent plasma concentrations [2]. Steur et al conducted a subsequent trial aimed at defining a scheme of infusion for children under 3 years. They performed a pilot study on 50 children undergoing TIVA, after which the dosage scheme was evaluated in 2271 children undergoing various surgical procedures. The final scheme was shown to provide

safe and smooth anaesthesia [3]. A propofol infusional scheme in children is presented in Table 1.

Table 1. Propofol infusional scheme in infants and children

	First 10 min	Second 10 min	Third 10 min	Fourth 10 min	Consecutive 1 h	Remaining Time
Under 3 months	25	20	15	10	5	2.5
3-6 months	20	15	10	-	5	2.5
6-12 months	15	10	-	-	5	2.5
1-3 years [3]	12	9	-	-	-	6
>3 years [2]	15	13	13	11		9

The pharmacokinetics of propofol in children can be described by a three compartment model. In healthy children, the volume of distribution is about 50% larger than in adults ($343 \text{ ml}\cdot\text{kg}^{-1}$ vs $228 \text{ ml}\cdot\text{kg}^{-1}$) and the clearance can be up to twice that in adults (up to $57 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ vs $27 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) [4, 5]. The clinical implications of these findings are that higher bolus doses are required to reach a given blood concentration and higher infusion rates are required to maintain a steady blood level. Specifically, clearance reflects the ability of the body to eliminate a drug (volume of the blood from which the drug is completely eliminated in unit time). It depends mainly on hepatic function, although renal excretion and metabolites may also be important.

TCI of Propofol

TCI is an infusion system programmed to achieve a user-defined drug concentration in a body compartment or tissue of interest. Otherwise, the anaesthetist is able to set the desired concentration (target-concentration) of the drug used and to change it based on the clinical signs and monitoring of the patient. The common available devices are the Diprifusor (Graseby Medical Ltd, Hertfordshire, UK) and the Paedfusor (Graseby Medical Ltd), and they deliver a BET format (B = loading dose, E = terminal elimination, T = transfer to peripheral compartment of the drug). A complex calculation through an algorithm is installed in a computer that controls the infusion pump. The multicompartmental pharmacokinetic models are used by TCI-systems to calculate the infusion rate required to achieve the target concentration.

The pharmacokinetic models are derived from previously performed population pharmacokinetic studies. The open-loop systems are referred to those systems in which no measurements of actual concentration is made, there are no measurable feedback signals. The opposite system is the closed-loop, where the measurements of the control variables are made, and the error between the set point and the actual value are used to alter the input to the system. Consequently, at any given

moment the input to the system (i.e. the drug delivery) is a function of the previous output (e.g. bispectral index (BIS), blood pressure, pulse rate). At this point there is a measurable feedback signal which completes the loop. This type of control is not available commercially, but is the subject of clinical investigation in adults. Most feedback systems use a specific drug as one input and one specific signal as an output. In the clinical setting, several drugs are given and several physiological variables are measured and monitored, and this is the gap that exists between closed loop systems and current clinical practice.

The vascular compartment is the central compartment of the pharmacokinetic models. Open-loop blood targeted TCI is the infusion system with the central compartment as target. Otherwise, the open-loop effect site targeted TCI is referred to the concentration at the site of action of the drug.

Children have a large central volume of distribution, almost double that of adults and a more rapid clearance of drugs used in TIVA. Varveris and Morton studied children aged 6 months to 16 years and confirmed the ease of use, clinical efficacy and the absence of adverse effects when using the Paedfusor [6]. The accuracy of the Paedfusor was also studied by Absalom et al in children undergoing cardiac surgery. The authors calculated the predictive indices of median performance error (MDPE) and median absolute performance error (MDAPE), and they found an MDPE of 4.1% and an MDAPE of 9.4%. This is far less than that found in adults, given that the MDPE of Diprifusor in adults is 16% and the bias of isoflurane and halothane is about 20%. Accuracy tends to be worse during the 'no flow' periods, probably because the amount of drug returning to the central compartment is greater than expected [7].

Infuser algorithms are based on population pharmacokinetics which do not cover all individuals. Anaesthesia in general terms provides an ED-95 to a population for a procedure and aims to maintain a narrow therapeutic window to ensure adequate anaesthesia that will result in a prompt recovery. There is at the moment no reliable technique for monitoring plasma concentrations of drugs used in TIVA and increased risk of awareness with TIVA. Whether a technique using BIS or other electroencephalogram derived monitoring is able to reduce the incidence of awareness is questionable, as the sensitivity of these instruments is not 100% [8]. Awareness in the paediatric population may be more difficult to define and little information is available about the interpretation of awareness in children and factors such as higher anaesthetics [9].

Performance of the Devices

The accuracy of the systems are previously validated in trials, comparing predicted plasma concentrations as set on the device with those actually measured. Performance comparisons are made using the following terms.

- **MDPE or bias:** this term represents the direction (over or under prediction) of the error.
- The **size** of the abovementioned error from the predicted value is reflected in the term MDAPE.

- The term **wobble** measures the potential of the infusion system to maintain a constant set point.

The two currently available systems are the Alaris Asena® PK (Alaris Medical Systems, Basingstoke, UK) and the Base Primea (Fresenius, Brezins, France).

The basic components of a TCI system are a user interface, a computer or a microprocessor and an infusion device. The computer controls the appearance of the user interface, implements the pharmacokinetic model, and accesses data input and instructions for the user. The user interface prompts and allows the user to enter the patients data such as age, weight, gender and height and the target drug concentration, whilst displaying useful numerical and graphical information. Typical TCI systems incorporate infusion device that are capable of infusion rates of up to 1200 ml/h, with a precision of 0.1 ml/h.

The general method of a TCI is characterized by a rapid infusion (bolus) that quickly fills the central compartment thereby giving an almost stepwise increase in blood concentration. The amount infused is calculated according to the estimated central compartment volume and the difference between the current calculated concentration and the target concentration. When the system calculates that the blood concentration has reached the programmed target, it stops the rapid infusion, and commences an infusion at a lower rate that gradually decreases, to replace the drug that is lost by distribution and elimination. Every 10 seconds the system repeats the calculation and alters the infusion rate. The infusion rate used to replace the redistributed drug is '*step wise decreasing*' and if a three compartment model is used, three superimposed infusions are required. When the anaesthetist decreases the target concentration, the system stops the infusion, and waits until it estimates that the blood concentration has reached the target concentration. The rate at which the blood concentration falls depends on the rate of elimination, and on the gradient between the concentration in the central and other compartments. Thus if the concentration in the central compartment is greater than that in the other compartment, the blood concentration will fall more rapidly, whereas if the reverse is true, the return of drug from the peripheral compartment will reduce the rate of decline in blood concentration. Once the system estimates that the blood concentration has reached the target, it will restart the infusion at a lower rate, once again calculating the changing infusion rates required to maintain the blood concentration at the target concentration.

Remifentanil

Remifentanil is a unique new synthetic opioid which undergoes esterase cleavage to virtually inactive metabolites in blood and tissues. Thus its clearance is independent of hepatic or renal clearance and this results in a very predictable termination of its effects however long the duration of administration and however high the dose. The context-sensitive half time (CSHT) of remifentanil is consistently around three minutes even when the duration of its infusion is trebled from 100 to 300 minutes, whereas the other 'short-acting' opioids have much longer CSHTs

which become longer as the infusion duration increases [10]. Remifentanyl is an opioid so produces analgesia, respiratory depression, nausea and chest wall rigidity and there is very limited information on its kinetics and dynamics in children. It should be particularly useful for controlling the stress response, in neonatal anaesthesia and in intensive care. It will be important to ensure that the esterase systems in neonates, infants and children are operational and that clearance of remifentanyl and its metabolites occurs as in adults [11].

There were no clinically relevant differences in the pharmacokinetic profile of the drug in those with renal or hepatic impairment, or based on gender. In surgical patients aged 0 to <18 years, after correction for bodyweight, there were no significant differences in pharmacokinetic parameters of remifentanyl in these recipients versus those in adults [12]. The usual dosage in children is presented in Table 2.

Table 2. Recommended starting infusion rates and dose range for remifentanyl during the induction and maintenance of general anaesthesia. Children aged 1-12 years

	Bolus injection (not recommended) (γ /kg/min)	Initial rate of remifentanyl (γ /kg/min)	Range (Dose titrated in 25-50% increments or decrements)
Halothane (starting dose 0.3 MAC)	1	0.25	0.05-1.3
Sevoflurane (starting dose 0.3 MAC)	1	0.25	0.05-0.9
Isoflurane (starting dose 0.5 MAC)	1	0.25	0.06-0.9
Propofol (starting dose 2 mg/kg maintenance 10 mg/kg/h)	1	0.25	0.06-0.9

Alfentanil

Alfentanil is a short-acting opioid with a rapid onset capable of providing intense analgesia. It has a low fat-solubility and is metabolized in the liver. The three compartmental model described by Maitre et al is the model commonly used in TCI alfentanil systems [13]. Several trials have been performed on its use in paediatric populations. Ganidagli et al [14] demonstrated that remifentanyl provides a more rapid recovery and adequate postoperative analgesia after TIVA for paediatric abdominal surgery, when compared with alfentanil. This explains the alfentanil context-sensitive decrement times, which provide slower recovery of respiratory function compared with remifentanyl. In paediatric ambulatory surgery remifentanyl showed superior recovery profiles than alfentanil, as studied by

Davis et al [15-18]. The commonly used dosages in paediatrics are 50 µg/kg as loading dose and 1 µg/kg/min as maintenance and the infusion titrated based on intraoperative analgesia.

TCI of Rocuronium

Similarly to propofol and remifentanyl, the neuromuscular blocking drugs (NMBD) may be administered via a target controlled infusion. The pharmacokinetic-pharmacodynamic relationship remains a very controversial point in paediatric age patients and the liver, kidney and neuromuscular maturation, both with the different distribution volumes, are responsible for the different effects of NMBD throughout childhood. Specifically, the administration of a loading dose followed by continuous infusion has the advantage of achieving a rapid and stable plasma concentration and clinical effect. At steady state, the pharmacokinetics are compensated by the TCI and a stable effect is obtained. Moreover, the plasma concentration represents the effect-site concentration.

Rocuronium, an intermediate acting muscle relaxant, has the suitable pharmacokinetic properties for continuous infusion. Using the Stanpump Pharmacokinetic Software (Stanford University, Stanford, CA), Saldien et al [19] studied the concentration in the effect compartment associated with a 50% drug effect (EC(50)) and with a 90% drug effect (EC(90)) in infants, children and adults. They found that the EC(50) is significantly smaller in infants (mean [SD]) (652 [215] ng/mL) than in adults (954 [276] ng/mL) and was the largest in children (1200 [295] ng/mL). The trial was performed during remifentanyl/propofol based anaesthesia. The conclusion was that at steady-state rocuronium revealed the most potency in infants, and the least in children [19].

Conclusions

Propofol is a widely used hypnotic drug for induction and maintenance in paediatric anaesthesia. Remifentanyl is commonly used with propofol infusion. A recent UK survey on paediatric total intravenous anaesthetic use [20] revealed that about 25% of paediatric anaesthetists use TIVA at least monthly, 40% rarely and the remaining anaesthetists never. Over the last year 13% of anaesthetists used TIVA in children under 1 year of age, and the two most common surgical specialties with which TIVA is used are ENT and orthopaedics. Lastly, TCI is still uncommonly used in children.

Even though this is the only European survey, it highlights that TIVA and TCI is still not a common practice for paediatric anaesthetists, but they perceive the anaesthetic and surgical benefits. The recent knowledge on pharmacokinetics in childhood together with the recent introduction of sophisticated devices have increased the perception of TIVA safety, even though further work is required to guide future anaesthetic practice.

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Depth of Anaesthesia Monitoring in Children

N. DISMA, S. PELLEGRINO, M. ASTUTO

Monitoring during anaesthesia is crucial for guiding the anaesthetist into anaesthesia and for ensuring that vital parameters are in the safe and physiological range, particularly for haemodynamic and respiratory consequences. What about the 'depth of anaesthesia'? Vital signs can be modified by a wide range of variables, including drug administration and surgical impact. Similarly, a large number of variables can interfere with the conduction of anaesthesia, such as age, concomitant disease or therapies, physiological parameters and human variability. Several devices for measuring depth of anaesthesia have been recently introduced in clinical practice. Some of these have been tested in adults with promising results. Much more difficult is their application in paediatric patients and the interpretation of data derived from monitoring.

Application of EEG Derived Monitors

Throughout the history of anaesthesia, the anaesthetist has used clinical signs to identify the right level of hypnotic state. The recently introduced EEG-based anaesthesia depth monitors have substantially modified this point of view. Many clinical trials have been performed to verify the feasibility of these monitors during anaesthesia in adults. Paediatric data are usually an extrapolation from adults. In this case some ethical and physiological consideration have to be carried out before results can be interpreted. Therefore, the application of a technology from one population to another requires a clear understanding of the physiology and the principles behind the technology applied. The physiology and neuroanatomy of infants and the technology applied to measure anaesthesia reveal that depth of anaesthesia monitoring is not as simple as it seems.

Neuroanatomy of Consciousness

The ascending arousal system is made up of an ascending monoaminergic pathway that passes from the brainstem and hypothalamus to the cortex and thalamus to increase wakefulness and vigilance. Cholinergic pathways from the pedunculopontine and laterodorsal tegmental nuclei and input from the parabrachial nucleus through the paramedian midbrain reticular formation also join this pathway. The

arousal system divides, with one branch entering the thalamus to activate and modulate thalamic relay nuclei and other thalamic nuclei with extensive and diffuse cortical projections, while the other branch travels through the lateral thalamic area where it is joined by basal forebrain and hypothalamic ascending pathways. Together these diffusely innervate the cortex. Lesions in either branch will impair consciousness.

Consciousness is defined as the ability to respond to the environment in a coordinated intentional manner, and is dependent on the activity of both cerebral hemispheres as well as the ascending arousal system. The state of sedation is characterized by blunting of higher cortical function. Otherwise, unconsciousness can be produced by either diffuse injury to the cerebral cortex, or a lesion in the ascending arousal system.

Model of Anaesthesia

To measure anaesthesia we can use a model. There are four principal clinical aims of anaesthesia:

- loss of consciousness
- amnesia
- lack of movement
- reduction of autonomic reflexes

These clinical signs are linked to varying degrees and the drugs are the specific link. Some drugs have very specific clinical actions, while others have more complex effects on the different components of anaesthesia. For example, neuromuscular blockers act in specific sites producing specific actions. Opioids are effective in reducing nociceptive stimulus, although they can produce unconsciousness in large doses. In short, some drugs may act on one component of anaesthesia, but may interfere on the other components. Similarly, measuring one component may or may not be a reliable indicator of another component.

A balance of arousal and concentration of various anaesthetic drugs determines the state of anaesthesia. In turn, a balance of drug concentration and nociceptive stimulus also determines the degree of arousal. Finally, the degree of nociceptive stimulus may also be directly influenced by drug concentration. Anaesthetic drugs can have direct and indirect effects at many points.

The concept of arousal is to some extent an abstract construct. We do not know anatomically where arousal is located; however, it may simultaneously act in the reticular system or other activating systems in the brain stem and thalamus.

Can We ‘Measure’ Anaesthesia?

A profound understanding of ‘what is anaesthesia’ is the necessary background for focusing on what we want to measure using anaesthesia depth monitors.

After having established a model of anaesthesia, the two spontaneous questions

are: what do we want to measure? How should a measure of anaesthesia be represented?

If anaesthesia is a binary phenomenon, it should be defined as 'adequate' or 'not adequate'. The word *depth* implies a surface and a linear extension below the surface. In this case a graded scale can be applied. If the component has ordinal or continuous characteristics then the measure may be represented as a scale or number that correlates with the effect. This is a key concept when assessing anaesthesia depth monitor output.

Memory and consciousness are two components of arousal which are very difficult to measure and to reproduce in an ordinal scale. Explicit memory is described as the most sensitive to increasing dose of anaesthesia, followed by implicit memory, and lastly consciousness. A measure of consciousness depends on the definition. In anaesthesia, measures of consciousness are usually measures of response to applied stimuli. Unconsciousness may be defined as no coordinated intentional response to a stimulus. In this respect, consciousness is a binary phenomenon; a person is conscious or unconscious! The issue becomes confused when scales use graded stimuli. The Observer's Assessment of Alertness/Sedation (OAA/S) scale, the University of Michigan Sedation Scale (UMSS), Glasgow Coma Scale and other measures of consciousness use increasingly intense stimuli to illicit a response. The deeply unconscious patient does not respond to an intense painful stimulus. A less deeply unconscious patient responds to an intense painful stimulus but not the human voice. However, both patients are unconscious, so what the scale is actually measuring is arousal, not consciousness. A low level of arousal results in no response. A higher level of arousal results in response with a lesser stimulus.

So, anaesthesia and sedation are dependent on

- the balances of arousal
- the concentration of drugs
- the strength of stimuli

Arousal can be measured indirectly by gauging the response to a stimulus. As response varies with the strength of the stimulus, arousal may be regarded as an abstract but basically linear construct. At the end of this excursion, it is arousal that sits most comfortably as a linear scale.

EEG and Anaesthesia

Von Marxow first noted the effects of anaesthesia on brain waves in 1890 and Berger demonstrated the effect of anaesthesia on the EEG in 1933. The EEG rhythm is derived from thalamocortical pathways and direct activity of the cortex; anaesthesia may slow the EEG by actions in the thalamocortical component of the ascending arousal system and produce decreases in arousal or unconsciousness, or by actions directly on the cortex. The differential effect depends on the drug, dose and the kind of anaesthesia performed.

Thus, from a physiological basis it is reasonable to assume some link between the EEG and a measure of anaesthesia. As mentioned above, the component of

anaesthesia most amenable to measurement appears to be arousal. However, such a link would have a degree of uncertainty and not be applicable to all situations.

The normal awake EEG changes with brain maturation. With increasing age the frequency of the awake dominant background activity increases:

- 6 months: 5 Hz
- from 9 to 18 months: 6-7 Hz
- 2 years: 7-8 Hz
- 7 years: 9 Hz
- 15 years: 10 Hz (adult levels)

Children <5 years old also have specific EEG patterns associated with the transition to, and from, sleep and drowsiness. Increasing the dose of a volatile anaesthetic first increases the amplitude of the signal, then with increasing dose the amplitude decreases and the predominant frequencies become slower. After further increases in anaesthetic an isoelectric EEG is achieved. During anaesthesia, there is a characteristic activation of the EEG followed by a slowing of the EEG.

- Anaesthesia may slow the EEG by actions in the thalamocortical component of the ascending arousal system, or by actions directly on the cortex. The differential effect may depend on the drug and dose.
- Anaesthesia may produce decreases in arousal or unconsciousness by actions in the thalamocortical component of the ascending arousal system or by actions directly on the cortex.

Uses of EEG-derived Anaesthesia Depth Monitors

In essence, there are two ways to use an EEG-derived anaesthesia depth monitor. First, as a machine that quantifies a component of anaesthesia, and second as a guide, or arbitrary scale, to guide the anaesthetist through anaesthesia using particular drugs. The component of anaesthesia most likely to be represented by the EEG-derived monitors is arousal.

As a measure of arousal they can give a fair indication of the possibility that a patient may be conscious or that they may switch to the conscious state with the appropriate stimulus. The mean values associated with consciousness are higher than those associated with unconsciousness, but there is a significant degree of imprecision and overlap. There is other indirect evidence which gives a measure of arousal. At constant levels of stimulation the values will change with anaesthesia concentration, and with constant drug concentration the values will change with stimulus. However, arousal is not a well-defined phenomenon so it is not surprising that it is unclear exactly what the numbers represent in a clinical setting. When the monitors are used for physiological studies this uncertainty must always be highlighted. Similarly, as the scales do not represent any defined physiological phenomenon it is more appropriate to regard the data as being on an ordinal rather than linear or interval scale.

If a patient is unrousable, even with maximal stimulation, then the degree of arousal might be regarded as zero. However, the brain concentration of anaesthetic drug may still rise resulting in further change in the EEG. This change in the EEG

is still useful information as the higher the brain concentration, the further it must fall before any measurable degree of arousal. At high concentrations of anaesthesia and low levels of arousal it is difficult to determine if the changes seen in the EEG are related to changes in arousal or to the direct effects of the anaesthetic agent on the thalamic or cortical neurons producing the EEG. This is particularly the case when burst suppression is occurring.

Aim of Anaesthesia in Neonates and Children

The aim of sedation, anxiolysis, and various forms of hypnosis is the reduction of the humoral stress response, pain, anxiety, and emotional distress. In contrast, general anaesthesia also aims to produce unconsciousness and amnesia. Unconsciousness is the complete lack of perception of any experience thus guaranteeing lack of any pain, anxiety, or distress. Immobility or the provision of surgical relaxation is another separate aim of general and regional anaesthesia.

What is the evidence that the neonate is actually conscious of the cold, incision or other painful stimulus? The issue becomes even more uncertain when one asks if the neonate can ever remember a distressing event. The discussion surrounding evidence of consciousness is profoundly philosophical. When we try to accurately measure unconsciousness and amnesia, the question of the development of consciousness and memory becomes far more practical. For infants to benefit from the precise delivery of these drugs, we need to understand exactly what we are hoping to achieve with these drugs in terms of unconsciousness and amnesia. In other words, what are the actual aims for general anaesthesia in a neonate and what end point do we use as adequate? No movement, no crying, no humoral stress response, no memory, or no consciousness? The question has an even greater relevance if these drugs are indeed found to be more toxic to the developing neonatal brain.

However, one thing is clear; measuring or guiding anaesthesia effect in infants using adult derived definitions of consciousness and amnesia is a difficult and perhaps futile exercise. When choosing drug or dose of drug, adult models of the effect of anaesthesia on memory and consciousness have only limited usefulness. In many circumstances, we have no idea if we are giving too little or too much. There is much room for further thought and investigation. Progress in understanding the physiology of consciousness and memory will become increasingly relevant to not only philosophers and psychologists, but to paediatric anaesthetists as well.

EEG-derived Devices

Do they work in children? Simply put, an anaesthetic depth monitor ‘works’ if it monitors anaesthetic depth, but what exactly do we mean by ‘anaesthetic depth’ in children? If they ‘work’ in adults can we assume they work in children? These

devices have all been derived from adult EEG data. In adults the difference between the EEG when awake and the EEG when anaesthetized is obvious. The EEG in awake children is well described and steadily changes with maturation, but our knowledge of the EEG during anaesthesia in children is scant and, at this stage, too limited to make any assumptions about extrapolating adult data to children. Therefore, they ought to be assessed specifically in children.

BIS

The BIS Monitoring System is a patient monitoring system designed to monitor the hypnotic state of the brain based on acquisition and processing of EEG signals. It processes raw EEG signals to produce a single number, called the bispectral index (BIS), which correlates with the patient's level of hypnosis.

Early studies have demonstrated the correlation between BIS and responsiveness in children. BIS significantly decreases with 3% of sevoflurane, if compared with 0.5% of sevoflurane [1]. Recent studies have also found a correlation between BIS and predicted propofol concentration [2]. Rodriguez et al showed that the sensitivity of BIS to detect consciousness was between 81 and 71% at emergence, and the positive predictive value of BIS to predict consciousness was between 53 and 63% [3]. Several other recent papers have demonstrated an influence of neuraxial blockade on BIS [4]. BIS falls with caudal block during general anaesthesia (in older children, but not in infants) and falls during spinal anaesthesia in infants.

Entropy

There are a number of concepts and analytical techniques directed to quantifying the irregularity of the EEG. One such concept is entropy. Entropy, when considered as a physical concept, is related to the amount of 'disorder' in the system. Entropy is an intuitive parameter in the sense that one can visually distinguish a regular signal from an irregular one. Entropy also has the property of being independent of absolute scales such as the amplitude or the frequency of the signal: a simple sine wave is perfectly regular, whether it is fast or slow. The starting point of the algorithm applied in the Datex-Ohmeda EntropyTM Module (Datex-Ohmeda Division, Instrumentarium Corp., Helsinki, Finland) is the spectral entropy, which has the particular advantage that contributions to entropy from any particular frequency range can be explicitly separated.

Davidson et al performed a pilot study between BIS and response entropy/state entropy [5]. They were low during anaesthesia and rose on awakening and a significant difference between values awake and during anaesthesia was found for all age groups and monitors. Klockars et al found a reasonable correlation between sevoflurane and spectral entropy and BIS for older children, but less clear correlation between sevoflurane and indices in infants [6].

Narcotrend

The Narcotrend™ (Monitor Technik, Bad Bramstedt, Germany) is an EEG monitor designed to measure the depth of anaesthesia. It was developed at the University Medical School of Hannover, Germany, and it has received US Food and Drug Administration approval. The Narcotrend algorithm is based on pattern recognition of the raw EEG and classifies the EEG traces into different stages from A (awake) to F (increasing burst suppression down to electrical silence). The newest Narcotrend software version includes a Narcotrend index from 100 (awake) to 0 (electrical silence). There are several recent studies evaluating the Narcotrend as a measure of anaesthetic depth in children. Weber showed a strong correlation between Narcotrend index and sevoflurane concentration, and Pk values were 1.0 for awake versus loss of consciousness and 0.95 for anaesthetized versus return of consciousness [7].

A-line ARX Index

The A-line ARX index (AAI) generated from the A-line monitor extracts the mid-latency auditory evoked potentials with an autoregressive model. This version of the AAI has now been superseded by the AAI-1.6, which incorporated passive EEG measures at deeper levels of anaesthesia.

Cerebral State Index

There has been a limited evaluation of the cerebral state index (CSI) in children. Disma et al compared the CSI and the AAI with the University of Michigan Sedation Scale (UMSS) in children aged from 8 months to 7 years. Both CSI and AAI decreased with induction and rose with emergence. There was also a strong correlation between CSI and sedation scores and AAI and sedation scores [8].

Depth of Anaesthesia Monitors and the Impact on Outcome in Children

This is the crucial point in the future application of these kinds of devices. Although the monitors are imprecise measures, it is incorrect to conclude that the monitors are without use. Indeed outcome studies have provided increasing evidence for their use to prevent awareness [9] and improve recovery times [10]. The logical way to apply these monitors is as a road map to guide the anaesthetist through an anaesthesia. The number generated to guide the anaesthetist can be called a 'depth of hypnosis'.

In spite of uncertainty surrounding maturational changes in the EEG, and the paucity of data about EEG changes during anaesthesia in children, there are several physiological studies indicating that the EEG-derived anaesthesia monitors give some measure of arousal in children [11]. The differences in infants may be due to the immaturity of the EEG or it may be that the nature of arousal in an infant differs

from adults, for example, infants may have a more marked 'switch'. If the relationship between arousal and consciousness is different in infants, then the relationship between the monitor and consciousness will also be different in infants. From the limited physiological studies, it can be concluded the EEG provides a similar measure of anaesthesia in older children as it does in adults. It is therefore possible that any clinical benefit derived from measuring the EEG in adults, such as improved recovery and reduced awareness, can also be derived in older children [12]. Time to discharge was shorter with BIS-guided anaesthesia in older children, but not in younger children. There are no studies evaluating EEG-derived monitors and actual discharge time or postoperative vomiting. It is important to note that EEG-derived benefits seen in adults can only be expected in children if the causes of delayed recovery and postoperative vomiting are similar and the improvements in outcomes are of similar clinical significance. Awareness occurs in children at least as frequently as in adults. The utility of EEG-derived monitors to prevent awareness in children is still unknown.

In some clinical trials the BIS-guided anaesthesia resulted in a shorter recovery period and discharge time [13]. Some trials investigated a possible relation between depth of anaesthesia and laryngospasm, both with sevoflurane and halothane, with a strong relationship with the last agent. Finally, no clear correlation was found between BIS and complications at laryngeal mask insertion and removal [14].

In conclusion, further clinical trials are needed to prove the real benefits in terms of outcome derived from the application of these devices, specially in paediatric patients.

Areas of Application

A large number of articles have been published on the clinical application of anaesthesia depth monitors during anaesthesia, procedural sedations and sedation in intensive care.

During procedural sedation the anaesthesia depth monitors have a well established role in improving safety, quality of sedation and recovery period. Sadhasivam et al published a validation study on BIS during sedation for invasive and non invasive procedures [15]. They concluded that BIS strongly correlates with sedation scales and can be considered a quantitative, non disruptive and easy to use depth of sedation monitor in children. Powers et al demonstrated that BIS can be a useful monitoring guide for the titration of propofol, to achieve deep sedation for children undergoing painful procedures [16].

With regard to its application in paediatric intensive care, some trials found a correlation between BIS and commonly used clinical sedation scoring systems, such as the COMFORT score, with a moderate correlation [17]. Crain et al studied the impact of BIS in sedated and mechanically ventilated children. They concluded that BIS can be considered useful for identifying and preventing oversedation [18]. Moreover, a specific area of application could be in those patients sedated and receiving neuromuscular blocking, with the aim of preventing inadequate sedation

in paralysed patients. Aneja et al performed a trial and highlighted the inadequacy of clinical scoring systems and the ability of BIS to detect children who were at risk of awareness and recall [19].

The real impact on outcome will nonetheless be the special topic of future trials. At present, the UK Paediatric Intensive Care Society Sedation and Analgesia and Neuromuscular Blockade Working Group does not recommend routine use of anaesthesia depth monitors in the paediatric intensive care unit due to the heterogeneous samples and results of the lack of gold-standard sedation protocols [20].

Conclusions

In recent years a wide variety of studies have been published on the clinical application of anaesthesia depth monitors in children, and BIS has been the most studied. Some interesting conclusions have been achieved regarding their applications, but the real benefits on outcome will be obtained after future and well designed trials. In any case, the increasing evidence is that these monitors work in older children, with possible and suitable implication on outcome. Which monitor is the most suitable in the different areas of application is the further topic of future trials.

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CARDIAC ARREST

New Aspects of Basic Cardiopulmonary Resuscitation Research: From Clinically Relevant Animal Models to Cells

G. RISTAGNO, T. WANG, W. TANG

Cardiac arrest is a dramatic event that can occur suddenly and often without premonitory signs. This condition is characterized by sudden loss of consciousness due to the lack of cerebral blood flow, which occurs when the heart ceases to pump. This phenomenon is potentially reversible if cardiopulmonary resuscitation (CPR) procedures are started early, but it becomes irreversible without interventions or delayed initiation of CPR [1].

As many as 400,000 Americans and 700,000 Europeans sustain cardiac arrests each year [2]. Despite major efforts to improve outcomes from sudden cardiac death, including worldwide publication of new CPR guidelines every 5 to 8 years for the past 3 decades, only 4 to 9% of victims survive [3-6]. Both in heavily populated larger cities and in sparsely populated rural communities, delayed response by rescue services compromises outcomes such that survival is even more disappointing, namely between 1% and 5% [7, 8]. Indeed, reduced post-resuscitation myocardial function has been implicated as an important mechanism accounting for fatal outcomes after successful resuscitation. Both clinical and experimental studies have demonstrated impairment of ventricular function after resuscitation from cardiac arrest. Current research is therefore directed not only to improving outcome from initial resuscitation but especially to understanding and preventing all the mechanisms involved in the evolution of post resuscitation myocardial dysfunction.

Clinically Relevant Animal Models of Cardiac Arrest

Popular models for sudden cardiac arrest have always been initiated by delivering alternating current (AC) into the right ventricle through a pacing catheter. Clinically, the majority of cardiac arrests however are “sudden death” due to coronary or other vascular events. In more than 65% of cardiac arrest events, the usual cause is an underlying acute or chronic ischaemic heart disease [9-11]. Accordingly, myocardial ischaemia and reperfusion have been involved in the triggering of malignant ventricular dysrhythmias [12, 13] and both the duration and the severity of myocardial ischaemia play important roles in developing myocardial cell damage [14]. Acute myocardial ischaemia due to occlusion of the left coronary artery is associated with greater risk of out-of-hospital ventricular fibrillation (VF).

Patients with an acute occlusion of the left anterior descending coronary artery (LAD), in particular, have a higher risk for VF [15].

In our experimental models, therefore, we therefore sought to introduce new approaches, including ischaemic initiation of cardiac arrest, and we studied the effects of the presence of such an ischaemic insult on outcomes from cardiac arrest. We previously investigated this issue in a rodent model of chronic heart failure [16, 17]. We hypothesized that in this rat model of chronic myocardial ischaemia animals would have been less likely to be resuscitated. If resuscitated, such animals would have been likely to have more severe post resuscitation myocardial dysfunction and decreased duration of post resuscitation survival. Male Sprague-Dawley breeder rats weighing 500+50g were randomised to serve as test or control animals. After thoracotomy, the LAD was exposed and partially constricted with a silk suture. Correct ligation of the LAD was initially assessed by observing ST elevation in the real time ECG recordings (Fig. 1). Identical procedures were performed in control animals except for LAD ligation. The chest was closed, and the animals were allowed to recover in separate cages for 4 weeks. Global cardiac performance prior to and 4 weeks after ligation was quantitated with a Sonos 2500 echocardiographic system utilizing a 7.5 Hz transducer (Model 21363A, Hewlett-Packard Co., Medical Products Group, Andover, MA). Coronary constriction provoked significant decreases in ejection fraction, increases in left ventricular end-diastolic volume, and left ventricular end-systolic volume at 4 weeks post intervention, just prior to induction of VF. VF was then induced by delivery of an AC current to the endocardium of the right ventricle. After 6 min of untreated VF, mechanical ventilation and precordial compression were started and continued for 6 min. Defibrillation was then attempted with a 2 J precordial biphasic shock. Identical procedures were followed in sham-ligated animals. A greater number of shocks was also required prior to successful defibrillation in animals with ischaemic heart failure, correspondingly 2 vs 5. Following resuscitation, worse myocardial function was observed in

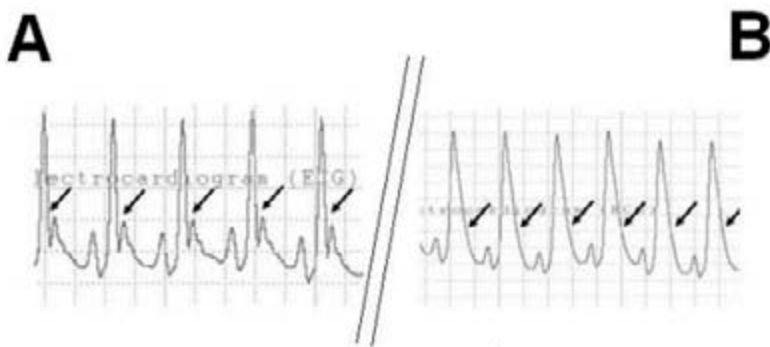


Fig. 1. Limb lead EKG. (A) Before LAD ligation. (B) After LAD ligation shows ST-segment elevation.

hearts subjected to LAD ligation (Fig. 2). Correct coronary artery constriction was confirmed by the gross morphologic appearance of the heart. Compared with the normal myocardial zone, the relative pallor of the wall of the left ventricle, mostly the anterior wall of the left ventricle, indicated the formation of fibrosis. A PE-50 catheter (Becton-Dickinson, Sparks, MD) with an attached syringe containing the coloured dye solution, Indocyanine Green (1 mg/ml), was then advanced through the ascending aorta into the aortic root before touching the aortic valve, where the coronary ostia arise. The catheter was tightly secured with a ligature. Approximately 2 ml of the coloured dye was then slowly injected. Gross visualization showed that the affected myocardium was not stained (Fig. 3).

We later moved to the porcine model, in order to introduce a method to ischaemically induce cardiac arrest. The distribution of the coronary artery blood supply in swine is very similar to that in humans [18-21]. Minimal preexisting collateral vessels are present and therefore occlusion of one branch of the coronary arteries can produce important myocardial ischaemia with a consequent mortality rate which could reach 30% [22, 23]. In experimental settings it was proved that during ischaemia loss of cell-to-cell electrical interaction develops [24-26]. Cell-to-cell electrical uncoupling contributes to failure of impulse propagation by creating pathways in which activation block occurs in one limb while conduction is preserved in another. These conditions are sufficient to create reentrant circuits which

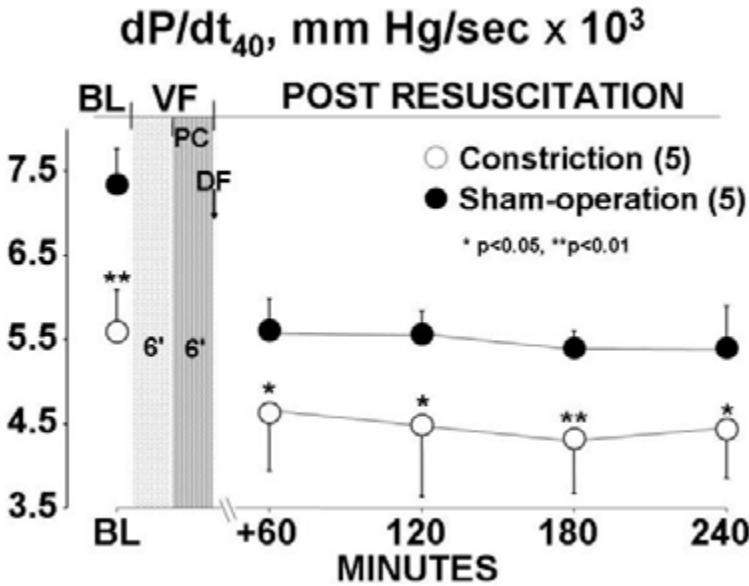


Fig. 2. dP/dt₄₀ measurements in rat with LAD ligation and sham control. During baseline (BL), ventricular fibrillation (VF), precordial compression (PC) and post resuscitation. DF = defibrillation

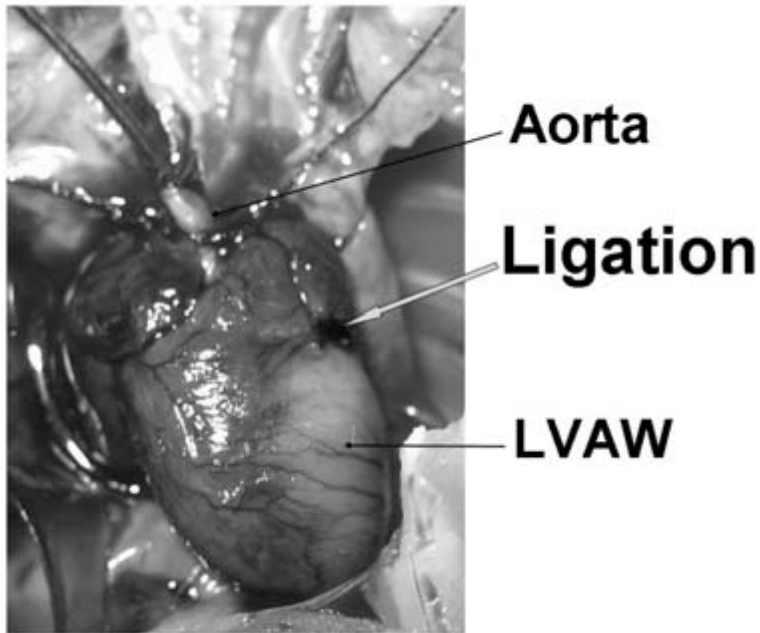


Fig. 3. Absence of perfusion in the LAD area after LAD ligation. Injection of colorant through the coronary ostia in the ascending aorta.

have proved to be the source of malignant arrhythmias and VF [27-30]. The balloon occlusion of one coronary artery branch represents a valid method to reproduce, in the experimental settings, the common cause of human cardiac arrest [31]. Global declines of left ventricle wall motion are reported after localized myocardial damage due to occlusion of the proximal part of the LAD in human patients [32]. In a canine model of acute progressive coronary artery occlusion, a progressive decrease in coronary flow reserve was also observed in the remote nonischaemic regions concurrent with an increase in the extent of ischaemia [33].

We therefore sought to establish a convenient and simple porcine model of acute myocardial ischaemia with consequent VF. Meanwhile, we examined whether there was any difference in outcome comparing this new model of cardiac arrest with the electrically induced one [34]. Myocardial ischaemia was induced in a closed-chest preparation by intraluminal occlusion of the LAD between the first and second diagonal branches, with the aid of a 7F balloon-tipped catheter (Abbott Critical Care 41216) inserted from the right common carotid artery. After confirmation of the LAD site with contrast medium (Renografin-76, Squibb Diagnostics, New Brunswick, NJ), the balloon of the catheter was inflated with 1 ml air to completely occlude the vessel, as verified with angiography and blood pressure. The angiogram and sharply decreased LAD pressure after occlusion strongly indicated the LAD was completely blocked. VF spontaneously occurred within an average of 6 minutes after intraluminal occlusion of the LAD. Electrocardiographic

elevation of ST segment was observed at 1 minute before onset of VF. The ischaemically induced VF required a significantly greater number of electrical shocks prior to being terminated in comparison to the electrically induced cardiac arrest. This model was also characterized by statistically greater duration of CPR efforts prior to final resuscitation and more frequent premature ventricular beats after resuscitation ($p < 0.05$). However, no differences in haemodynamics and survival were observed, demonstrating that the induced acute myocardial ischaemia did not cause more severe cardiac injury than the electrical model. This was probably related to our intervention of disclosing the LAD prior to beginning cardiopulmonary resuscitation by withdrawing the LAD catheter.

These results prompted us to further investigate a clinically more relevant model of ischaemically induced cardiac arrest. Coronary thrombi can in fact be successfully pharmacologically lysed or mechanically compressed or surgically removed in the majority of patients, reducing the interval of ischaemia [35]. These techniques applied during CPR have also showed better outcomes [36-38]. Performing a mechanical or a pharmacological conversion of an occluded branch of the coronary tree, however, requires hospital settings and therefore is not applicable in the prehospital setting. For these reasons we sought to compare our established model of ischaemically induced VF to a new approach, in which after transient total occlusion of the LAD to induce VF, a partial occlusion of the vessel, approximately 75%, was maintained during the resuscitative procedures [39]. In this study VF was induced by LAD occlusion with a balloon tipped catheter in 16 domestic male pigs weighing 41 ± 2 kg. After a 7 minute interval of untreated VF, the LAD balloon occlusion was deflated and the catheter withdrawn in 8 animals. In the other 8 animals the LAD balloon was deflated but the catheter was kept in place in order to maintain a partial occlusion of the LAD, which was approximately 75% of the internal lumen. CPR, including chest compression and ventilation with oxygen, was then performed for 2 minutes prior to attempted defibrillation. Thirty minutes following successful resuscitation the LAD catheter was withdrawn in the animals with partial occlusion of the LAD. In the animals that had the LAD totally withdrawn prior to starting CPR, each animal was successfully resuscitated and survived for more than 72 hours with better neurological recovery during the initial 24 hours post resuscitation than did the partially occluded group. When a partial occlusion of the LAD was maintained during CPR, 6 out of 8 animals were resuscitated and only 4 of these survived for 72 hours. A significantly greater number of electrical shocks prior to return of spontaneous circulation (ROSC) were required when a partial occlusion of the LAD was maintained during CPR. Significantly greater severity of post resuscitation myocardial dysfunction was observed in animals resuscitated with a partial occlusion of the LAD (Fig. 4). The present model with a partial occlusion of the LAD did lead to a greater condition of myocardial ischaemia, as also confirmed from the macroscopic necropsy, and this accounted for the less favourable outcomes and for the severity of post resuscitation myocardial dysfunction. This model may thereby represent a new approach to better study the efficacy of resuscitation efforts and relate the results to humans.

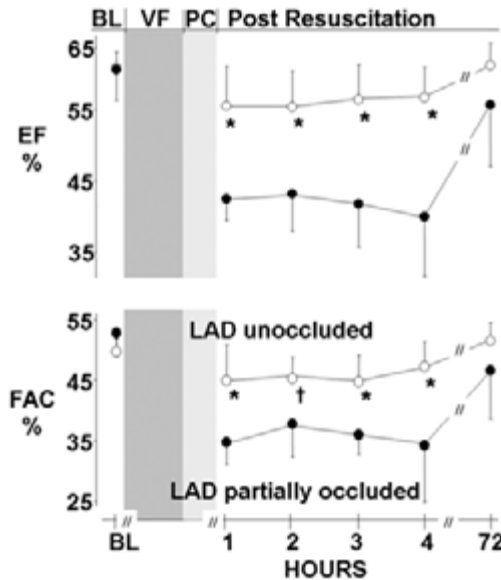


Fig. 4. Myocardial function during baseline (BL), ventricular fibrillation, precordial compression (PC) and 1, 2, 3, 4 and 72 hours post resuscitation.

Black circle: animals with partial occlusion of the LAD; white circle: animals with converted LAD.

Baseline measurements are taken in 8 animals per each group; following resuscitation data include 8 animals for the “converted LAD” group and 6 for the “LAD partially occluded” during the initial 4 hours. 72 hours post resuscitation data for the group “LAD partially occluded” include only 4 animals.

Moving Cardiopulmonary Research into the Myocyte Level

More than 50% of all patients initially resuscitated from cardiac arrest subsequently die before leaving the hospital. Studies in animals and in human patients support the notion that the majority of these deaths are due to myocardial impaired function [40-44]. Electrical defibrillation is the unique treatment for VF, however, high energy defibrillation is recognized to increase the severity of post-resuscitation myocardial dysfunction [45]. We have previously demonstrated in a rat model of cardiac arrest and resuscitation that upon increasing the energy of defibrillation from 2 to 20 Joule the post-resuscitation myocardial function correspondingly decreased. In isolated tissue cultures of myocardial cells, irregularities of contraction followed a single shock with a peak intensity of 80 or more V/cm [46]. The mechanism of the generation of this cell injury is not clear. Free ascorbyl radicals are generated after defibrillation with electrodes applied directly to the epicardium and the concentration of these radicals increases proportionally to the magnitude of the delivered energy. The free radicals may cause sarcolemmal and mitochon-

drial damage with consequent calcium overload and impaired mitochondria functions [47, 48].

Myocyte contractility is a complex process initiated by electrical excitation. Calcium ions (Ca^{2+}) are the central players in the excitation/contraction coupling, by which contraction and relaxation of the heart are generated. After the electrical signal, Ca^{2+} enter the myocytes via voltage-gate channels which induces further Ca^{2+} release from the sarcoplasmic reticulum. These increases in intracellular Ca^{2+} concentration subsequently activate cell contraction. Abnormalities in the cytoplasmatic Ca^{2+} concentration, therefore, are determinant for contractile dysfunction and arrhythmic diseases [49, 50].

We hypothesized that increasing the defibrillation energy would produce a corresponding reduction in myocyte contractility and impairment of intracellular Ca^{2+} dynamics [51]. Ventricular cardiomyocytes, obtained from adult Sprague-Dawley rat hearts, were loaded with Fura-2/AM. The myocytes were then placed in a chamber mounted on an inverted microscope and superfused with a buffer solution at 37 °C. The cells were field stimulated to contract at 0.5 Hz with a field stimulator (IonOptix Corporation, Milton, MA). Mechanical properties were assessed using a video-based edge-detection system (IonOptix Corporation, Milton, MA) and expressed as cell shortening percentage. Intracellular Ca^{2+} dynamics were evaluated with a dual-excitation fluorescence photomultiplier system (IonOptix Myocam System) and inferred from the ratio of the fluorescence intensity at the two different wavelengths [52] (Fig. 5).

Myocytes were randomized into 4 groups of 10 cells each, to receive: (1) a single

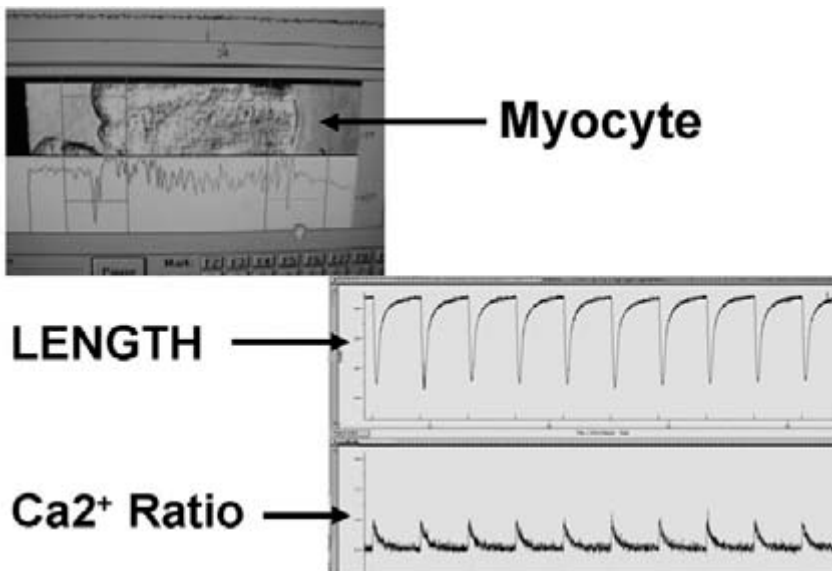


Fig. 5. Myocyte inside the window of the IonOptix acquisition system (upper part). Contractility and calcium ions changes during pacing (lower part).

0.5 Joule biphasic shock; (2) a single 1 Joule biphasic shock; (3) a single 2 Joule biphasic shock; and (4) a control group without shock. The myocytes were paced for additional 4 min after the shock. A 0.5 Joule shock did not have effects on cardiomyocyte contractility and intracellular Ca^{2+} dynamics. Higher energy shock, i.e. 1 or 2 Joule, significantly impaired cardiomyocyte contractility and intracellular Ca^{2+} dynamics ($p<0.01$), (Fig. 6). These adverse effects were greater when higher energy was employed ($p<0.01$), as shown in Table 1.

Table 1. Myocyte contractility and Calcium dynamics before and after defibrillation.

	Control	0.5 Joule	1 Joule	2 Joule
Contractility, Shortening %:				
• Baseline	7.4 ± 2.6	7.7 ± 1.6	7.8 ± 2.4	7.4 ± 2.4
• 4 min post shock	7.7 ± 2.4	7.8 ± 2.3	4.3 ± 1.6 *	1.9 ± 1.9 *†
Ca^{2+} dynamics, ratio %:				
• Baseline	74 ± 38	76 ± 27	67 ± 26	74 ± 39
• 4 min post shock	70 ± 34	79 ± 19	37 ± 10 *	16 ± 12 *†

* $p<0.01$ vs baseline measurements and vs control and 0.5 Joule groups;

† $p<0.01$ vs 1 Joule group

In the present study we demonstrated at the cellular level what has already been reported in vivo and in isolated and perfused hearts. Higher defibrillation energy significantly impairs myocyte contractility. Reductions in cardiomyocyte shortening and intracellular Ca^{2+} dynamics abnormalities are greater when higher energy shock is employed.

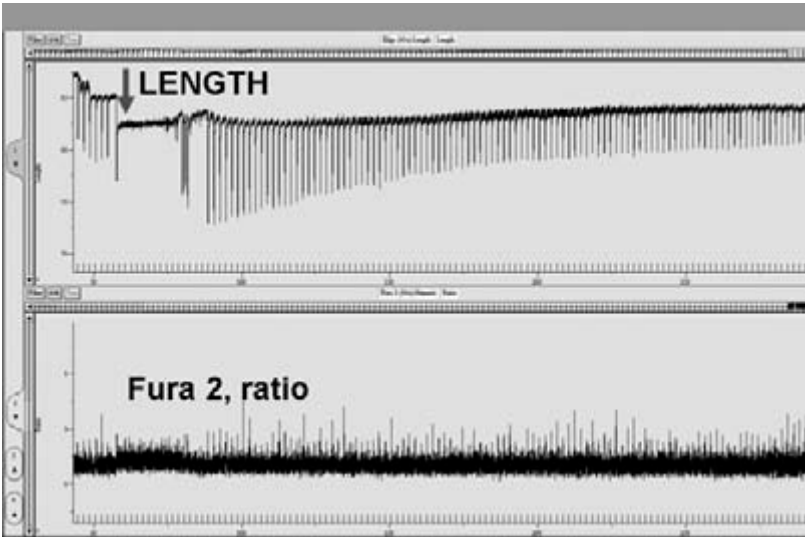


Fig. 6. Myocyte contractility (upper part) and calcium ions changes (lower part) during pacing. Arrow = delivery of 1 Joule electrical shock.

Is Stem Cell Injection the Future?

Cellular mechanisms underlying the development of cardiac ischaemic disease and dysfunction consist in reductions of functional cardiomyocytes [53, 54]. In ischaemic ventricular tissues, apoptosis of cardiomyocytes leads to regional contractile dysfunction [55], and necrotized cardiomyocytes are progressively replaced by fibroblasts resulting in non contractile scar tissues [56]. Loss of functional cardiomyocytes and the inability of the remaining cells to adequately compensate through hypertrophic or hyperplastic responses contribute therefore to the development of cardiac disease and dysfunction [57].

Bone marrow mesenchymal stem cells (MSCs) are a new therapeutic strategy to restore contractile function and angiogenesis in postischaemic hearts [58-60]. In response to stimulation from proper external milieu, MSCs can quickly and easily proliferate in vitro [61], being capable of genotypic and phenotypic differentiation into functional cells [62]. Experimental and clinical studies have confirmed that MSC injection can improve cardiac dysfunction after myocardial ischaemia [63-66]. We sought to examine the effects of three different sites for delivery of MSCs, including intravenous, intraventricular and intramyocardial injection in a rat model of myocardial ischaemia [67]. A thoracotomy was performed under general anaesthesia. Myocardial ischaemia was induced by ligation of the LAD, as described in the previous paragraph. One month later, animals were randomized to receive 5×10^6 MSCs labelled with PKH26 in phosphate buffer solution (PBS) or PBS alone as a placebo by injection into right femoral vein or directly into the left ventricular cavity or into the ischaemic zone in the anterior ventricular free wall. Haemodynamics and myocardial function were measured four weeks after administering MSCs or PBS. MSCs were also counted in 5 μ m sections obtained with cryostat from each harvested heart. Significant improvements in ejection fraction and cardiac index (Fig. 7), as well as in other myocardial function parameters (dp/dt₄₀, -dp/dt, and LVDP) followed injection of MSCs. Numerous MSCs were observed and counted in the heart sections as shown in Figure 8. We therefore showed that regardless of the site of injection, myocardial function was comparably improved in all groups of animals treated with MSCs.

Table 2. Myocardial function following mesenchymal stem cell (MSC) injection.

	Baseline	Postresuscitation	
		2 hr	4 hr
dp/dt ₄₀ (mmHg)			
MSCs	7046±278**	5089±456*	5009±254**
PBS	6099±668	4367±512	4042±706

Values are means ± SD

* $p < 0.05$; ** $p < 0.01$ MSCs vs PBS

MSCs are easily obtained from bone marrow and because of their multilineage potential and immunological advantage, are ideal candidates for allogeneic cell therapy [68, 69]. Clinical trials for allogeneic MSC therapy have received FDA

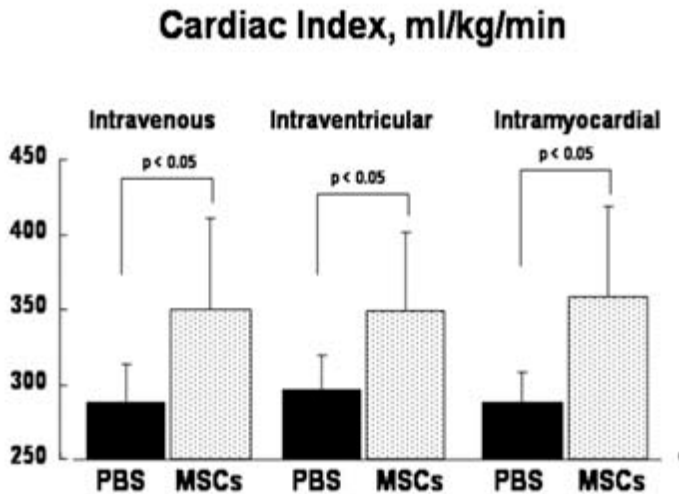


Fig. 7. Haemodynamic data of cardiac index 4 weeks after intravenous, intraventricular or intramyocardial MSC or PBS injection.

approval [69] and transplantation of cultured MSCs into the damaged myocardium has been proposed as a future method for the treatment of myocardial infarction [70, 71]. These results suggest that the mechanism that accounts for functional improvement after MSC transplantation is likely to be related to the replacement of lost cardiomyocytes [63, 72] and perhaps to the release of soluble factors (paracrine mechanisms) from the transplanted MSCs [73, 74]. Release of growth factors, which limit apoptosis and inflammation, may play another important role in conferring organ protection [75]. Other explanations that MSCs improved cardiac function may include neovascularization [73, 76, 77] and reorganization of the extracellular matrix [78].

We later sought to investigate outcomes of cardiopulmonary resuscitation after injection of MSC treatment in a rat model of myocardial ischaemia. A thoracotomy was performed under general anaesthesia in 54 rats, weighing 450–550 g. Myocardial ischaemia was induced by ligation of the LAD. Four weeks later, the animals were randomized to receive 5×10^6 MSCs marked with PKH26 in PBS or PBS alone as placebo. 4 weeks after MSC or PBS injection, VF was electrically induced. After 6 min of untreated VF, CPR including chest compression and ventilation was performed for 6 min prior to defibrillation. Echocardiographically measured ejection fraction was quantitated two and four weeks after administering MSCs or PBS. Haemodynamics, including cardiac index (CI), left ventricular dp/dt_{40} (dp/dt_{40}), left ventricular negative dp/dt ($-dp/dt$) and left ventricular diastolic pressure were measured before inducing VF and hourly following ROSC. Significant improvements in dp/dt_{40} and $-dp/dt$ were confirmed following injection of MSCs prior to inducing VF. Following ROSC, myocardial function was significantly better in animals pretreated with MSCs and the survival time was significantly longer in this

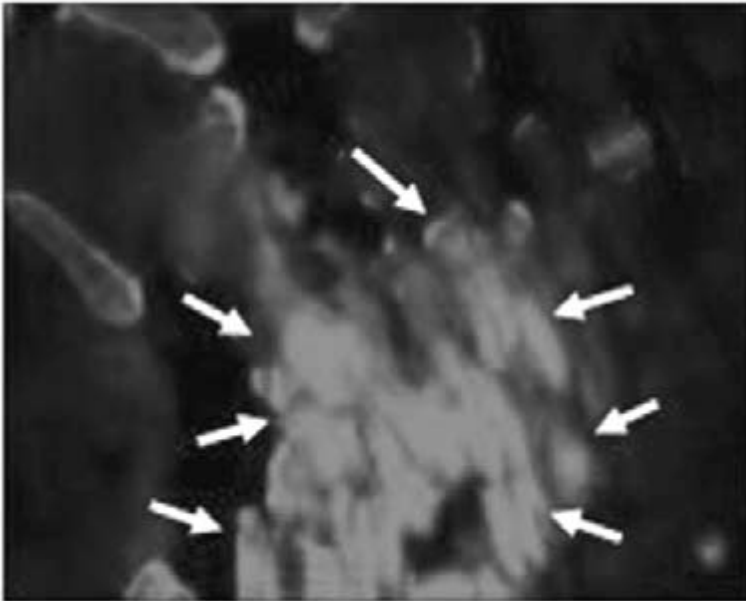


Fig. 8. Labelled MSCs in the heart.

group of animals, compared PBS-treated animals (65 hours vs 39 hours, $p < 0.05$).

Once again we confirmed that MSC treatment significantly improves myocardial function before and after CPR and significantly increases survival time after successful resuscitation. Moreover, significant improvements in behavioural tests (adhesive-removal, motor, and neurological severity score) were observed. Marked MSCs were also found in 5 μ m sections obtained from each harvested brain with cryostat, especially in the midbrain. MSCs delivered to ischaemic brain tissue through an intravenous route may therefore improve brain functional deficits after cardiac arrest [Wang T, et al. 2007, data submitted for publication].

Conclusions

Heart failure and myocardial dysfunction are the most important post resuscitation cardiovascular health problems and are characterized by high mortality. There is a need to develop more effective therapeutic strategies to reduce and treat these phenomena. New models of cardiac arrest, more closely related to the clinical physiology as well as a new cellular approach to the basic research, are important tools for pursuing this goal. Finally, stem cells may be an attractive therapeutic way to improve postresuscitation myocardial function and we truly encourage further studies to confirm these initial positive results and to further prove the safety of MSC injection.

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Warning Symptoms of Sudden Cardiac Death

G. BERLOT, A. VERGOLINI, C. CALDERAN

Despite decades of research and the implementation of advanced protocols, the prognosis of patients with out-of-hospital cardiac arrest (OHCA) remains grim, with a large rate of survivors suffering from devastating neurological consequences [1]. Since the time elapsing from the diagnosis and the restoration of spontaneous circulation (ROSC) is considered the main variable conditioning the outcome, these poor results can likely be ascribed to a delay in the initiation of the cardiopulmonary resuscitation (CPR) due to multiple factors, including the absence of witnesses, the failed recognition of the event, difficulties in reaching the victims etc. Conversely, different investigations have demonstrated that in-hospital cardiac arrest (IHCA) is associated with an overall survival ranging from 15 to 34% [2-4], which is consistently higher than that reported in most series of OHCA arrest [1, 4]. Thus, one might assume that patients who experience an IHCA have the advantage of the presence of professionals trained to recognize the arrest and provide CPR and/or, even better, able to prevent the progression of pathophysiological disturbances which eventually lead to its occurrence. In actual fact, a number of investigations have consistently demonstrated that although IHCA can be preceded by an array of symptoms, unfortunately, their relevance is frequently underestimated [5-8]. Therefore, it appears reasonable that prompt and correct recognition of these circumstances could in many cases alter the sequence of events causing the IHCA and further improve outcome.

Incidence of IHCA

Several factors cooperate to confound the data deriving from the studies dedicated to IHCA. First, many different definitions of IHCA exist, based on the location, the characteristics of the patients studied, the initial rhythm etc. [9]. Second, as far as the location of IHCA is concerned, it should be recalled that the hospital cannot be seen as a unicum, but rather as a spectrum of environments each with different clinical and instrumental capabilities. As a consequence, patients in regular wards are less closely surveilled than patients in the intensive care unit (ICU), in the operation room (OR) or in the emergency room (ER). In most Italian hospitals, step-down units and sub-intensive care units are not present such that patients who recently recover from a critical illness after having spent a long time in the ICU are often transferred directly from a high-tech environment with beat-to-beat moni-

toring to regular wards where the so-called vital signs (i.e. heart rate, arterial pressure and diuresis) are recorded twice a day. Third, in many studies it is not clear if the IHCA simply represented the biological conclusion of the existence of patients affected by multiple severe underlying diseases or a truly unexpected event that, if successfully prevented, might not have caused the death of the subject. With these limitations in mind, the incidence of IHCA can be calculated either as (a) the rate of events/number of beds/year; or as (b) the number of events/number of admissions. Using the first method, Peberdy et al [4], in the largest study currently available which enrolled more than 14,000 patients, demonstrated an incidence of 0.175 IHCA/bed/year; with the second method, other investigators demonstrated a rate of 1-5 IHCA/1000 patients [10-12].

ROSC and Survival in Patients with IHCA

The success of CPR in patients with IHCA can be expressed in term of ROSC, short and long term survival and degree of neurological impairment, if any, at distance. According to Sandroni et al [13], survival to hospital discharge is the most quoted outcome measure, ranging from 0 to 42%. Several factors account for this wide difference, including different patient populations, underlying disorders, the enrolment of patients with do-not-resuscitate orders and the location of the event. This latter issue appears particularly relevant as patients suffering an IHCA in the ICU present a better prognosis [13] despite their more severe underlying conditions. This paradoxical finding can be explained by closer monitoring, the presence of more trained personnel and the selection of patients admitted to the ICU. The outcome appears influenced also by other factors, but their role is not straightforward. First, advanced age appears related to a worse prognosis in many but not all studies [11, 14-16]. This discrepancy can be explained by the different cut-off values used to define advanced age (60 vs 65 vs >70 years), the presence of comorbidities, a less aggressive attitude toward elderly patients etc. Second, although this variable is not commonly taken into account, one study demonstrated a better outcome for females than males experiencing an IHCA [17], after adjusting for age, cause of arrest, location and initial cardiac rhythm. Third, the underlying conditions likely plays a major role, as concomitant sepsis, advanced cancer, stroke, renal failure and home-bound condition are associated with a poor prognosis [13]. Severity scores commonly used in the ICU setting, including the APACHE II and III, failed to identify survivors from IHCA with sufficient precision [13]. Fourth, the initial monitored rhythm is associated with the outcome, being this latter better when the initial recorded rhythm is ventricular fibrillation (VF) or ventricular tachycardia (VT) (survival range 18-64%) and poor in case of asystole and pulseless electrical activity (PEA) (survival range 1.2-14%); once again this difference is likely associated with the time of recognition of the event and both the rapidity and adequacy of CPR: actually, both VT and VF are electrically treatable rhythms, whereas asystole and PEA do not respond to defibrillation and in most cases represent the terminal evolution of VT and VF [13].

Anticipating Events of IHCA

As stated above, the survival of patients with cardiac arrest and their quality of life after discharge is primarily based on the prompt recognition of the event and by the immediate initiation of CPR procedures. Compared with out-of-hospital cardiac arrest, hospitalized patients should benefit from a shortening of the time elapsing from the start of the event and the initiation of CPR. As stated above, although some investigators demonstrated a better prognosis in IHCA than in OHCA patients of between 15 and 20% [2, 4, 18], which is consistently higher than that reported in most series of out-of-hospital cardiac arrest [1], others failed to confirm these findings [19, 20]; the higher mortality of IHCA reported in these studies was attributed either to the advanced age of many patients and/or to the presence of severe coexisting diseases making resuscitation unlikely. However, other factors could explain these differences, including the failed recognition and/or interpretation of some signs or symptoms appearing or worsening in the hours prior to the event. Actually, different investigators have demonstrated that in many instances cardiac arrest occurring in a theoretically protected environment such as the hospital cannot really be considered sudden and unexpected as it can be preceded by anticipating events which, in a post-hoc analysis, could be regarded as true warning signs. Franklin et al [5] demonstrated that a deterioration of the patients' conditions severe enough to be reported and/or to request some diagnostic or therapeutic intervention occurred in two thirds of patients suffering a cardiac arrest in the subsequent 6 hours, and that these events had been overlooked or misinterpreted by both nurses and physicians, either house officers or intensivists. The rate of warning signs seems to vary with the timeframe considered, ranging from 51% in the 24 hours before the arrest to 84% when a period of 8 hours had been chosen [5, 21]. Using a timeframe of 6 hours Berlot et al [8] demonstrated in a cohort of 148 patients admitted to regular wards that IHCA had been anticipated by clinical events relevant enough to be reported in the nurse and/or medical records; moreover, none of these patients had suffered from disease associated with a poor prognosis in the mid term, according to McCabe's classification [22].

Several factors can account for these findings. First, although basic life support is learned during the training of both doctors and nurses, less emphasis is put on the sometimes subtle symptoms preceding the event, including the appearance of arrhythmias and the deterioration of mental status. Second, the unrelenting shortage of nurses determines a diminished surveillance in the regular wards: during the night hours, two nurses are expected to take care of 25-30 medical or surgical patients: it has in fact been demonstrated that the increased workload of the nursing staff is associated with an increased mortality [23]. The relevance of this issue is further underscored by the finding that in Berlot's [8] study the night calls for cardiac arrest double during the daytime, when the nurse-to-patient ratio improves, more doctors and residents are present, thus making more promptly recognizable the occurrence of new symptoms or the worsening of pre-existing conditions. Third, as a result of the measures adopted, it appears that (a) in many patients the investigations performed were not symptom-oriented; and, (b) in a relatively large

number of patients, no investigations at all were performed. In reality, a gradual, multifactorial and unrelenting decrease in blood oxygenation and/or cardiac output accounts for most if not all the reported clinical antecedents, which could have been quite easily detected by the implementation of a more appropriate diagnostic workup, which should initiate with a pulse oximetry or blood gas analysis (BGA) if the former is unavailable in normal wards. This particularly applies to patients with unexpected alterations of mental status, which in many cases is attributed to advanced age, to a drug effect or both. On the other hand, one should recognize that some subjective symptoms, such as dyspnoea or palpitations, are rather unspecific and can be attributed to a host of potentially non lethal causes; (d) the nurse-to-doctor communications are often poor, as demonstrated by the inconsistencies between the nurse and medical records; different causes can account for this finding, including the co-citation surrounding a CPR procedure and a long-lasting suboptimal flow of information between the staff and the physicians [5, 24], which in many cases probably prevented correct triage and the possible referral to the CCU or ICU of patients who subsequently suffered a cardiac arrest. A significant albeit not constant rate of unrecognized anticipating events of IHCA has also been reported by other investigators [5-7, 21].

Regardless of the rate of anticipating events, it is clear that the main limitation of these studies lies in the lack of epidemiological studies which aim to identify the overall incidence of a given symptom associated with the later occurrence of IHCA and thus to establish its sensitivity and specificity; in other words, although it is true that cough is a constant symptom in patients with pneumonia, not all coughing patients have pneumonia. With these datasets available, it could become reasonably possible to prepare a list of warning signs whose presence could trigger a response aimed at raising the surveillance around the patients presenting the symptoms. This approach has been used by Hodgetts et al [25], who initially identified the symptoms presented by patients who suffered an IHCA and later on developed a score system mainly based on the degree of physiological derangement which enables either the identification of the patients at risk and the grading of the response according to the total score. The afferent arm of the response is based on the activation of a medical emergency team (MET) which offers consultation on the wards, indicates the necessary diagnostic investigations and, when indicated, admits the patient to the ICU.

Conclusions

From the above it is clear that in most cases in-hospital sudden and unexpected death is neither sudden nor unexpected. A number of symptoms, reflecting ongoing pathophysiological derangements, often precede IHCA and are noticed but underestimated. Unfortunately, they are sensitive but not specific, and, to be valuable, must be isolated from the background noise constituted by the host of complaints presented by patients.

The current policy of training hospital professionals in CPR and early defibril-

lation does not even consider that IHCA can be foreseen and in many cases prevented. The more rational approach consists in (a) the gathering of data from any specific hospital to evaluate the local situation; and (b) the training of both nurses and physicians in the early recognition of those symptoms which are most often associated with IHCA.

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Vasopressors During Cardiac Arrest

G. CAMMARATA

After almost five decades of the so-called modern era of cardiopulmonary resuscitation (CPR) the survival percentage of patients affected by cardiac arrest is rarely above 5-6%. Post resuscitation myocardial dysfunction accounts for most deaths during the first 72 hours after the return of spontaneous circulation. When the heart stops beating, all cardiomyocytes undergo ischaemic damage, the severity of which increases with the duration of no flow, as previously demonstrated in experimental and clinical studies [1, 2].

With the use of transoesophageal echocardiography our group has demonstrated an important contracture of the heart in animals subjected to CPR, the so-called “stony heart”. This contracture mainly consists of a significant increase in the thickness of the interventricular septum which adversely affects the stroke volume [3].

At the cellular level, the stony heart is explained by intracellular calcium overload during ischaemic injury. During the no-flow state our body physiologically responds with the release of endogenous catecholamines. As a result of our knowledge of this natural process, vasopressor drugs have come to play the most important role within advanced cardiac life support (ACLS). Nevertheless, their use is still controversial and, most of all, it is not supported by a real increase in hospital discharge.

The aim of the use of vasopressor drugs during cardiac arrest is to increase coronary perfusion pressure (CPP), the value of which is presumed and not certain. On the other hand the stimulation of β -receptors increases the imbalance between oxygen demand and oxygen supply, and its detrimental effect on an ischaemic heart is well known.

In 1995 our group reported that administration of exogenous epinephrine during cardiac arrest increases the severity of post-resuscitation myocardial dysfunction and decreases the duration of post-resuscitation survival, when compared with an α -agonist such as phenylephrine. When the β -adrenergic effects of epinephrine were blocked by prior administration of a β_1 -selective blocker in rats, the effects of epinephrine and phenylephrine on outcomes of CPR were comparable [4]. Our results are in agreement with the previous observations made by Ditchey [5]. A decrease in myocyte ATP follows ischaemia and this condition adversely affects the survival of the heart's cells after the return of spontaneous circulation [6].

Adrenergic Vasopressors

Epinephrine

Epinephrine is a nonselective adrenergic agonist. As already reported, the use of this drug during CPR aims at increasing the aortic diastolic pressure and with it the pressure of coronary perfusion.

Nevertheless, clinical data like those reported in a study published by Holmberg et al do not support the efficacy of epinephrine. This study was based on the administration of epinephrine in 14,065 patients during cardiac arrest. Of the 10,966 resuscitated patients, epinephrine was administered to 4,566 or 42.4% of cases, and 156 (3.4%) patients survived one month compared to 388 (6.3%) of the 6,207 patients in whom the drug was not given ($p < 0.0001$). Treatment with epinephrine was an independent predictor of the lower likelihood of survival, independently of gender, incidence of arrhythmias, witnessed or unwitnessed arrest and bystander-CPR [7]. These data are supported by Laurent et al, who reported that administration of epinephrine was associated with a lower cardiac output in survivors of out-of-hospital cardiac arrest [8]. Increases in peripheral resistance or afterload as a result of peripheral arterial vasoconstriction increases workload in the heart and decreases cardiac output. Gonzales et al also found a decrease in end-tidal carbon dioxide with increased doses of epinephrine a finding indicative of the pulmonary arteriovenous shunting produced by this drug [9].

In agreement with the above, the research team of Weil recently demonstrated that the administration of epinephrine during cardiopulmonary resuscitation in an animal model is associated with an important reduction in microcirculation either in the peripheral tissues [10, 11] or in the brain. In the latter case, data were obtained on domestic male pigs, weighing 40 ± 2 kg, on which a bilateral frontoparietal craniotomy was created before the induction of cardiac arrest. The blood flow of the cerebral cortex microcirculation was quantitated with orthogonal polarization spectral imaging and cerebral cortical tissue carbon dioxide was measured concurrently using a miniature optical sensor. After one minute of CPR the animals were randomized to receive central venous injection of equipressor doses of epinephrine (30 $\mu\text{g/kg}$) or vasopressin (0.4 U/kg). Both the drugs produced an important decrease in cortical microcirculation. However, this reduction and with it the severity of cerebral ischaemia was greater after epinephrine [12, 13].

Even though we have no proof to date that the use of epinephrine is correlated with a real improvement in the outcome of the patients in cardiac arrest either inside or outside the hospital, this drug is still recommended by the American Heart Association and the European Resuscitation Council guidelines. For obvious ethical and legal problems there is no randomized clinical study which compares epinephrine with placebo. Nevertheless, actual human data are not encouraging, showing survival percentages below 10% for almost 5 decades [14, 15]. It is clear that these results come from several mistakes, but there is now no doubt that epinephrine is one of them.

Norepinephrine

Even norepinephrine is a nonselective adrenergic agonist and as such has the same advantages and disadvantages of epinephrine.

The effects of these drugs have been compared by Lindner et al in a group of 50 patients in cardiac arrest. Even though norepinephrine had initially shown a better capacity to restore pulse on the scene, no differences were found in terms of hospital discharge [16]. The same findings were reached in a larger, randomized, clinical study [17].

Selective Alpha-agonist

At the time of writing most of our knowledge of this group of drugs comes from experimental data. Yet in the second half of the 1980s it was shown that the outcome produced by drugs with prevalent α_1 action, like phenylephrine and methoxamine, was the same [18, 19] or even inferior to epinephrine [20, 21]. Accordingly, a double-blind randomized clinical study aimed at comparing the effects of phenylephrine and epinephrine in patients with out-of-hospital cardiac arrest did not find any differences between the drugs [22].

Among the α_2 selective agonists the most studied for its inability to pass the blood brain barrier is α -methylnorepinephrine (α -MNE). Unlike α_1 receptors, the α_2 are absent on the myocardium. Alpha-2 selective stimulation produces an increase in arterial pressure without increasing heart oxygen consumption.

Several experimental studies support the use of α -MNE during CPR. Recent observations on different animal models of cardiac arrest have shown that the use of this drug during CPR improves the return of spontaneous circulation, post-resuscitation myocardial function and the percentage of survival [23, 24]. Table 1 shows the results of a study comparing α -MNE with the two vasopressors currently suggested by ACLS guidelines.

Table 1. Comparison of α -MNE with two vasopressors

Group	CPR time (min)	N° of defibrillations	ROSC	Survival (h)
α -MNE	6.1 $\pm$ 0.2	1.8 $\pm$ 1.3	5/5	57 $\pm$ 14*
VPN	6.2 $\pm$ 0.3	2.4 $\pm$ 1.9	5/5	41 $\pm$ 8 †
EPI	6.1 $\pm$ 0.2	1.6 $\pm$ 1.3	5/5	31 $\pm$ 10 †
CONTROL	6.1 $\pm$ 0.2	2.0 $\pm$ 1.4	5/5	15 $\pm$ 6

Klouche K et al [24]

α -MNE= α -methylnorepinephrine, VPN= Vasopressin, EPI= Epinephrine, ROSC= Return of spontaneous circulation.

* $p < .01$ vs control, $p < .05$ vs VPN and EPI; † $p < .05$ vs control.

Beta-Blockade Drugs: The Laboratory Experience

At the beginning of the 1970s Maroko demonstrated that the use of propranolol, a non selective β -blockade, was associated with an improvement in the electrocardiographic trace after cardiac ischaemia either in experimental or in clinical settings [25, 26]. Obeid et al also demonstrated that propranolol preserves the ATP store in the ischaemic myocardium [27].

These and many other studies have shown how dangerous β -adrenergic stimulation of the heart is in conditions of poor oxygen supply. For many years this concept has been extended to cardiac arrest which actually produces global ischaemia.

In 1994 Ditchey produced experimental evidence that either the return of spontaneous circulation or post-resuscitation myocardial function were improved in animals treated with propranolol [28].

In his canine model of cardiac arrest two groups of dogs, 11 each, received 15 $\mu\text{g/kg}$ of epinephrine after the induction of ventricular fibrillation. One of the groups was pretreated with 2 mg/kg of propranolol. In this group the animals had a significantly higher coronary perfusion pressure, a better percentage of return of spontaneous circulation (9/11 vs 6/11) and a reduction in post-resuscitation myocardial dysfunction. In other words, the use of a nonselective β -blockade during cardiac arrest produced a reduction in ischaemic injury without compromising the success of resuscitation in the experimental setting. Our own research group subsequently confirmed these findings in rats [29].

Data coming from scientific literature continues to underline how detrimental β -adrenergic stimulation is on an ischaemic heart. As an alternative, α_2 selective agonist could be considered solutions deserving attention [24, 30].

Non Adrenergic Vasopressor

Vasopressin

The effects of this non-adrenergic vasopressor have been studied by several researchers. Interest in the drug grew particularly after the observation made by Lindner et al over a group of patients in cardiac arrest. They noticed a better outcome in those patients in whom the concentration of endogenous vasopressin was much higher when compared with patients who did not have return of pulse [31]. This finding suggested the possibility that vasopressin might have been a good choice during CPR.

Clinical observations together with experimental data [32, 33] prompted Lindner to test vasopressin in patients in cardiac arrest refractory to standard resuscitation. Eight patients were enrolled. After the failure of standard procedures 40 U of vasopressin were injected in the patients during rescue manoeuvres. All patients were successfully resuscitated and three of them were discharged from the hospital without neurological damage [34].

These encouraging findings prompted the same researchers to start a randomized study to compare vasopressin with epinephrine. The study enrolled 40 patients with out-of-hospital cardiac arrest. No difference was found in terms of hospital discharge or neurological recovery, although there was a small trend in favour of patients treated with vasopressin [35].

A wider randomized clinical study performed by a Canadian group and enrolling 200 patients with in-hospital cardiac arrest failed to find any advantage of vasopressin when compared with epinephrine [36] (Table 2).

Table 2. Hospital discharge (%)

	VPN	EPI	
<i>Rhythm</i>	N=104	N=96	<i>p</i>
<i>PEA</i>	9	10	NS
<i>ASY</i>	6	8	NS
<i>VF</i>	25	33	NS
<i>ALL</i>	12	13	NS

Stiell IG et al [36]

N= number of patients, VPN= Vasopressin, EPI= Epinephrine,
PEA= Pulseless electric activity, ASY= Asystole, VF= Ventricular fibrillation.

In a letter to the editor Lindner explained that vasopressin proves to be superior to epinephrine especially in marked conditions of acidosis. So vasopressin would be the best drug in patients with out-of-hospital cardiac arrest in whom the time window of no-flow state is longer and the acidosis is greater [37].

Starting from this assumption, Lindner et al performed another randomized study to compare vasopressin and epinephrine. They enrolled 1,186 patients with out-of-hospital cardiac arrest. Again, in contrast to expectations, no differences were found between the drugs with the only exception of patients in asystole in whom, in contrast with the Canadian group, vasopressin was more efficacious than epinephrine [38] (Table 3).

Table 3. Hospital discharge (%)

	VPN	EPI	
<i>Rhythm</i>	N=589	N=597	<i>p</i>
<i>PEA</i>	5.9	8.6	NS
<i>ASY</i>	4.7	1.5	0.04
<i>VF</i>	17.8	19.2	NS
<i>ALL</i>	9.9*	9.9*	NS

Wenzel V et al [38]

N= number of patients, VPN= Vasopressin, EPI= Epinephrine,
PEA= Pulseless electric activity, ASY= Asystole, VF= Ventricular fibrillation,
* 2.2 % is represented by patients in coma.

Further studies need to be done to have objective confirmation regarding the effects of vasopressors during CPR. At the time of writing, neither epinephrine nor vasopressin can be considered optimal drugs for CPR.

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INFECTIONS, SEPSIS, ORGAN DYSFUNCTION

Candida Infection in Critically Ill Patients

P.H.J. VAN DER VOORT

Some decades ago, yeasts were not recognized as pathogens [1, 2]. Since the 1980s the pathogenicity of fungi has gained more and more attention, first in immunocompromised patients and later on in critically ill patients as well [3]. Critically ill patients are frequently colonized with yeasts. Amongst other reasons, extensive use of broad spectrum antibiotics in critically ill patients lead to overgrowth in the digestive tract and other organs. Overgrowth is the most important factor in the development of fungal infection. This sequence of events is amplified by decreased motility of the digestive tract during critical illness. In addition, contributing to yeast infection is the fact that critically ill patients are immunodeficient, especially in the cellular immune functions.

The most important fungal infections in critically ill patients can be classified in (1) bloodstream infections, (2) abdominal infections, (3) urinary tract infections and (4) pulmonary infections. As urinary tract infections and pulmonary tract infections are either infrequent or clinically less relevant, this chapter shall focus on bloodstream and abdominal infections.

Epidemiology of Candidiasis in the Intensive Care Unit

The use of broad spectrum antibiotics in particular penicillins leads to a reduction in endogenous aerobic and anaerobic flora. In this situation yeasts can grow and lead to extensive colonization and overgrowth of the critically ill patient [4, 5]. It is therefore not surprising that the incidence of secondary (nosocomial) fungal infections in the intensive care unit (ICU) has increased over the years [6]. The incidence rose from 2 to 3.8 nosocomial fungal infections per 1,000 discharges over the period 1980 to 1990 in the USA [7]. The incidence has risen at all organ sites, but has been particularly marked in bloodstream infections. Risk factors for fungal infections are particularly present in the critically ill patient and include major surgery, burns, indwelling vascular catheter, parenteral nutrition, assisted ventilation and haemodialysis [8]. In addition, most patients in the ICU receive extensive antibiotic therapy leading to widespread yeast carriage and overgrowth.

From Carriage to Overgrowth and Infection

Yeast carriage has been proven to be an independent risk factor for fungal infection, especially bloodstream infections. It has been shown that increasing colonization (overgrowth) enhances the risk for infection [9, 10]. This concept is nicely shown by Pittet et al and condensed in a colonization index [10]. Voss et al proved this concept with DNA research by showing that the *Candida* strains which are found during candidaemia were also present as colonization before the bloodstream infection occurred [11]. The colonization index is the ratio of the number of colonized sites to the total number of sampled sites. A colonization index of 0.5 or more is associated with infection and may be subject to preemptive therapy.

The most important infections that may occur are the following.

Bloodstream Infection

The incidence of bloodstream infections with yeasts is low: between 0.2% [12] and 1.5% [13], however, the mortality is high: 60-80% [13].

Abdominal Infection

Primary fungal peritonitis is an infrequent reason for intensive care admission. In contrast, the most frequent fungal abdominal infection is secondary peritonitis due to a perforated gut. Sandven [14] analysed abdominal fluid from patients with a perforation of the digestive tract and found *Candida* in 64% of perforated stomach and duodenum, 53% for small bowel, 4% for perforated appendicitis, 50% for large bowel including rectal perforation. Other perforations were associated with a 17% prevalence of *Candida* in abdominal fluid. The study, however, did not analyse the number of patients colonized with *Candida* in the digestive tract. Dupont et al found in 271 patients with faecal peritonitis that *Candida* was present in abdominal cultures in 83 patients (31%) [15]. Calandra found *Candida* in 39% of all patients with perforated digestive tract [16]. Dupont found in his study that predictive factors of *Candida* in peritoneal fluid include heart failure, female gender, previous antibiotic therapy and location of the perforation in the upper gastrointestinal tract [17]. Although these studies inform us about the proportion of positive cultures, it is unknown whether this corresponds with the proportion of patients who are colonized with *Candida* in the digestive tract.

Pulmonary Infection

Pulmonary *Candida* infection is extremely rare but may occur [18]. When *Candida* is found in bronchial secretion, this is usually not an indicator of infection [19]. On the other hand, a high colonization index is associated with infection as previously explained. *Candida* in tracheal aspiration contributes to a high colonization index.

From that point of view, reduction of the number of colonized sites, including the lungs, may prevent invasive *Candida* infection, in particular fungaemia.

A French survey showed that a quarter of French intensivists treat colonization of the airways, defined as the presence of *Candida* in tracheal aspirate, with antifungal agents [20]. In our ICU, we usually treat *Candida* colonization of the airways with topical agents such as a 5-mg dose of aerosolized amphotericin B four times daily.

Urinary Tract Infection

Magill et al found that a statistically significant number of patients with urinary candidiasis more frequently developed invasive candidiasis compared to those without candiduria [21]. This was also true for respiratory and rectal carriage of *Candida*. However, in contrast to other sites, candiduria at any time of intensive care treatment was associated with an increased ICU mortality with an odds ratio of 2.86 (95% CI 1.05-7.74).

The Yeast Carriage Data of a Dutch Mixed ICU

Over one calendar year in one 12-bedded ICU (Medical Centre Leeuwarden, The Netherlands) all cultures were analysed from 519 patients. Cultures were taken from organ sites as well as the throat and rectum. The routine culture scheme for each patient is shown in Table 1. A total of 5050 cultures were taken, 2501 from organ sites and 2549 from the throat and rectum. The pathogens that were identified are shown in Figure 1.

Table 1. Cultures taken to detect fungal carrier state

Site	On admission	Surveillance
Throat	x	Twice weekly
Rectum	x	Twice weekly
Sputum	x	Twice weekly
Wounds	x	Twice weekly
Urine	x	On indication
Drains	x	Twice weekly

Yeasts were identified in 936 out of these 5050 culture samples (18.5%). The distribution of yeast positive cultures is shown in Figure 2. In 928 cultures the *Candida* could be classified (Figure 3). *Candida glabrata* was not identified as such although it is likely that it makes up the majority of the *Candida* species.

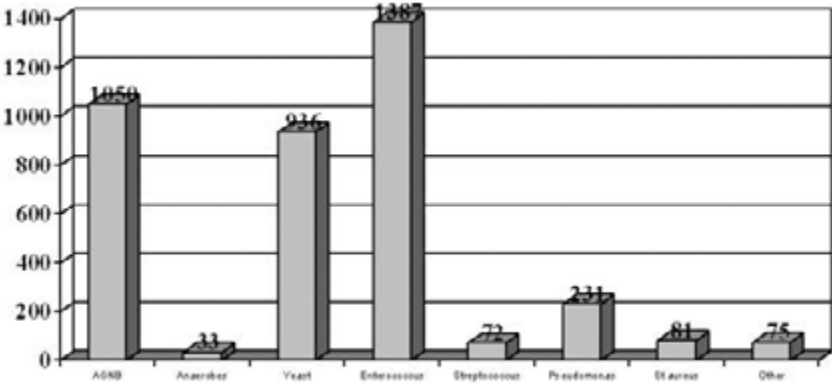


Fig. 1. The microorganisms detected in 5050 cultures of 519 critically ill patients. AGNB: aerobic gram negative bacilli

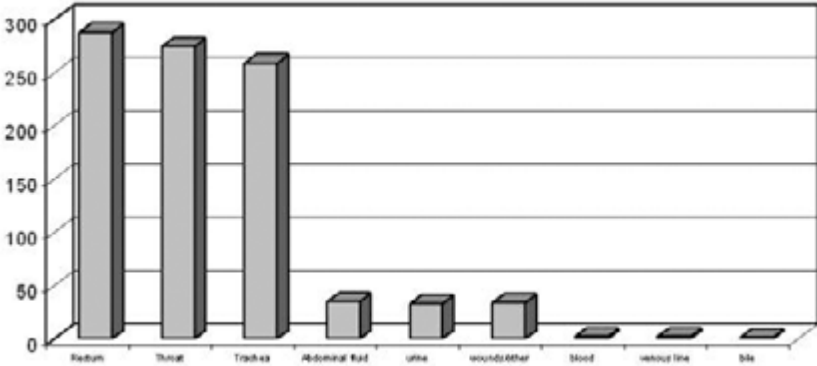


Fig. 2. Distribution of yeast positive cultures taken from 519 critically ill patients over one calendar year

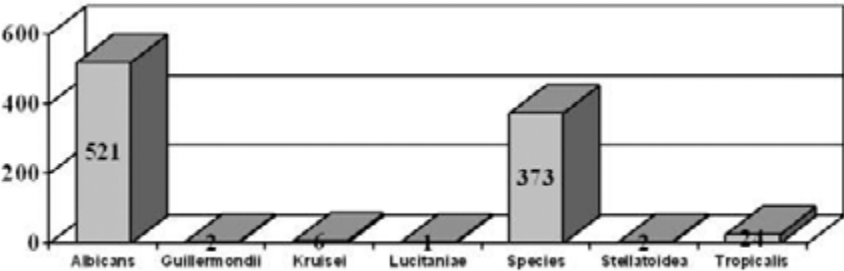


Fig. 3. The distribution of *Candida* species in 928 cultures containing yeasts

Prevention

When carriage and overgrowth promote and precede infection, this implies that reducing and eliminating carriage will lead to a decrease in fungal infections. The aim of selective decontamination of the digestive tract (SDD) is the eradication of actual colonization at the beginning of treatment and the prevention of secondary colonization of potential pathogenic microorganisms (PPM) including aerobic gram negative bacteria (AGNB) and yeasts. A meta-analysis concluded: *In critically ill immunocompetent patients who are at high risk of fungal infection, topical nonabsorbable gastrointestinal antifungal prophylaxis was associated with a reduced incidence of urinary fungal infections and a trend toward reduction in respiratory fungal infections and fungaemia* [22]. A largely similar conclusion was drawn by Silvestri et al in a meta-analysis on SDD on fungal carriage and infection. Carriage of yeasts was decreased with an odds ratio of 0.32 and fungal infections under SDD were reduced with an odds ratio of 0.30 [23]. Unexpectedly, the incidence of fungaemia was not reduced by SDD. There were 20 patients infected by fungi in the SDD group (20/1,577, 1.3%) and 62 controls (62/1,605, 3.9%). These data demonstrate that SDD significantly reduces the fungal infection (OR 0.30, 95% CI 0.17-0.55). Thirty-eight patients needed to receive SDD to prevent one fungal infection (NNT 38.54, 95% CI 38.53-38.55).

The antifungal agent used in SDD is usually amphotericin B but the reduction in colonization and infection was also seen when nystatin was used. Both polyenes are not absorbed, thus they exhibit a pure topical action in the digestive tract.

In addition to the elimination of yeasts from the digestive tract, the colonization index can be further decreased by decontaminating the lower airways as well. Aerosolized amphotericin B was shown to reduce pulmonary colonization with *Aspergillus* [24]. In our experience it is also effective in yeast colonization. The recommended dose is 5 mg four times daily by nebulizer. The respiratory filter should be changed after each nebulization.

Prophylactic Therapy

Eggiman in 1999 prophylactically treated high risk surgical patients with fluconazole or placebo [25]. In the fluconazole group 1 out of 23 patients (4%) developed *Candida* peritonitis postoperatively compared to 7 out 20 patients (35%) in the placebo group. All patients with *Candida* peritonitis were previously colonized with *Candida*. All-cause mortality was not different, although 4 patients in the placebo group died because of *Candida* peritonitis.

Garbino [26] found that high-risk ICU patients less frequently suffered from *Candida* infection (in particular candidaemia) when treated with fluconazole in addition to SDD. In this study, the SDD did not contain an antifungal component such as amphotericin B or nystatin. Pelz showed a 55% reduction in *Candida* infection in high-risk surgical ICU patients who were prophylactically treated with fluconazole [27]. In a meta-analysis fluconazole/ketoconazole reduced total mor-

tality by one quarter (relative risk 0.76, 95% CI 0.59-0.97) and invasive fungal infections by about one half (relative risk 0.46, 95% CI 0.31-0.68). No significant increase in the incidence of infection or colonization with the azole-resistant fungal pathogens *Candida glabrata* or *Candida krusei* was demonstrated, although the confidence intervals of the summary effect measures were wide [28]. Another meta-analysis on prophylactic fluconazole treatment also showed a significant reduction of fungal infections (pooled OR, 0.44; 95% CI, 0.27-0.72; $p < 0.001$) but no improvement of survival was observed [29].

Preemptive Therapy

Preemptive antifungal therapy is the early treatment of the infection with the use of clinical, laboratory, or radiological surrogate markers of disease in high-risk patients before clinical signs and symptoms or full-blown disease develop.

This therapy may include patients with a faecal abdominal spill perioperatively and treated with an antifungal agent postoperatively. The case for starting antifungal treatment is that at least 50% of the population is colonized with *Candida* in the digestive tract (see above). Pure preemptive therapy has been studied occasionally. Piarroux described preemptive treatment with fluconazole for 2 weeks in surgical intensive care patients every time that a corrected colonization index (CCI) of more than 0.4 was present. The CCI is the ratio of highly positive samples to the total number of samples cultured. The study was a before-after design [30]. The preemptively treated cohort had significantly less proven *Candida* infections.

Empirical Therapy

Empirical antifungal therapy is the treatment of high-risk hosts who exhibit signs and symptoms of the disease, even in the absence of positive cultures or other evidence of disease. Included are patients with sepsis and a possible fungal genesis.

Jacobs et al studied patients with septic shock. They were treated with fluconazole or placebo on admission to the ICU [31]. Eighteen patients with pneumonia and 14 patients who were diagnosed with abdominal sepsis were treated with fluconazole. Nineteen patients with pneumonia and 20 with abdominal sepsis were the control group. A significant lower mortality rate was found in the treatment group which was entirely due to the abdominal sepsis group. In fact, it can be postulated that this effect on mortality was reached because of early treatment of abdominal *Candida* infection.

Empirical Treatment of Critically Ill Patients with Abdominal Sepsis in a Dutch ICU

Over an episode of 2.5 years, in our ICU 141 patients were admitted with multiple organ failure in the course of peritonitis. All patients had a perforation of the digestive tract (either upper or lower). The standard antibiotic therapy was empirically cefotaxime 4 td 1000 mg, ciprofloxacin 2 td 400 mg, metronidazole 4 td 500 mg and SDD for all patients. The SDD consists of oral paste and gastric suspension 4 td with 2% polymyxin E, tobramycin and amphotericin B. In addition, all patients received 0.5 mg/kg amphotericin B by continuous infusion i.v. When abdominal cultures revealed *Candida* species, the amphotericin B was increased to 1.0 mg/kg i.v. and flucytosine was added. The dose of flucytosine was adapted to renal and liver function between 2.5 and 5.0 g per day by continuous infusion guided by serum levels (target 80-100 mg/l).

In 36% (51 patients) *Candida* was cultured from abdominal fluid. In total, 93 cultures of abdominal fluid revealed *Candida*. Of these 93 isolates, 58 were *C. albicans* and 35 were non-albicans. *C. krusei* was found in none of the cultures.

The results of this empirical antibiotic and antifungal strategy was an APACHE II related standardized mortality ratio (SMR) of 0.75 for all patients, with or without *Candida* in the peritoneal fluid. The patients with *Candida* species had an SMR of 1.07. The mortality of patients with *C. albicans* was significantly lower compared to patients with non-albicans species (figure 4). The median length of stay of patients with *Candida* was 17.4 days compared to 10.9 for the complete group of patients with peritonitis.

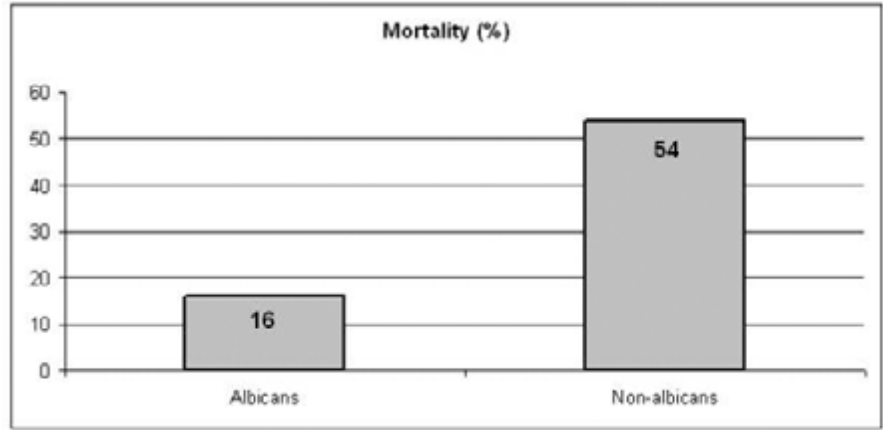


Fig. 4. The hospital mortality of *C. albicans* vs. non-albicans in abdominal fluid of critically ill patients with abdominal sepsis. $p=0.007$ (Chi-square test)

Therapy of Established Infection

The treatment of established fungal infection in the specific group of critically ill patients has not been studied thoroughly. Again, two kinds of infections are of interest: abdominal infection and fungaemia.

In two comparative studies of fluconazole versus amphotericin B the efficacy was similar [32, 33]. Rex found a slightly better outcome for amphotericin B in some additional analyses [32].

Amphotericin B is increasingly seen as an old-fashion drug for the treatment of invasive fungal infection [34]. The newer agents are not more effective but are in most studies less toxic. However, toxicity is dependent on cumulative dose and rate of infusion. A continuous infusion guided on serum levels may be effective and safe but needs further study. Eriksson et al [35] compared 39 patients with continuous infusion of amphotericin B with 31 patients treated with bolus infusion. The continuous infusion group suffered significantly less from side effects including renal failure [35, 36]. Imhof et al treated 33 patients with increasing doses of amphotericin B by continuous infusion starting with 1.0 mg/kg and increasing to 2.0 mg/kg [37]. In 5 patients the serum creatinine declined to less than half of the serum level at the start of therapy. Few patients experienced a mild increase in serum creatinine level, and none of the patients required dialysis. A problem in the assessment of toxicity is that in critically ill patients with multiple organ failure it may be difficult to determine whether organ failure is due to the disease or results from treatment.

Treatment of Abdominal *Candida* Infection or *Candida* Peritonitis

For the treatment of the specific situation of critically ill patients in multiple organ failure after perforation of the digestive tract, no randomized studies are available. Abele-Horn et al described 9 out of 36 patients treated with amphotericin B combined with flucytosine compared to 8 out of 36 treated with fluconazole. Clinical cure was reached in 55% with amphotericin B and flucytosine compared to 25% in patients treated with fluconazole [38]. However, a rise in serum creatinine was seen in 31% of the patients with amphotericin B – flucytosine. When amphotericin B is used for *Candida* peritonitis, it was shown that intraperitoneal amphotericin B levels above MIC will be reached when serum levels are above 0.5 mg/l [39]. For reasons of effectiveness and toxicity, amphotericin B levels of 0.5-1.0 mg/l should be aimed for during continuous infusion. In my opinion, amphotericin B is still a valuable drug for the treatment of fungal infections in critically ill patients because of its high efficacy combined with low costs. However, most studies use fluconazole as a first line antifungal agent. The main risk with the use of fluconazole is an initially ineffective treatment when *C. krusei* or *C. glabrata* are present. Voriconazole has no apparent advantage above fluconazole for yeast infections but is the drug of choice for *Aspergillus* infections. When fluconazole resistant *Candida* species are suspected, Caspofungin is a costly but reliable agent, as is the 'old

fashioned' amphotericin B. When amphotericin B is used it is advised to guide therapy on serum levels both for effectiveness and toxicity (target level 0.5-1.0 mg/l). A disadvantage for fluconazole is the relatively large volume of infusion and the interaction with several frequently used medication in the ICU. Surveillance cultures or previously taken clinical cultures may guide the choice of the antifungal agent.

Conclusions

Fungal infection is associated with significant morbidity and mortality. Invasive infection is virtually always preceded by excessive colonization and overgrowth. Consequently, infection can be prevented by eliminating colonization and overgrowth. The most effective and studied strategy to obtain that situation is SDD by topical administration of amphotericin B at all colonized sites. When infection occurs, systemic treatment with an antifungal agent is obligatory. Amphotericin B is effective and cheap. Toxicity can be limited by continuous infusion and the use of serum levels. Other agents, all with their specific pros and cons, are fluconazole, voriconazole and caspofungin.

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Predisposition to Sepsis

J.C. MARSHALL

«It is much more important to know what sort of patient this disease has,
than what sort of disease this patient has ...»
- William Osler

Sepsis is defined as the host response to invasive infection [1]. But while the trigger – infection – typically originates outside the host, the response that drives the phenotype of the illness arises endogenously. As a consequence, it is highly, and perhaps counterintuitively, shaped by pre-existing factors within the host that predispose him or her to a distinctive risk of acquiring infection, and having acquired that infection, of surviving the acute illness.

As efforts to better stratify patients with sepsis gain momentum, characterization of factors that result in a differential risk of adverse outcome, or a differential potential to respond to intervention, become increasingly important. A candidate model – the PIRO model – was proposed by an international consensus conference in the early part of this decade, based on the assumption that factors reflecting baseline predisposition, the nature of the insult, the character and degree of response, and the degree of organ dysfunction present at baseline [2]. This brief review considers dimensions of baseline predisposition that can alter the clinical course of severe sepsis or septic shock (Table 1).

Table 1. Predisposition to sepsis

Genetic factors	Gene deletions Single nucleotide polymorphisms (SNPs) Copy number variation (CNV)
Age	Prematurity or advanced age
Sex	
Race	
Medical co-morbidities	Chronic illness (diabetes, congestive heart failure), pre-existing organ dysfunction (cirrhosis, renal failure), physical impairment, mental impairment
Previous clinical intervention	Major surgery, endotracheal intubation, antibiotics
Religious or cultural attitudes	

Genetic Predisposition to Sepsis

The role of genetic factors in determining outcome from infectious diseases was demonstrated convincingly by a Scandinavian, population-based study of premature mortality in adopted children [3]. The investigators studied 960 children born between 1924 and 1926 and adopted into and raised in unrelated families, assessing the risk of premature death before the age of 50 in this cohort and their adoptive and biological parents. They found that although environmental factors were associated with an increased risk of premature death from cancer or cardiovascular disease, genetic factors were most strongly associated with premature death from infection (Figure 1).

Genetic factors can influence both susceptibility to sepsis and prognosis for an unfavourable outcome when infection develops. A brief review of the biology of gene expression is in order.

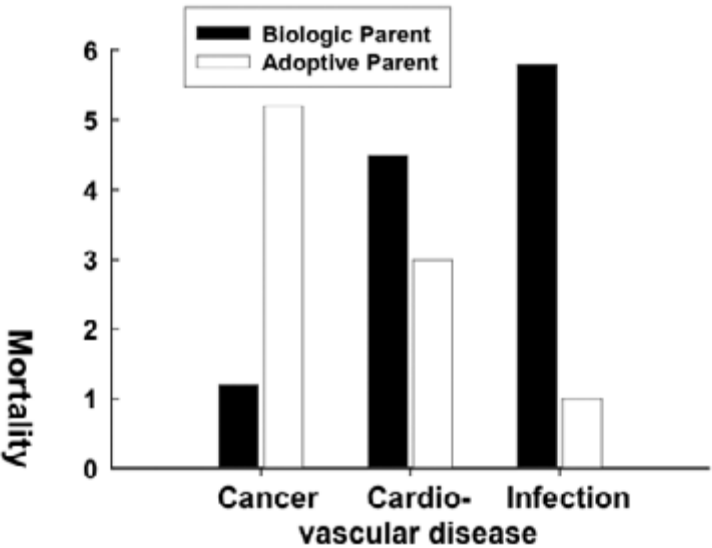


Fig. 1. The impact of environmental and genetic factors on premature mortality from common disease processes. This population-based study of adoptees and their biological and adopted therapy considered early mortality to be a consequence of genetic factors when both the adoptee and the biological parent died a premature death from the same cause (dark bars), and of environmental factors when the adoptee and the adopted parent died from the same cause (clear bars). For patients dying of infection, the impact of environmental factors was minimal, whereas genetic factors resulted in an increased mortality risk of almost six-fold. Data are from [3].

Gene Expression

Biological information is encoded in deoxyribonucleic acid, or DNA, contained in the nucleus of the cell. A single strand of DNA is a polymer of more than 3 billion individual nucleotide bases attached to a backbone of phosphate and sugar residues. There are four distinct bases in humans: adenine (A), cytosine (C), guanine (G), and thymine (T). Each pairs with a complementary base – A with T and G with C – to create the double helix of the DNA molecule. Sections of the DNA molecule known as genes are transcribed into RNA (in which T is replaced by uracil or U) which, in turn, is translated on ribosomes into new protein. The sequence of the 20 different amino acids that comprise a newly formed protein is determined by the sequence of codons – sequences of three consecutive base pairs – in the RNA molecule; each codon designates a specific amino acid. Since there are 64 possible sequences for a codon (4^3), a given amino acid is typically specified by more than one codon. For example, the amino acid tyrosine is specified by the sequences UAU and UAC, the amino acid leucine by UUA, UUG, CUU, CUC, CUA, or CUG, and the amino acid histidine by CAC. The sequence AUG (methionine) initiates the process of translation, while the sequences UAG, UGA, and UAA stop translation, and are known as stop codons.

The information specifying the translation of a specific protein is contained in gene sequences known as exons; an exon comprises a portion of the open reading frame that is translated into protein. Between these exons lie stretches of DNA that do not participate in protein translation, and whose function is poorly understood, known as introns (Figure 2). Specific nucleotide sequences at the 5' end of the gene

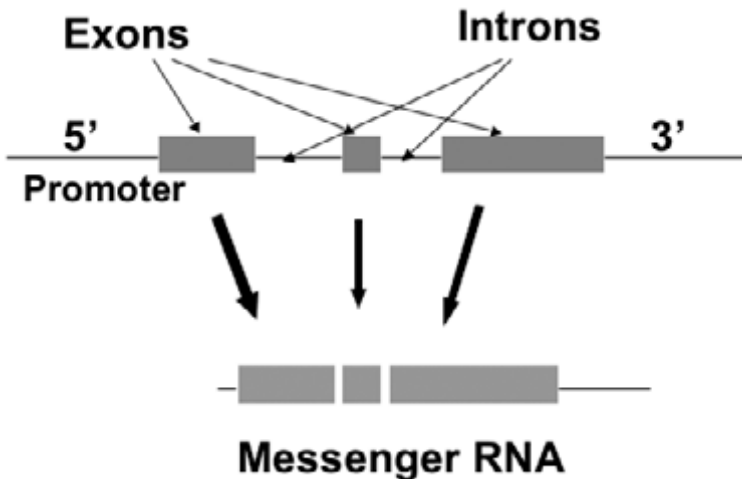


Fig. 2. A schematic representation of the transcription of DNA to RNA. Only certain segments (introns) are transcribed, while the exons are spliced out. Specific sequences in the proximal (5') and distal (3') end of the gene regulate the rate of transcription and the stability of the resulting message, respectively.

(the site where the process of gene transcription begins) bind proteins known as promoters that regulate gene expression. The end of the gene consists of a sequence of non-translated nucleotides known as the 3' untranslated region; this portion of the gene plays an important role in message stability.

Single Nucleotide Polymorphisms

The best characterized genetic alterations involved in disease susceptibility arise through mutations in a single nucleotide in a gene; these mutations are known as single nucleotide polymorphisms (SNPs). The impact of the mutation depends on the role of the involved nucleotide in gene expression. If it is in the coding region, the amino acid structure of the resulting protein will be altered, with the result that the tertiary structure of the protein may be changed, and hence its function altered. Alternatively, if the mutation is in the promoter sequence, the rate of gene transcription may be altered, while if it is in the 3' untranslated region of the gene, the stability of the gene may be affected; both of these changes can affect the amount of protein product that is ultimately translated. A mutation may also result in the erroneous insertion of a stop or start codon in a gene sequence, and so alter transcription of that gene. Even mutations in the non-coding intronic regions of the gene can alter the function of the resulting protein, pointing to a role for these sequences in gene expression.

It is estimated that SNPs occur once in every 1000 base pairs throughout the genome, and that there are between 10 and 20 million discrete SNPs in the human genome [4]. The HapMap project – an international consortium formed to document variability in the human genome – has identified more than one million SNPs in samples from 269 individuals derived from four distinct populations [5]. SNPs are particularly prevalent in genes involved in innate immunity [6], reflecting, perhaps the rapidly changing immunological prerogatives that arise from exposure to new infectious threats from the environment. Many of these have been linked to differential susceptibility to adverse outcome in sepsis [7, 8]. The mere association of an SNP with an altered risk of adverse outcome, however, is not sufficient to establish a specific causal role for the gene. Multiple factors can result in spurious associations between a genetic variant and a phenotypic effect [9].

Table 2 summarizes known polymorphisms in cellular receptors or soluble proteins involved in the initial recognition of tissue invasion by micro-organisms or their products. Well-characterized polymorphisms are also present in cytokines, cytokine receptors, components of the coagulation cascade, genes involved in signal transduction and gene expression, and genes involved in programmed cell death, or apoptosis. A detailed description is beyond the scope of this brief review; a number of excellent recent reviews can provide a more comprehensive overview [7, 8, 10-12]. However, several specific polymorphisms are worthy of discussion here.

Table 2. Genetic polymorphisms in proteins involved in pathogen recognition and associated with differential outcomes in sepsis

Gene	Polymorphism	Consequence
TLR2	753 Arg→Gln T-16933A	Increased risk of staphylococcal infection [61] Increased risk of Gram positive infection [62]
TLR4	299 Asp→Gly 399 Thr→Ile	Increased susceptibility to Gram negative infection [63, 64] Increased risk of Candida infection [65]
TLR5	392 Arg→Stop	Increased risk of Legionnaire's disease [66]
TLR9	1635A/G	Progression of HIV infection [67]
CD14	C-159T	Increased risk of Gram negative infection [62] Increased risk of septic shock and death [68]
MD2	C-1625G	Increased risk of sepsis following trauma [69]
NOD2/CARD15	Leu1007fsinsC	Increased risk of mortality [70]
Mannose-binding lectin	Various	Increased risk of pneumococcal infection [71] Increased septic shock, ARDS [72, 73]
LBP	98 Cys→Gly	Increased sepsis in males [74]
CRP	A-717G	Increased mortality from <i>S. pneumoniae</i> [75]

Tumour Necrosis Factor

Tumour necrosis factor (TNF) is a cardinal pro-inflammatory mediator that is released within hours following experimental exposure to endotoxin [13]. As one of the first endogenous cytokines whose neutralization was shown to prevent lethality in a variety of animal models of sepsis [14, 15], TNF was an attractive therapeutic target for early studies of mediator manipulation in sepsis. Thirteen phase II and phase III trials, enrolling more than 7000 patients, have been undertaken to assess the efficacy of anti-TNF therapy (both neutralizing antibodies and soluble receptor constructs) in sepsis. Only one of these showed improved survival following neutralization of TNF [16], however when the results of all are combined using meta-analytic techniques, there is evidence of a consistent, though small survival benefit of approximately 3% [17]. Anti-TNF therapies have not been approved for clinical use in sepsis, although they have found a therapeutic role in chronic inflammatory diseases such as rheumatoid arthritis [18] and inflammatory bowel disease [19].

A G-A polymorphism in the promoter region of the TNF α gene, i.e. 308 base pairs proximal to the transcription initiation site, is associated with increased release of TNF, and with increased susceptibility to a number of autoimmune and infectious diseases [20, 21]. Epidemiologic studies have reported that the presence of the -308A polymorphism is also associated with increased rates of sepsis, and an increased risk of death from septic shock [22, 23], although results are not always consistent across studies. Pooled data from studies of anti-TNF therapies for rheumatoid arthritis reveal that the greatest benefit accrues to patients with the -308A promoter polymorphism [24]. Thus future trials of anti-TNF therapies in

critically ill patients may best be directed towards the approximately 20% of patients who carry this polymorphism.

Protein C

Protein C is a key anticoagulant protein produced in the liver, and activated through its interaction with thrombomodulin on endothelial cells. Following activation, protein C blocks coagulation by inhibiting factors V and VIII [25], and downregulates inflammatory gene expression following its binding to the endothelial protein C receptor [26]. Because both the synthesis and activation of protein C is impaired in sepsis, a recombinant version of the activated protein, known as drotrecogin alpha activated, was evaluated as an adjuvant treatment for sepsis, and shown to significantly improve survival for the sickest patients [27].

An A/G polymorphism is present at -1641 in the promoter region of the protein C gene. The AA genotype is associated with an augmented inflammatory response, increased organ dysfunction, and reduced survival in patients with severe sepsis [28]. A polymorphism in the factor V gene known as factor V Leiden renders factor V resistant to inactivation by activated protein C. A large population-based study based in Denmark found that the factor V Leiden mutation is associated with an increased risk of skin infections, and an increased risk of death for patients hospitalized with sepsis [29]. Thus it appears plausible that diagnostic genotyping may be useful in determining which patients are best treated with activated protein C.

Pre-B Cell Colony Enhancing Factor/Visfatin

Pre-B cell colony enhancing factor (PBEF) is a multifunctional protein that is upregulated in neutrophils from patients with sepsis, and whose activity contributes to prolonged neutrophil-mediated inflammation by inhibiting neutrophil apoptosis [30]. As an intracellular enzyme, PBEF is the rate-limiting step in the biosynthesis of NAD [31], while as an extracellular cytokine-like molecule, it binds to the insulin receptor, exerting both agonist and antagonist activity [32], and upregulates the expression of IL-6 and IL-8 [33].

PBEF expression is increased in both sepsis [30] and acute respiratory distress syndrome (ARDS) [34]. Two polymorphisms in the promoter region of the PBEF gene have been linked to differential effects in critical illness. Patients with a T-1001G polymorphism have a significantly greater risk of developing ARDS, and an increased risk of ICU mortality, whereas a C-1543T polymorphism is associated with a decreased risk of ARDS in patients with sepsis, with a decreased duration of mechanical ventilation, and with a decreased risk of ICU mortality [35]. An improved understanding of the functional consequences of these two polymorphisms will shed light on fundamental mechanisms underlying risk in patients with ARDS.

Other Mechanisms of Genetic Variability

Studies of the role of SNPs in critical illness have tended to focus on SNPs in discrete mediator molecules. However, polymorphisms in intracellular proteins involved in transducing a signal from the cell surface, and in regulating gene expression in response to that signal, have also been recognized. A T1595C polymorphism in the IRAK-1 gene results in increased nuclear translocation of NF κ B, and is associated with an increased risk of shock, organ dysfunction, and 60-day mortality in sepsis [36]. A SNP in the caspase-12 gene transforms a stop codon into an amino acid, and results in the transcription of a longer caspase-12 protein. This caspase-12L protein is found at higher frequencies in African-Americans, and is associated with hyporesponsiveness to lipopolysaccharide, and an increased risk of sepsis [37]. In addition, a polymorphism in the coding region of the gene for Mal – a component of the intracellular signal transduction mechanism for signals from TLR2 and TLR4 – results in the replacement of a serine by a leucine. Heterozygosity for this trait is protective against malaria, pneumococcal disease and tuberculosis in widely divergent patient populations [38].

While SNPs have received the most attention as genetic variations associated with functional consequences, other abnormalities in DNA structure including deletions, inversions, duplications, and variable number tandem repeats (VNTRs) are associated with phenotypic and functional consequences. Large deletions or duplications in DNA are known as copy number variations (CNVs), and are an important source of genomic variation, with more than 1200 specific CNVs having been identified to date [39]. Their role in predisposition to sepsis is unknown.

Age, Sex, and Race

The likelihood of developing sepsis, and of surviving the illness once it has occurred, is significantly affected by the age and sex of the patient.

Although severe sepsis may develop in patients of all ages, it is disproportionately a disorder of the very young and the very old (Figure 3) [40, 41]. In the neonate, immaturity of innate and adaptive immune defences, together with inborn immune deficiency states contribute to an increased risk of developing severe sepsis. The problem is particularly severe in the developing world, where physiological immaturity and poverty interact to result in approximately 4 million neonatal deaths a year [42]. At the other end of the spectrum of age, impaired humoral and cell-mediated immunity, often in the context of chronic co-morbid illness, combine to effect a striking increase in predisposition to sepsis that becomes evident after the age of 60, and continues to increase exponentially [43]. In fact, although persons over 65 account for only 12% of the American population, they represent 64.9% of patients with sepsis, a relative risk of 13.1 (95% CI, 12.6-13.6) when compared with those under 65 [44].

Age is not only a risk factor for susceptibility to sepsis; as it can also differentially affect the response to treatment. For example, therapy with activated protein

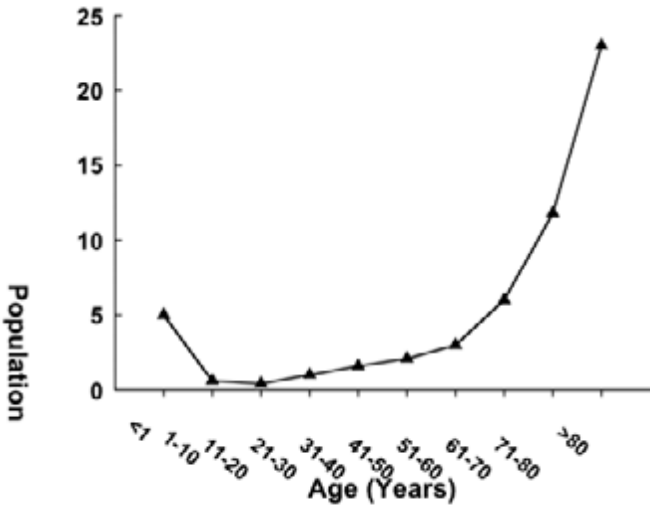


Fig. 3. The impact of age on rates of sepsis in the United States. Highest rates are seen in the very young and the old. Adapted from [48].

C appears to be particularly effective in patients older than 75 years of age, albeit at the cost of an increased risk of bleeding [45]. Conversely, the drug has not shown efficacy when used in paediatric patients with sepsis [46]. In animal models, age appears to differentially affect the response to antibiotics, with younger animals deriving a survival benefit that is not apparent in older animals [47].

Sepsis develops more significantly frequently in men, with a mean annual relative risk of 1.28 (95% CI 1.24-1.32) [48], and men are disproportionately represented in clinical trials testing novel sepsis therapies (Figure 4). Whether sex is associated with differential clinical outcomes or response to treatment is less clear, although women appear to have a higher mortality associated with hospital-acquired pneumonia or other infections resulting in ICU admission [49, 50].

Rates of sepsis are higher in African-Americans than in whites [44]. Both rates of hospitalization and mortality are increased for black patients [51], although the relative importance of genetic factors, socioeconomic factors, and co-morbidities in differential outcomes is difficult to evaluate.

Medical Comorbidity – Chronic and Acute

Severe sepsis and septic shock commonly arise as a complication of another potentially life-threatening disorder, and clinical course and risk are significantly impacted by the preceding disease process [52]. More than half of patients with severe sepsis or septic shock have a concomitant medical condition that can independently alter prognosis [41], for example, diabetes, chronic lung disease,

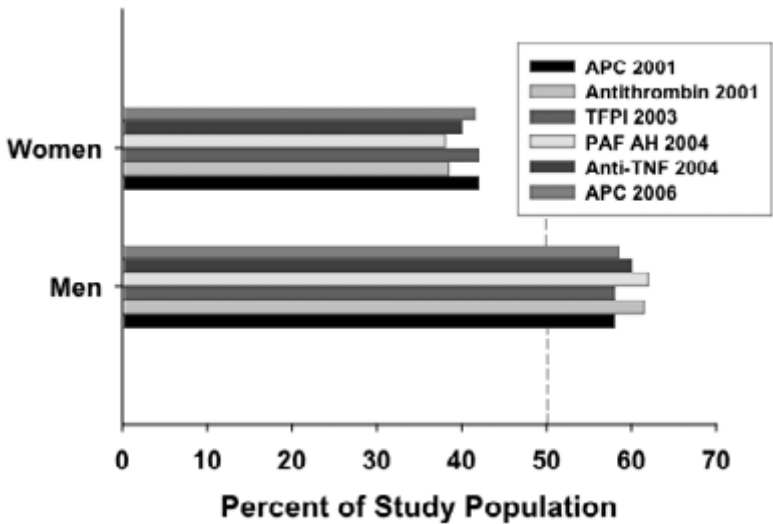


Fig. 4. The impact of sex on predisposition to sepsis. Consistently in large clinical trials of novel therapeutic agents for sepsis, men are significantly over-represented; characteristically the population of enrolled patients is 60% males and 40% females. Data are from 6 recent large trials of mediator-targeted therapy for sepsis [27, 76-80].

congestive heart failure, cirrhosis, malignancy, neuromuscular disorders, or HIV/AIDS. The presence of a rapidly or ultimately fatal underlying disorder – particularly liver or cardiovascular disease – is associated with late death from sepsis [53].

The impact of chronic medical comorbidity is complex. Certain disorders such as cirrhosis, congestive heart failure or chronic renal failure are associated with altered patterns of colonization by the endogenous flora of the gastrointestinal tract [54], and in particular, by proximal gut overgrowth with Gram negative organisms and increased concentrations of circulating endotoxin in the blood [55-57], indicating that chronic exposure to bacteria or their products is increased. Multiple abnormalities of innate and adaptive immunity have been described in such patients, but it has not been possible to attribute an increased risk to any discrete derangement. Chronic illness is commonly associated with a decreased physiological reserve, and so with an incapacity to mount the type of adaptive physiological response that is needed to meet the increased metabolic needs of sepsis. Finally, comorbidities may alter patient preferences for prolonged supportive care, and so impact the intensity of ICU support.

Critical illness can be both the consequence and the cause of severe sepsis and septic shock. When nosocomial infection complicates the course of multiple trauma or other life-threatening acute illness, the risk of mortality is increased, although the morbidity directly attributable to the infectious episode is difficult to quantify. Studies in pre-clinical models show that a prior acute insult such as

haemorrhage modifies the host response to a second insult, generally priming for a greater degree of injury than would have occurred with the second insult alone [58, 59].

Social, Cultural and Religious Factors

Sepsis develops in human beings who inhabit a complex world, and so multiple social, cultural, religious, and economic factors that are present prior to the onset of the acute illness can impact its outcome. The baseline risk of mortality, for example, varies significantly from one country to the next, even within areas such as Europe where economic differences are minimal. The mortality of sepsis in European ICUs ranges from a low of 10% in Switzerland to 35% in its neighbour to the immediate south, Italy [60]. The reasons for these differences are poorly understood, but likely to include differences in case-mix, ICU organization, ICU admission criteria, and socio-economic factors. When outcome from sepsis is measured at an early time point such as 28 days following ICU admission, religious or cultural differences regarding prolongation of life-sustaining care can artefactually influence survival statistics.

Conclusions

Sepsis is a disease process that affects a population of patients rendered particularly vulnerable to infection by virtue of a host of factors, including genetic predisposition, age, sex, and race, acute and chronic co-morbidities, and a complex series of social and cultural influences. Genetic variability is of particular importance in defining who might or might not benefit from specific targeted adjuvant therapies, while sociological differences may reflect practice variability and differential responses to a broad variety of interventions. As we refine our capacity to stratify patients with sepsis – both for clinical research and clinical practice – a more sophisticated approach to the description, measurement, and staging of these elements of predisposition should translate into more targeted and effective therapeutic interventions.

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SOFA Score: A Keystone for Grading Multiple Organ Dysfunction

J.-L. VINCENT

Multiple organ failure is the leading cause of death in critically ill patients. Scoring systems are now widely used in the intensive care unit (ICU) to describe organ dysfunction and predict survival. Early systems focused primarily on survival prediction or the presence or absence of organ failure, but newer scores can describe the evolution of individual and multiple organ dysfunction over time. The sequential organ failure assessment (SOFA) score is one of the most widely used organ dysfunction scores and in this chapter we will discuss its development, its current role in intensive care patients, and its likely use in the future.

Background to Organ Dysfunction Scores

Characterizing ICU patients according to their severity of illness and likely outcome is important in terms of prognostication, ICU organization and resource allocation, and for the inclusion in and the interpretation of clinical trials. Over the years various scores have been developed for this purpose; these can be largely grouped into admission outcome prediction scores, such as Acute Physiology Chronic Health Evaluation (APACHE) II [1] or Simplified Acute Physiology Score (SAPS) II [2], and organ dysfunction scores, such as SOFA [3] or Multiple Organ Dysfunction Score (MODS) [4]. Prediction scores, by providing an estimation of the risk of mortality, do offer some information regarding disease severity, but give no detail about the patterns of organ failure or about changes in disease severity over time. Organ dysfunction scores, however, can describe organ failure as a continuous variable rather than an on/off phenomenon. Critical care medicine is a very dynamic environment and the degree of organ dysfunction experienced by a patient can improve or worsen with time. Patterns of organ dysfunction can also change over time. Organ dysfunction scores therefore need to be able to take this time factor into account, assessing organ function as a continuum rather than a single present/absent event, and to be able to separate out evaluation of the individual organ systems to provide detail of how patterns of organ function differ over time and in response to therapy. Many of the earlier organ dysfunction scores are no longer or rarely used because they do not meet one of these two important criteria [5-10].

With increasing realization of the importance of multiple organ failure as a

cause of death in the ICU, there was a new impetus for the development of an effective means of assessing organ dysfunction over time. The MODS score was one of the first of the newer scores and was developed from a literature review of all the studies of multiple organ failure published between 1969 and 1993 [4]. Six organ systems were selected to be included (respiratory, cardiovascular, renal, hepatic, central nervous, and coagulation) and a score of 0 (normal) to 4 (most dysfunction) awarded for each system giving a total maximum score of 24. The creators of the MODS score used an artificial variable, the pressure-adjusted heart rate (heart rate $\times$ central venous pressure/mean blood pressure), to assess cardiovascular dysfunction, which can limit the use of the score in patients who do not have a central line. One year later, the SOFA score was developed from the MODS.

Development and Validation of the SOFA Score

The SOFA score (Table 1) was developed during a consensus conference organized by the European Society of Intensive Care and Emergency Medicine in Paris in December 1994 [3]. The aim of the conference was to develop a score that could be used to describe quantitatively and as objectively as possible the degree of organ dysfunction/failure over time in ICU patients [3]. The 51 conference participants selected the same six organ systems that had been used in MODS: respiratory, cardiovascular, renal, hepatic, central nervous, and coagulation. Other systems, e.g., the gastrointestinal and metabolic systems, were felt to be important but were either too complex to evaluate or there was no simple variable that could be used as a marker of assessment. Again, similar to MODS, a score of 0 (normal function) to 4 (most abnormal) is given to each organ system using the worst values on each day. The main difference between the SOFA and MODS systems is in the choice of variable for the cardiovascular system. The SOFA working group chose to use vasopressor requirements as the criteria for the cardiovascular system; although acknowledging that a treatment-dependent variable is not ideal because treatment decisions are not objective and may vary among physicians and institutions and over time, the participants were unable to find a better alternative.

The SOFA score was validated in the general ICU population [11] and has since been validated and applied in specific patient groups, including medical and surgical cardiovascular ICU patients [12-14] and trauma patients [15].

SOFA-Derived Parameters

The SOFA score can be separated into its individual organ components to describe the changing pattern of organ dysfunction in individual patients. The most common patterns of organ dysfunction in patients with multiple organ failure include the cardiovascular and respiratory systems [16]. Increasing SOFA scores for each organ are associated with increased mortality rates [3, 17]. In a study using data from 1449 patients from 40 ICUs, the cardiovascular SOFA component was asso-

Table 1. The Sequential Organ Failure Assessment Score [3]

SOFA score	0	1	2	3	4
Respiration PaO ₂ /FiO ₂ , mmHg	> 400	≤ 400	≤ 300	≤ 200 with respiratory support	≤ 100
Coagulation Platelets x 10 ³ /mm ³	> 150	≤ 150	≤ 100	≤ 50	≤ 20
Liver Bilirubin, mg/dL (μmol/L)	< 1.2 (<20)	1.2 - 1.9 (20 - 32)	2.0 - 5.9 (33 - 101)	6.0 - 11.9 (102 - 204)	> 12.0 (> 204)
Cardiovascular Hypotension	No hypotension	MAP < 70 mmHg	dopamine ≤ 5 or dobutamine (any dose) *	dopamine > 5 or epinephrine ≤ 0.1 or norepinephrine ≤ 0.1 *	dopamine > 15 or epinephrine > 0.1 or norepinephrine > 0.1 *
Central nervous system Glasgow coma score	15	13 - 14	10 - 12	6 - 9	< 6
Renal Creatinine, mg/dL (μmol/L)	< 1.2 (<110)	1.2 - 1.9 (110 - 170)	2.0 - 3.4 (171 - 299)	3.5 - 4.9 (300 - 440)	> 5.0 (> 440)
or urine output				or < 500 ml/d	or < 200 ml/d

* adrenergic agents administered for at least one hour (doses given are in mcg/kg/min)

ciated with the highest relative contribution to outcome (odds ratio 1.68) followed by the renal component (odds ratio 1.46) [11].

While the individual scores provide valuable detail on individual patterns of organ failure, the global score is also of interest as it provides an assessment of the total amount of organ dysfunction present at the time in question. The admission SOFA score provides an assessment of the amount of organ dysfunction already present at the time of admission and could be used to stratify patients according to disease severity, for example, for inclusion in clinical trials. It is correlated with outcome [11]; in a prospective study of 352 consecutive ICU patients, an admission SOFA score of up to 9 corresponded to a mortality rate of less than 33%, while for an admission SOFA greater than 11 the mortality rate was 95% [18]. However, the admission SOFA may be influenced by admission policies of individual units. The maximum SOFA score provides a measure of the degree of organ dysfunction reached by each patient during an ICU stay; as the maximum SOFA score increases, so too does the mortality rate [17]. Another useful measure is the delta SOFA. This represents the change in SOFA score during an ICU stay or other time period. Lopes Ferreira et al [18] reported that, regardless of the initial SOFA score, an increase in SOFA score over the first 48 hours of the ICU stay was associated with a mortality rate of 53%; if the SOFA score remained unchanged in the first 48 hours, the mortality rate was 31%, and when it decreased, mortality was 23%. The delta SOFA score could, therefore, potentially be used as a means of evaluating patient response to treatment or even to guide treatment decisions.

The Future

Diagnosis and disease definition is often difficult in the heterogeneous ICU population, particularly for conditions like sepsis. This heterogeneity also makes it difficult to conduct randomized clinical trials, especially of therapeutic interventions, and randomized trial evidence to support ICU interventions is often lacking [19]. The ability to characterize patients better would help in clinical trial development, by providing more homogenous patient groups; it may also help in the targeting of therapies. Organ dysfunction scores, such as SOFA, can provide a means of grading multiple organ failure by assessing the degree of individual and global organ dysfunction at any point in time. These systems could be used alone or incorporated into more complex systems, such as the PIRO (predisposition, infection, response, organ dysfunction) system suggested for the characterization of patients with severe sepsis [20].

Another field where organ dysfunction scores are being increasingly used is as an endpoint in clinical trials of therapeutic interventions. In recent years, we have begun to witness a swing towards assessing outcomes other than just mortality in clinical trials in ICU patients [21, 22]. Recent clinical trials have used the SOFA score to assess effects of therapeutic interventions on organ dysfunction. For example, in the PROWESS study on drotrecogin alpha (activated) [23], endpoint data related to the development, course, and severity of organ dysfunction were collected

prospectively using the SOFA score. There were no overall differences in mean total scores between the treatment and placebo groups when averaged over days 1-7 or over days 1-28 [24]. However, for individual organ scores, treated patients had significantly lower mean cardiovascular scores throughout the 28-day study period, and treated patients showed significantly faster resolution of cardiovascular and respiratory dysfunction and slower onset of haematological dysfunction than placebo-treated patients in the first 7 days [24]. Other randomized controlled studies have similarly used the SOFA score to assess the effects of interventions on organ dysfunction [25-28].

Conclusions

The majority of ICU patients die from multiple organ failure. The ability to characterize the degree and pattern of organ dysfunction over time with organ dysfunction scores such as the SOFA is important in ongoing decisions about therapy and prognosis. The simple nature of the SOFA score components means that it can be easily measured in all units and rapidly calculated at the bedside. The regular assessment of the SOFA score will increasingly become a routine part of patient monitoring in the ICU.

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PERIOPERATIVE CARE

Operating Theatres: Organization, Costs and Audit

M. KLIMEK, M. VAN HOUDENHOVEN, T. OTTENS

The operating room (OR) is the heart of the hospital. Most patients have some contact with the OR, the most expensive devices are used in the OR, the greatest amount of manpower concentrated on one patient can be found in the OR, the most money is earned – and lost – in the OR. Therefore, all ideas about OR organization have an impact on costs and – as a secondary endpoint – on the quality of care and vice versa. Therefore, this chapter deals with three aspects of OR management: organization, costs and audit.

Organization

Structure and Architecture

OR organization in most cases is predetermined by the architecture of the OR.

Some larger hospitals are built in a kind of pavilion system with, for example, an eye clinic and an ENT department, each in separate houses with separate, small OR units. Here the facilities will be used by the different disciplines and exchange of material and personnel between the OR units is difficult or impossible. This depends especially on the question of ownership of the facilities: whether, for example, (the chairman of) the ENT department owns the equipment and is responsible for the nurses, or whether one common, large OR department owns and runs all the facilities in all pavilions. In the latter scenario exchange of material and personnel between the units is much easier. Small OR units have some advantages: the people working there know each other very well, they know the daily routine exactly, and have tend to have a higher level of positive identification with “their” department and “their” patients. On the other hand, small OR units are fragile: absence of one nurse might lead to severe disturbances of the daily routine, fixed role models block innovation and inefficiency might be high, because free capacity cannot be used by other disciplines.

Most hospitals have one central OR complex, where all surgical disciplines come together and facilities like X-ray and endoscopy devices, as well as human resources (nurses and anaesthesiologists) are “used” by the different branches of surgery. The idea of a common pool of equipment and people can be developed on different levels: even in these large central ORs the formation of smaller units is possible (e.g. all disciplines operating in the head and neck, all disciplines operating

in the abdomen [general surgery, urology, gynaecology]), because it will be difficult to find a nurse who is able to assist a cerebral and an abdominal aneurysm repair with the same level of competence.

The Place of the Anaesthesia Department

If the OR is run by an OR-department on its own, the place of the anaesthesia department must be determined: one can be a part of the other, they can work in peaceful coexistence on the same level and some mixed organization models are common. The people and the equipment are managed by an independent OR department, but the daily OR schedule is coordinated by the anaesthesia department or an independent OR coordinator. From the anaesthesiological point of view, an independent anaesthesia department and a strong influence on the daily schedule are considered crucial for the self-esteem of the discipline and for professional development.

How to Match Request and Capacity

As long as the productivity of an OR is directly linked with the income that is produced, it seems desirable that the OR runs 24/7. However, in many hospitals, contracts exist on the “surgical output” – the global amount of procedures that insurance companies will cover. Producing more or less than this amount will not be profitable. In this way, OR productivity becomes predictable, plans can be made and the capacities needed – personnel as well as, for example, the storage of hip prostheses – can be calculated.

OR capacity is the OR time available for each branch of surgery to perform their procedures. Therefore, it is wiser not to talk about the numbers of the cases, but rather the minutes available for a certain branch of surgery. It makes a big difference, whether an inguinal hernia repair takes 20 or 60 minutes, if you perform a caseload of 400 procedures per year. The big “time-cake of OR capacity” can be divided into an enormous number of pieces, and the question is: who is the one to cut the cake – the board of directors or the OR coordinator? However, each piece can only be eaten once. We think that the board of directors should take this important strategic decision. The fixed amount of time and the strategic dimension of the decision encourage the various branches of surgery to carefully monitor their time resources and to work with high efficiency. Furthermore, a bonus-malus regulation can be implemented, stimulating reliable planning and efficient working.

Based on such a model, the anaesthesia support needed should be calculated as well. However, things like nonclinical activities (management, research or teaching), pre- and postoperative visits, emergency care as well as holidays and illness of staff members must be taken into consideration when calculating the number of anaesthesia staff needed to provide a certain amount of time-capacity.

How to Handle Emergency Procedures

Next to predictable elective care, most ORs provide emergency care as well. This can be done by declaring one theatre as the “emergency OR” and linking this with a special team experienced in the most common emergency procedures of all disciplines. Experience shows that this team is (mis)used in the daily routine to handle semi-elective procedures, because it would be a waste to just have these people waiting for an emergency that fails to come when you expect it. Secondly, this available emergency team is sometimes used to replace sick colleagues in regular teams. An alternative is a different model of planning the daily routine: based on the principle “predict the unpredictable”, the daily time needed for emergency procedures from every discipline can be calculated. The occurrence per day and the number of emergency procedures, combined with their duration gives the possibility of calculating the amount of time needed, within certain boundaries, to perform the various emergency procedures without overtime and cancellation of planned patients. In our hospital for example, this time is 5 minutes for ophthalmology and 75 minutes for traumatology. If daily routine planning of all disciplines takes this time into account when setting up a daily schedule, the “white spots” in the planning create the space of a “virtual emergency team” on a “virtual emergency OR”, which makes it possible to interrupt the program on different ORs with the real emergency cases whenever they occur, without putting the elective program at risk of not being completed during office hours.

Numbers, Numbers, Numbers

The OR is a location with many stakeholders and many interfaces. To avoid the impression that one group of surgeons is preferred, transparent numbers should be communicated as much as possible in the planning. There are some important numbers with severe impact on the daily organization which should be defined by the OR management:

1. The variability of the procedures performed in the OR
2. The reliability of the schedule (i.e. the number of that may run out of time)
3. The maximum efficiency in OR usage that must be reached by a special discipline

These numbers are highly interdependent: if in a certain OR only very simple, very predictable procedures are performed (e.g. cataract surgery), planning should be extremely precise. The variability is almost zero, the reliability should be high and the OR should be used for almost 100% of the time-capacity dedicated to this procedure.

In another OR, where for example intestinal tumour procedures are performed, the variability is high (from colonic resection via a Whipple procedure to oesophagectomy and not forgetting the open-close procedures in case of unexpected metastasis or irresectability), the duration of a certain procedure can vary enormously between different surgeons and different patients and is much less predictable. It would be impossible to use such an OR with a 100% efficiency of the dedicated time as well.

Monitoring these data, reporting these data and planning on these data is the basis of successful OR management.

Costs

Operating theatres are expensive: many people are involved in the preoperative care, doctors, nurses and a lot of logistic and supportive staff. To avoid waste of these expensive human resources and the high costs of overtime, high productivity during working hours (and within the limits of the European Working-Time Laws) must be reached. As well as these human resources, an OR has some fixed and some production-dependent material costs: the most technical devices and maintenance of the building are independent of the OR caseload, whilst the number of expensive vascular and joint prostheses as well as the number of blood products and antibiotics used is directly linked with OR productivity.

The only important question about costs is: Who pays for what? There are different views, depending how the budgets are distributed inside the hospital:

1) The one who creates the needs and problems pays

The board of directors of a hospital can decide that the OR is a facility centre, and everybody who wants to use some of the facilities has to pay for all the facilities used, including space, time, people, equipment and disposables. In this scenario, the OR earns its budget back by internal re-imbursement from the departments who use the facilities. Such an OR can also provide services to external clients, who, for example, rent the OR for a weekend programme. The crucial questions here are: who determines the quality of the facilities that are provided? Who has influence regarding issues such as the type of prosthesis provided and the anaesthesia delivered? Who decides which major investments (e.g. microscope) will be made? From the anaesthesiological point of view, in this scenario a blood product that is given due to surgical blood loss will be billed to the surgeon as well. However, this may raise the issue of whether this packed cell is really indicated now...

2) The one who provides the service and solves the problems pays for it

Here the board of directors of a hospital decides to reserve a certain budget for the OR (and anaesthesia) department, which is linked to the agreed surgical production. With this budget, the OR has to satisfy the needs of the different surgical disciplines. In this setting, the OR might determine which devices and disposables are bought, and surgeons have to conform to this decision.

3) The budget is linked to a certain clinical pathway and distributed between the participating disciplines depending on their impact on the patient care inside and outside the OR

This is the most modern and most probably the best approach, because it looks at the total costs of care linked to a certain patient with a certain diagnosis and a certain treatment. This approach encourages all disciplines involved to provide the best care, to avoid complications, to cooperate and to standardize clinical care. In this model, investing for example at one point of the clinical pathway (e.g. the choice of anaesthetic drugs and PONV prophylaxis) will create a cost reduction at

another point (the general ward), which finally leads to lower total overall costs.

In daily OR routine, one of these principles is followed, albeit perhaps slightly modified. For an anaesthesia department, which in general has no generation of income of its own, it is very important to be aware of the money streams and the principles of re-imbursement inside the hospital. Next to this, the costs for training and teaching activities (e.g. simulation!) should also be taken into consideration, because these are important cost factors as well. While on the one hand, simulation is an expensive procedure, on the other hand, the total costs of an anaesthesia disaster produced by a badly trained anaesthetist will be much higher.

Audit

OR management can be audited. Clinical auditing is a quality improvement process, and means reviewing the current practice of a department against explicit criteria – or in simple words: ensuring that what *should* be done is *being* done.

Auditing can be done on three principle aspects of the quality of care: the structure, the processes and the outcome. Translating this to the reality of an OR department prompts consideration of the following aspects.

Structure is defined as the resources that are available. These are, for example, the ventilators and monitors in the OR, the different types of sutures stored, but also the staff available for emergency procedures or Sunday morning 3.15 a.m., their level of training and experience, the existence of a recovery room and much, much more.

Processes are the pathways followed and the procedures performed: is there a protocol for patient transfer from the recovery to the general ward? Are the procedures started up with a time-out procedure and how is crew resource management performed? How are HIV and MRSA patients dealt with? How are the clips and drapes counted at the end of the procedure?

Results can be measured in different ways: some examples include the number of procedures performed, the amount of resources used to do so, the number of infected IV lines, the number of cancelled procedures, and the time between the first announcement of an emergency caesarean section and the incision.

If audits based on the same criteria are performed in different hospitals, even benchmarking between the hospitals is possible, which some might find threatening. However, health care insurers, who want the best care for their members, will pay increasing attention to these results when signing contracts with hospitals.

In this way, audits become the starting point of a sometimes challenging change in management processes.

Conclusions

Modern OR management is more than just ensuring that the procedures planned will be finished before the next sunrise. Modern OR management is the application

of logistical principles to clinical care. Organizational and economic factors play an important role, and the pressure from insurance companies and the community to work with the highest efficiency is continually on the rise. To optimize patient care, audits on the structure, processes and results of an OR department should be performed and benchmarking should be encouraged.

Suggested Reading

- Marjamaa RA, Kirvelä OA (20047) Who is responsible for operating room management and how do we measure how well we do it? *Acta Anaesthesiol Scand* 51(7):809-814
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- Soudée M (2005) Accreditation and quality approach in operating theatre departments: the French approach. *Acta Chir Belg* 105(5):442-449
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Use and Misuse of Preoperative Cardiac Testing for Noncardiac Surgery

H.-J. PRIEBE

Perioperative cardiac morbidity and mortality are of substantial medical and economic concern. Thus, the primary goal of effective perioperative management is to implement strategies that reliably improve outcome. It is the (as yet unproven) premise that preoperative risk stratification based on the results of preoperative cardiac testing is one of such measures that will improve cardiac outcome, due to the modifying effects it can have on overall perioperative management.

Goals of Cardiac Assessment

The initial preoperative cardiac evaluation has several goals: (i) identification of patients with unacceptably high cardiac risk – in such cases, surgery needs to be postponed or even cancelled; (ii) identification of patients with cardiac disease that can be improved or even cured preoperatively – e.g. initiation or optimization of medical therapy, or insertion of a pacemaker to treat symptomatic arrhythmias; and (iii), identification of patients who might benefit from preoperative coronary revascularization – this is one of the most difficult and controversial areas of preoperative cardiac evaluation and decision making.

Statistical Considerations of Cardiac Testing

Preoperative risk stratification is based on the results of preoperative clinical investigations (risk factors, risk indices), noninvasive investigations (ECG, echocardiography, myocardial scintigraphy) and invasive investigations (coronary angiography). As the results of these investigations frequently form the basis on which patients are informed about expected perioperative complications, and on which the perioperative anaesthetic (and in some cases the surgical) management is based, knowledge of indications and limitations of the various investigations is essential. This is especially important if a statistically derived “average” risk probability is applied to an individual patient. However, the individual patient is obviously more interested in his/her personal rather than in an average risk probability.

Tests performed in the context of preoperative risk stratification should fulfil several requirements [1]: (i) they should be accurate (high sensitivity and specificity; high positive and negative predictive values; adequate likelihood ratios for positive and negative test results); (ii) they should result in a change of the pre-test likelihood; (iii) they should have a favourable harm/benefit ratio; and (iv), they should modify perioperative management and outcome. It is important to realize that the prevalence of a disease (e.g. coronary artery disease) or the incidence of an event (e.g. perioperative myocardial infarction) considerably affect the interpretation and clinical relevance of a test result. Even when using an excellent screening test, if prevalence and/or incidence in a tested population are low, then only few patients with a positive test result (e.g. high classification in a cardiac risk index or positive ECG exercise test) will actually have the disease or experience an adverse perioperative outcome (i.e. there will be a high rate of false positive results). Accordingly, if one were to act on every positive test result without taking into consideration prevalence of the disease and incidence of the event of interest (i.e. the pre-test likelihood), one would expose the patient to considerable and entirely unnecessary inconveniences and risks associated with additional noninvasive and invasive tests, and would cause considerable additional costs (related to personnel, equipment and time required to perform such tests).

In general, the incidence of false positive and false negative results varies in an inversely proportional relationship to prevalence and incidence. Even with a test of high sensitivity and specificity, the positive predictive value is highly dependent on prevalence and incidence. If the indication for a subsequent investigation is restrictively handled, the sequential performance of different tests may sequentially increase the positive predictive values (i.e. the post-test likelihood) by sequentially increasing the pre-test likelihood (for a disease or an event), thereby resulting in a more reliable preoperative risk stratification. Purely theoretically, the sequential performance of an ECG at rest, an exercise ECG and a dobutamine stress-echocardiogram (DSE) in an individual tested unequivocally positive in the preceding test could increase the positive predictive value for coronary artery disease from approx. 25% (ECG at rest alone) to approx. 40% (exercise ECG following a positive ECG at rest) and ultimately to approx. 80% (DSE following a positive exercise ECG) [2, 3]. However, as the positive predictive values for coronary artery disease do not necessarily correlate with those for a perioperative cardiac event, such a sequential proceeding must be expected to be of hardly any clinical benefit in most cases. Using a nomogram based on Bayes' theorem [4], post-test likelihood can be derived from the likelihood ratio of the test and the pre-test likelihood (i.e. the prevalence of the disease or the incidence of the event).

Routine Preoperative Cardiac Assessment

History, physical examination and (where indicated) a resting 12-lead ECG still form the basis of any preoperative cardiac evaluation. They allow: (a) detection of symptomatic cardiac disease (e.g. coronary artery disease, valvular disease, ar-

rhythmias); (b) assessment of severity and stability of disease (based on information about functional capacity or recent cardiovascular therapy); and (c) detection of relevant comorbidity (e.g. diabetes mellitus, peripheral vascular disease, pulmonary or renal insufficiency) which unrecognized and untreated, would adversely affect perioperative cardiac outcome.

However, it is important to be aware that history, physical examination and resting ECG – despite being essential requirements of the initial cardiac assessment – have diagnostic deficiencies that limit their usefulness in confirming or excluding coronary artery disease. Up to 75% of all ischaemic episodes and 20-30% of all myocardial infarctions are “silent”. There are no prodromal symptoms in 35-90% of all myocardial infarctions, and up to half of all extensions of infarctions are silent. The resting 12-lead ECG is normal in 25-50% of patients with coronary artery disease, nondiagnostic in an additional 20-50% of patients (related to left bundle branch block, Wolf-Parkinson-White syndrome, left ventricular hypertrophy), and diagnostic in only 25-50% of patients with previous myocardial infarction.

Clinical Markers

The preoperative assessment of perioperative cardiovascular risk relies on the evaluation of clinical markers, functional capacity and surgery-specific risk. On the basis of such evaluations, different levels of risk can be defined [5]. Clinical markers of increased perioperative cardiovascular risk for myocardial infarction, congestive heart failure and death can be placed in three categories: *major* (unstable coronary syndromes, decompensated congestive heart failure, significant arrhythmias, severe valvular disease); *intermediate* (mild angina pectoris, prior myocardial infarction (30 days old), compensated or prior congestive heart failure, diabetes mellitus); and *minor* predictors (advanced age, abnormal ECG, rhythm other than sinus, low functional capacity, history of stroke, uncontrolled systemic hypertension). In conjunction with the concomitant degree of functional capacity and the anticipated surgical risk, the severity of the clinical marker will influence the decision making for additional preoperative cardiac testing.

Functional Capacity

In daily life functional capacity (“medical” or “physical fitness”) best reflects the “quality” of biological age in clinical practice. It is one of the most important predictors of perioperative outcome in the surgical patient. Poor exercise tolerance may reflect the severity of the underlying disease or a lower functional capacity. Functional status can be expressed in metabolic equivalent task (MET) levels.

1 MET corresponds to the oxygen consumption of a 70-kg, 40-year-old man in a resting state, which is approximately 3.5 mL/kg per minute. Multiples of the baseline 1 MET value can be used to define the aerobic demands for specific activities. Functional capacity is assessed by the history taking of daily activities

and has been classified as *excellent* (greater than 10 METs = affirmative answer to the question “Can you participate in strenuous sports like swimming, singles tennis, football, basketball or skiing?”), *good* (8-10 METs = affirmative answer to the following questions: “Can you do heavy work around the house like scrubbing floors or lifting or moving heavy furniture?” – “Can you participate in moderate recreational activities like golf, bowling, dancing, doubles tennis, or throwing a baseball or football?”), *moderate* (4-7 METs = affirmative answer to the following questions: “Can you walk on level ground at 4 mph or 6.4 km/h?” – “Can you run a short distance?”), *poor* (less than 4 METs = affirmative answer to the following questions only: “Can you take care of yourself?” – “Can you eat, dress, or use the toilet?” – “Can you walk indoors around the house?” – “Can you walk a block or two on level ground at 2-3 mph or 3.2 - 4.8 km/h?” – “Can you do light work around the house like dusting or washing dishes?” – “Can you climb a flight of stairs or walk up a hill?”) or *unknown*. Such a clinical questionnaire provides an estimate, but not an objective measurement, of functional status (such as exercise testing). Patients unable to meet a 4-MET demand during most normal daily activities carry an increased perioperative short-term and long-term cardiac risk [5].

Surgical Procedure

Surgery-specific cardiac risk is related to two factors: type of surgery and degree of haemodynamic cardiac stress associated with a particular surgical procedure. The combined perioperative incidence of myocardial infarction and/or death is 5% or higher for high-risk procedures (emergent major operations, particularly in the elderly; aortic, other major vascular and peripheral vascular surgical procedures; anticipated prolonged surgical procedures associated with large fluid shifts and/or blood loss), generally <5% for intermediate-risk procedures (carotid endarterectomy; head and neck surgeries; intraperitoneal, intrathoracic and orthopaedic procedures; prostate surgery), and generally <1% for low-risk procedures (endoscopic procedures, superficial procedures; cataract and breast surgery).

Cardiac Stress Tests

Pharmacological and exercise stress tests have excellent negative predictive values (90-100%) and an adequately low likelihood ratio for a negative test result (0-1.05), but low positive predictive values (6-67%) and nonprognostic likelihood ratios (0.9-5.9) for a positive test result. Not surprisingly then, it remains to be demonstrated that additional noninvasive preoperative cardiac testing improves outcome [6].

Coronary Angiography

A preoperative coronary angiography only makes sense if the patient is a potential candidate for preoperative coronary revascularization. After all, coronary angiography in patients scheduled for vascular surgery carries a cardiovascular morbidity and mortality of up to 0.2-0.5% and 0.1-0.5%, respectively [7].

Coronary Revascularization

A single randomized trial has studied the effect of preoperative coronary revascularization (interventional and surgical) on long-term outcome in 510 patients undergoing vascular surgery [8]. Patients with severe coronary artery disease (CAD), poor left ventricular function and severe aortic valve stenosis were excluded. Percutaneous coronary intervention (PCI) and coronary artery bypass surgery were not randomized. Approximately 2½ years following surgery, mortality was comparable between groups. It is noteworthy that during and after coronary revascularization, but before the planned surgery, 4 patients died and 17 suffered a myocardial infarction. Previous nonrandomized studies which postulated a benefit of preoperative coronary revascularization on outcome did not account for this considerable risk of coronary angiography and revascularization in high-risk patients. It is also noteworthy that two years after randomization, the majority of patients of both groups were taking beta-blockers (approx. 80%), aspirin (approx. 85%) and angiotensin-converting-enzyme inhibitors (approx. 55%).

Following PCI with or without coronary stent placement, severe perioperative haemorrhage (due to perioperative continuation of dual antiplatelet therapy with clopidogrel and aspirin) as well as lethal coronary artery thromboses in the territory of the stented coronary artery (due to preoperative discontinuation of dual antiplatelet therapy) have been reported during subsequent surgery [9]. Although no randomized study has yet addressed the effect of preoperative PCI on perioperative outcome, the existing observational reports are consistent with a considerable risk associated with preoperative PCI. The risk seems to be dependent on the time interval between stent placement and surgery (<3-6months vs. >3-6months), the type of PCI (with vs. without stent placement), and the type of stent (bare-metal vs. drug-eluting) [9-12]. The overall evidence suggests that preoperative coronary revascularization is of no benefit in patients with stable CAD who are on optimal cardiac medication [13-15]. The indications for preoperative coronary angiography and revascularization should thus be the same as those in the nonoperative setting [16, 17].

Algorithm of Preoperative Cardiac Evaluation

The algorithms for preoperative cardiac evaluation as developed by the American Heart Association (AHA) and the American College of Cardiology (ACC) have

served as guidelines [5]. Similar recommendations have been published by the American College of Physicians [18, 19]. The decision for or against additional preoperative cardiac testing depends on the answers to successive questions. The first question is: *How urgent is the planned surgical procedure?* In the case of emergent surgery, considerations regarding additional preoperative cardiac testing are irrelevant. Cardiac investigations and risk stratification are carried out postoperatively. In the case of urgent or elective surgery, the next question then is: *Has coronary revascularization been performed in the past 5 years?* If this is the case, and if the patient is able to meet a >7 MET demand during most normal daily activities, surgery can be performed as scheduled. Has coronary revascularization not been performed in the past 5 years, or has the patient become clinically symptomatic despite coronary revascularization within the past 5 years, the question that needs to be answered next is: *Has the patient recently been seen by a cardiologist?* If this is the case, further management will depend on the results of noninvasive tests (like exercise ECG, dipyridamole-thallium scintigraphy, dobutamine stress-echocardiography). In the presence of low-risk results and unchanged clinical symptoms, surgery can proceed as planned. In the presence of high-risk test results and recent worsening of symptoms, the question comes up: *What kind of clinical predictors are present?* In the presence of major clinical predictors, the surgical procedure may need to be postponed or even cancelled, and coronary angiography should be considered. In the presence of intermediate or minor clinical predictors, subsequent management will depend on the answer to the questions: *What is the degree of functional capacity?* and *What type of surgery is planned?* In the presence of intermediate clinical predictors and poor functional capacity (<4 METs) and/or a scheduled high-risk surgical procedure, additional noninvasive cardiac testing should be considered. In case of intermediate (4-7 METs) to good (>7 METs) functional capacity and planned surgery of intermediate risk, or (irrespective of functional capacity) with planned surgery of low risk, surgery can proceed as planned. If additional noninvasive test results are unremarkable, surgery can also proceed as planned. However, if the test results are pathological, and if the patient is a potential candidate for coronary revascularization, coronary angiography should be considered. In the presence of merely minor clinical predictors, any kind of surgery can be performed without additional cardiac testing under the following circumstances: poor functional capacity but only low- or, at most, intermediate-risk surgery; or intermediate or good functional capacity. This algorithm requires assessment of functional capacity at various decision points. If such assessment is impossible due to physical or mental limitations, the indication for performing dipyridamole-thallium scintigraphy or dobutamine stress-echocardiography should be rather liberal.

Conclusions

Based on increasing knowledge of the nature of atherosclerotic coronary artery disease [20], and in view of the poor positive predictive value of noninvasive cardiac

stress tests and the considerable risk of coronary angiography and coronary revascularization in high-risk patients [21], the paradigm is shifting from an emphasis on extensive noninvasive preoperative risk stratification to an emphasis on a combination of selective noninvasive testing (to reliably identify those patients who truly benefit from preoperative intervention, such as cancellation of surgery, preoperative coronary revascularization, initiation or optimization of cardioprotective medication), and aggressive pharmacological perioperative therapy [22-28]. Perioperative plaque stabilization by pharmacological means such as statins [29-38], aspirin [39] or β -blockers [40-42] may be as important in the prevention of perioperative myocardial infarction [43, 44] as is an increase in myocardial oxygen supply (by coronary revascularization) or a reduction in myocardial oxygen demand by β -blockers or α_2 -agonists [45-47].

In view of the considerable limitations of preoperative cardiac testing and lack of evidence that risk stratification along the ACC and AHA guidelines [5] improves outcome [48], and in an attempt to not only identify high-risk patients but also reduce the perioperative cardiac event rate, modified algorithms for preoperative risk stratification have been suggested which combine identification of high risk patients on purely clinical grounds with aggressive perioperative therapy with cardioprotective drugs [1, 25, 28, 49, 50].

In summary: (i) indications for additional cardiac testing are the same as those in the nonoperative setting, but timing is dependent on urgency and type of operative procedure, and patients' risk factors; (ii) preoperative cardiac testing should be limited to circumstances in which the result is likely to affect treatment and outcome; (iii) preoperative coronary revascularization to merely "get the patient through surgery" is usually not indicated, and is possibly only of benefit in very few patients at very high perioperative cardiac risk; and (iv) preoperative evaluation along the ACC/AHA guidelines is expected to reduce preoperative cardiac testing, an assumption not yet proven. As no prospective randomized trial exists demonstrating that proceeding according to the ACC/AHA guidelines on perioperative cardiac evaluation improves outcome, rather than putting the emphasis on extensive preoperative cardiac testing, it may be equally (and possibly more) effective (and definitely cheaper) to put the emphasis on preoperative identification of risk factors associated with adverse perioperative cardiac outcome, on the institution or continuation of aggressive perioperative prophylactic pharmacological treatment (statins, β -blockers, α_2 -agonists, aspirin), and on aggressively controlling heart rate perioperatively [1, 27, 28, 51].

Addendum

At the writing (July 2007), a major revision of the ACC/AHA guidelines for perioperative cardiac care is about to be published. This revision will reflect a change in attitude towards preoperative cardiac testing compared to the previous guidelines and will no longer contain algorithms. It may possibly contradict a number of statements made in this review.

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Perioperative Beta-Blockade: Myths and Realities

G. HOWARD-ALPE, P. FOËX

In 1997, the American College of Physicians published a guideline for assessing and managing patients with coronary artery disease who undergo major noncardiac surgery [1]. An important recommendation was that all eligible patients should receive a beta-blocker (atenolol).

Such a conclusion was not surprising because a large proportion of the cardiac complications of anaesthesia and surgery result from coronary events [2] and beta-blockers are very effective in the management of angina and myocardial infarction. Beta-blockers reduce the mortality of myocardial infarction [3] and protect against the risk of reinfarction; the mortality reduction can be as high as 36% [4].

In the UK, 60% of the 20,000 patients who die within 30 days of surgery annually have evidence of coronary heart disease [5] and the number of cardiac deaths is approximately 9000 per annum [6]. In addition to cardiac deaths, there are many cardiac complications. Their number can be estimated at between 90,000 and 180,000 per annum. This is in keeping with observations in the USA [2]. Worldwide approximately 100 million surgical procedures are carried out. It is estimated that 500,000 patients die from a perioperative cardiac event and over 1 million suffer myocardial infarction, based on the known prevalence of such events [7, 8].

The major cardiac complications of anaesthesia and surgery include myocardial infarction, unstable angina, life-threatening arrhythmias, and acute left ventricular failure. Postoperative myocardial infarction occurs in between 2.5% of unselected patients aged over 40 years and 8.6% of patients in whom suspicion of coronary artery disease is sufficiently strong to justify myocardial perfusion scintigraphy [9]. In patients with confirmed significant coronary artery disease on dobutamine-sensitized echocardiography, or myocardial perfusion scintigraphy, vascular surgery may be associated with a 30% risk of myocardial infarction or cardiac death [10, 11].

In the face of such a major health risk, active steps must be taken to protect patients as these complications also significantly impair their long-term prognosis [12]. In addition the cost of such complications is considerable: approximately Euro 2250 for the treatment of the acute phase of each complication [13]; the annual cost to health services is enormous as it must also include the cost of managing the long-term consequences of the perioperative events.

Identification of High-Risk Patients

This can be difficult as the medical history may be unrevealing and obvious clinical manifestations of coronary artery disease may be absent. While coronary angiography is the gold standard for the evaluation of coronary heart disease, noninvasive screening tests are often the first coronary investigation. These tests are based on the imposition of a physical (exercise) or pharmacological challenge (dobutamine, dipyridamole or adenosine) used together with electrocardiography, echocardiography, radionuclide angiography, or myocardial scintigraphy. Reversible ischaemia (ST-segment depression, reduced ejection fraction, new wall motion abnormalities, reversible perfusion defects) indicates the presence of significant coronary artery lesions and justifies coronary angiography. Depending upon the severity of the lesions, coronary revascularization or medical treatment must be considered, including beta-blockade.

Coronary Revascularization

In the presence of significant coronary lesions should coronary revascularization be offered? It is generally accepted that patients with coronary lesions and/or symptoms that constitute a clear indication for coronary revascularization, independently of impending noncardiac surgery, should undergo revascularization prior to surgery [14]. By contrast purely prophylactic coronary revascularization should be limited to patients with significant coronary disease undergoing high-risk major surgery as stated in the American College of Cardiology/American Heart Association (ACC/AHA) guideline [14].

This approach has been challenged because a prospective study has shown no benefit of coronary revascularization (coronary bypass surgery or angioplasty with stent insertion) before vascular surgery [15]. However, patients with severe coronary disease (main left coronary artery) or severe cardiac dysfunction were excluded. Moreover, all patients were on maximum medication including beta-blockers (85%), statins (55%), and antiplatelet drugs (70%). The majority of patients underwent angioplasty with insertion of stents rather than coronary bypass surgery. To date there is little evidence that percutaneous coronary interventions (PCI), in contrast to coronary bypass surgery, offer protection against perioperative events. This study does not prove that revascularization is ineffective in *all* patients as those most likely to benefit from coronary bypass surgery had been excluded and revascularization was not universally surgical.

In the face of some uncertainties regarding coronary revascularization, an alternative approach is to consider that all eligible patients with risk factors for coronary artery disease should be treated with beta-blockers during the perioperative period and beyond [1, 16].

Role of Beta-Blockers

Beta-blockers reduce myocardial oxygen demand, decrease the effects on the heart of perioperative sympathetic overactivity, may reduce overall sympathetic activity, redistribute coronary blood flow towards compromised areas, and modulate dys-regulated cytokines [17]. As there is increasing emphasis on the role of inflammatory mediators in the development of unstable coronary syndromes [18], this property may contribute to their efficacy.

Medical Patients

Beta-blockade reduces the mortality of myocardial infarction [3] and protects against the risk of reinfarction, with a mortality reduction as high as 36% [4]. Beta-blockers reduce the incidence of silent ischaemia in ambulatory patients and this is accompanied by a significant reduction in the relative risk of a cardiac event [19].

Beta-blockers are used extensively in the management of patients with heart failure. The in-hospital and long-term survival of patients with severe left ventricular dysfunction (ejection fraction less than 30%) who undergo major vascular surgery has been shown to be significantly better in those on beta-blockers [20].

Until recently, beta-blockers played an important role in the management of arterial hypertension and were used as a first line of treatment. However, a systematic review [21] and the interruption of the Anglo-Scandinavian cardiac outcomes trial (ASCOT) [22] cast doubt on the efficacy of beta-blockade in the management of hypertension. Indeed, the most recent UK guideline on the management of hypertension has removed beta-blockers from first line treatment, except in patients with evidence of coronary artery disease [23].

Surgical Patients

Acute Beta-Blockade

In the early days after the introduction of beta-blockers in clinical practice, it was generally accepted that their administration should be discontinued two weeks before surgery because of the risk of circulatory collapse [24]. However, a very detailed haemodynamic study of beta-blockade in hypertensive patients undergoing surgery showed that beta-blockade did not cause circulatory dysfunction, but did reduce the risk of perioperative myocardial ischaemia, and prevented ventricular arrhythmias [25]. As a result maintenance of treatment with beta-blockers became accepted practice. The prevention of ischaemia was confirmed by later studies [26, 27]. In 1987, Pasternack et al were able to show that beta-blockade decreased the risk of perioperative myocardial infarction and arrhythmias [28]. This was confirmed by Yeager et al in a case control study [29]. Benefits were also shown in other studies.

An American College of Physicians guideline recommending the use of beta-blockers [1] was published shortly after a randomized study by Mangano et al [30].

This study included 200 patients with, or at risk for, coronary artery disease who were randomly allocated to receive 100 mg atenolol or placebo for seven days starting the day of surgery. While there was no difference with respect to immediate perioperative mortality or myocardial infarction, event-free survival up to two years was significantly better (91%) in beta-blocked patients than in the placebo group (81%). While these results appeared very convincing, the study was later criticized because beta-blockade was stopped in some patients before randomization, there were more patients with diabetes in the placebo group, and the in-hospital events were not included in the final analysis.

In 1999, Poldermans et al [10] published a study of patients undergoing vascular surgery in whom severe coronary artery disease was demonstrated by the presence of reversible ischaemia on dobutamine-sensitized echocardiography. Patients were randomized to treatment with bisoprolol (started at least one week before surgery and continued for 30 days after surgery), or standard care. The authors reported lower 30-day perioperative mortality (3.4% vs 17%) and reduced incidence of myocardial infarction (0% vs 17%) in patients treated with the beta-blocker. Favourable effects were also observed over a two-year follow-up period [31]. However, the benefits of beta-blockade demonstrated in this study cannot be extrapolated to all patients with risk factors for coronary artery disease because treatment was given only to patients in a very high-risk category. From an initial group of more than 1,350 patients with one or two risk factors for coronary artery disease, over 800 underwent dobutamine-sensitized echocardiography prior to vascular surgery and 173 patients satisfied the selection criteria. Of these many were already on beta-blockers; as a result only 59 patients received bisoprolol and 53 standard care. The study was stopped at an interim analysis. The 100% reduction in the risk of perioperative myocardial infarction is a surprising finding as most studies of beta-blockade in myocardial infarction show a risk reduction ranging between 16% and 36% [4].

Notwithstanding reservations about these important studies, beta-blockade seems to be the logical answer for the prevention of cardiac complications of anaesthesia and surgery in patients with risk factors for, or with, coronary heart disease. Indeed, as early as 1988, an editorial in *Anesthesiology* was entitled "should we all have a sympathectomy at birth, or at least preoperatively?" [32]. However, the efficacy of perioperative beta-blockade failed to reach statistical significance in some randomized controlled trials, as can be seen in recent systematic reviews [33, 34].

In 2002, an ACC/AHA guideline [14] stated that "*appropriately administered beta-blockers may reduce the risk of myocardial infarction and death in high risk patients. Where possible beta-blockers should be started days or weeks before elective surgery, with doses titrated to achieve a resting heart rate between 50-60 beats per minute*". The latter statement echoes the major importance of heart rate control in the prevention of myocardial ischaemia [35, 36].

More recently several systematic reviews of perioperative beta-blockade have shown differing results. The meta-analyses by Auerbach et al [37] and Stevens et al [38] showed benefits of beta-blockade but relied heavily on the study of Poldermans [10]. The reviews included only 5 and 7 randomized controlled trials, respectively.

Recent more comprehensive meta-analyses have been carried out by Devereaux et al [33] and Weisbauer et al [34].

The systematic review by Devereaux et al included 22 trials with 2,432 patients undergoing noncardiac surgery. The reduction of cardiac events did not reach statistical significance and there was a significant incidence of bradycardia needing treatment [33]. By contrast Weisbauer et al [34] included both cardiac and noncardiac surgery in their meta-analysis of 69 randomized controlled trials (more than 4,400 patients). In both cardiac and noncardiac surgery, the reductions in mortality and myocardial infarction did not reach statistical significance.

Further important information was obtained in a very large cohort study of more than 663,000 patients, of whom more than 122,000 had received a beta-blocker within two days of surgery (probably because of long-term treatment). In this study, the odds ratio for in-hospital death was significantly worse for patients with a revised cardiac risk index (RCRI) [7] 0 or 1 (representing 580,000 patients) and significantly reduced in those with RCRI 2, 3 or 4 (representing only 83,000 patients) [39]. This study suggests that only relatively high-risk patients should be considered for perioperative beta-blockade.

Further support for a selective use of beta-blockers comes from the observation that the efficacy of beta-blockade in intermediate risk patients is relatively small. The numbers need to treat (NNT) is 10 for myocardial ischaemia, 63 for major complications in vascular surgery, and 833 for major complications in nonvascular surgery [40]. NNTs as large as 63 and 833 suggest that the benefits of beta-blockade are small and the risk of treatment may outweigh them.

A revised ACC/AHA guideline was published in 2006 [41]. It states that patients on beta-blockers should be maintained on their treatment during the perioperative period; patients undergoing vascular surgery with coronary artery disease or multiple risk factors should be treated with beta-blockers. The indication is less strong for those with intermediate risk factors.

The absence of benefits in two randomized controlled trials involving 496 patients (MaVS) [42] and 100 patients (POBBLE) [43], respectively, is contributing to the uncertainty surrounding the use of beta-blockers for perioperative protection. It is hoped that the perioperative ischaemic evaluation (POISE) trial [44], a randomized controlled trial of metoprolol versus placebo in surgical patients, will provide important information on perioperative beta-blockade, its risks and its benefits. The POISE trial stopped on 31 July 2007, having enrolled more than 8,000 patients.

Though doubts exist as to the efficacy of perioperative beta-blockade, the US Agency for Healthcare Research and Quality [45] states that *"beta-blockade is a quality measure for health care for all patients at risk for coronary disease"*. As pointed out recently by London, *"the mandatory use, especially used as a measure of quality of care, is still a hypothesis awaiting adequate supporting data"* [46]. It must be noted that the recommendation of the Agency for Healthcare Research and Quality predates the new guidelines and the publication of several important systematic reviews.

Why, after more than 30 years, are there still uncertainties as to the value of

perioperative beta-blockade and discrepancies in the results of studies? There are several possible reasons:

1. Different studies used different doses of different beta-blockers.
2. Doses may have been fixed or variable with or without titration to a target heart rate.
3. The duration of treatment as well as the delay between initiation of beta-blockade and surgery differed among studies. This is relevant as some antiinflammatory effects of beta-blockade may take several weeks to develop. Such effects would be missing if treatment is started the day of surgery.
4. Studies differed widely in their inclusion criteria (risk factors) and the types of surgery.
5. Beta-blockers may have been temporarily stopped during the perioperative period or the dose reduced to ineffective levels.
6. Genetic differences in beta-receptors may have influenced outcome and are yet to be investigated.

Several years ago, the importance of tight control of heart rate was recognized [35]. Recently Feringa et al have shown that patients in whom heart rate is lower than 70 bpm have a better outcome than those with heart rates between 70-80 bpm, or greater than 80 bpm [36]. Indeed the ACC/AHA guideline suggests that heart rate should be kept under 50-60 bpm [14].

It is possible that the protection provided by beta-blocker therapy would be more effective if treatment was started at least one or two weeks before surgery, given in doses titrated to a slow heart rate (where blood pressure allows), maintained for several weeks after surgery, and used mostly in relatively high risk patients undergoing intermediate or high risk surgery [41, 47].

The risk that attends the perioperative interruption of beta-blocker therapy is well known and has been confirmed by a recent observational study: the hazard ratio for 1 year mortality was 2.7 (confidence interval 1.2-5.9) for those in whom beta-blockade was stopped [48].

The role of genetic differences is only starting to emerge. In acute coronary syndromes, responses to beta-blockade may differ depending upon receptor genotype: adrenoreceptor beta2 genotype 79CC and 46GG reduce the efficacy of beta-blockade [49]. As far as perioperative beta-blockade is concerned there is also a worse prognosis in some patients according to the genotype of beta-receptors and outcome appears to relate more to the genotype than to the presence or absence of beta-blockade [50]. It may be that discrepancies are the result of different genetic "mixes" in the groups of patients studied.

Chronic Beta-Blockade

Surprisingly, evidence for perioperative protection by chronic beta-blockade is lacking except in coronary bypass surgery [51]. In noncardiac surgery, the incidence of perioperative silent myocardial ischaemia is not reduced in patients on long-term beta-blockers [52]. A recent meta-analysis of observational studies failed to demonstrate any protection [53]. This may reflect the presence of more severe

coronary disease in patients on chronic beta-blockers, beta-receptor up-regulation [54], increased number and sensitivity of beta₂-adrenoceptors when selective beta₁-blockers are used, or simply inadequate beta-blockade. It is also known that the heart rate at which ischaemia develops is lower in chronically beta-blocked patients [55]. Therefore, relatively small, apparently innocuous, increases in heart rate during the perioperative period could cause ischaemia in chronically beta-blocked patients, thereby negating the beneficial effects of these agents. Patients on chronic beta-blocker therapy cannot be assumed to be protected: vigilance is essential. It may be that titration of beta-blockade to a slow heart rate would provide protection.

Possible Hazard of Beta-Blockade

While acute beta-blockade appears to be legitimate, it is important to stress that it may not be without some hazards. When given as premedication, beta-blockers were found to decrease the incidence of myocardial ischaemia. However, some patients developed hypotension [56]. Several recent studies were carried out in patients admitted to high-dependency or intensive care units. In such environments adverse effects, if any, could be easily detected and corrected. This may not be the case if patients are admitted to an ordinary ward. Therefore, the safety of introducing perioperative beta-blockade when patients are on the ward needs to be demonstrated. The statistically significant increase in the risk of bradycardia needing treatment [33] must be taken into consideration.

Clearly, beta-blockade should not be initiated in patients with obstructive lung disease or conduction disorders. Moreover, although beta-blockers are now part of the treatment of cardiac failure, their introduction immediately before surgery in patients with poor left ventricular function is contraindicated. If they are introduced caution is essential as, in patients with cardiac failure, beta-blockade always starts with very low doses and titration takes several weeks [57].

Conclusions

A selective approach to using beta-blockers in the perioperative period is legitimate; their administration may be made safer by starting treatment at least a week or more before surgery [14], by titrating to an appropriate heart rate, and by increasing the extent of monitoring of blood pressure and heart rate during the postoperative period, with clear protocols for their omission should hypotension or bradycardia develop. If this can be achieved, beta-blockers could probably be used in more patients, thus reducing the risk of cardiac complications of anaesthesia and surgery.

The uncertainties with respect to beta-blockade indicate that consideration should be given to other cardiovascular drugs such as nitrates, calcium channel blockers, alpha₂-adrenoreceptor agonists, potassium ATP-dependent channel openers, sodium/hydrogen blocking agents (cariporide), and ACE inhibitors. Un-

fortunately, the efficacy of most drugs is either lacking or is limited [38]. It may be that most drugs have limited efficacy because they do not influence the release and/or the effects of inflammatory mediators. By contrast, several recent publications have shown that statins, because of their known antiinflammatory properties, protect surgical patients against cardiac complications of anaesthesia and surgery with significant risk reduction of the order of 30% [58-61].

As the efficacy of beta-blockade and other drugs is relatively limited, it remains essential to identify high risk patients. This often requires testing their coronary reserve by an exercise- or pharmacologically-sensitized test such as echocardiography, radionuclide angiography, or myocardial scintigraphy. This is the best way of making decision about the patient's management including coronary revascularization, prophylactic drug therapy and properly informed consent.

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Management of Hypoxia During One Lung Ventilation

J.B. BRODSKY

Thoracic operations are usually performed with the patient in the lateral position with selective one-lung ventilation (OLV) to the dependent lung. Even after the non-dependent, operated lung is intentionally collapsed it continues to be perfused with blood. Even under the best of circumstances this wasted perfusion, or “shunt”, remains 20-25% of cardiac output. Even so, the majority of patients undergoing thoracic operations are able to maintain adequate arterial oxygen tension (PaO₂) during OLV. The extent of shunt is determined by many factors [1]. If hypoxia does occur during OLV then efforts are directed toward optimizing the matching of ventilation with perfusion (V/Q) in the dependent ventilated lung and/or increasing the oxygen content of the shunted blood returning from the collapsed lung.

Table 1. Strategies to maximize oxygenation during one-lung ventilation

A. Operated Lung

A. Oxygenate Shunt Blood

- Continuous O₂ insufflation (not effective)
 - Intermittent single-breath with O₂
 - Continuous positive end-expiratory pressure (CPAP)
 - CPAP_(upper-lung)/PEEP_(dependent lung)
 - High frequency ventilation
- B. Decrease Shunt
- Vasoconstriction (phenylephrine, noradrenalin, almitrine)
 - Pulmonary artery obstruction

B. Non-Operated Lung

A. Optimize Ventilation

- High FiO₂
 - Large tidal volume ventilation vs pressure-controlled ventilation
 - Positive end-expiratory pressure (PEEP)
- B. Improve Perfusion
- Selective vasodilation (iNO, PGI₂)
-

Determinants of Shunt

Gravity

Gravity is probably the major determinant of shunt and perfusion. This has been demonstrated in several studies. In one study patients undergoing right thoracotomy were divided into three groups (supine, left semi-lateral decubitus, left full-lateral position) [2]. All patients were ventilated with fraction inspired O_2 (FiO_2) 1.0 with the right lung collapsed. PaO_2 progressively decreased in all groups. Nine of 11 supine patients experienced oxy-haemoglobin saturation (SaO_2) < 90%, while only 1/9 patients in the semi-lateral group and 1/13 patients in the full lateral group experienced hypoxaemia. Time for PaO_2 to decrease to 200 mmHg was 354 sec in the supine group, 583 sec in the semi-lateral group and 794 sec in the full-lateral group.

Another study compared the effects of position and fraction of inspired oxygen (FiO_2) during thoracic surgery. Randomly assigned patients were ventilated with FiO_2 of 0.4, 0.6 or 1.0 during periods of two-lung ventilation (TLV) and OLV in the supine and lateral positions [3]. PaO_2 decreased more during OLV compared to TLV in all groups in both positions and in all three FiO_2 groups PaO_2 was significantly higher during OLV in the lateral than in the supine position. These studies demonstrate that during OLV in the lateral position gravity augments the re-distribution of perfusion to the ventilated dependent lung resulting in a better V/Q match and a higher PaO_2 .

Hypoxic Pulmonary Vasoconstriction

Regional hypoxia in the lung causes arteriolar constriction with diversion of blood flow away from the hypoxic segment to normal areas of lung (hypoxic pulmonary vasoconstriction, HPV). By redistributing cardiac output from poorly ventilated hypoxic areas to better-ventilated regions, V/Q is maximized. Under experimental conditions HPV is an important regulator of blood flow to the atelectatic lung.

All intravenous anaesthetic and sedative agents (barbiturates, benzodiazepines, opioids, ketamine, droperidol) do not alter HPV [4], and propofol may actually enhance HPV. For the inhalational agents there are conflicting results between in vitro and in vivo studies due to their complex effects on cardiac output, O_2 consumption, mixed venous O_2 tension (PvO_2), and other mechanical factors (surgical manipulation, use of positive end-expiratory pressure (PEEP)) in patients undergoing thoracic operations. All inhalational anaesthetics directly increase shunt through partial inhibition of HPV resulting in a reduction in PaO_2 . However, if the anaesthetic lowers cardiac output more than it decreases O_2 consumption it also lowers PvO_2 , thus producing a potent stimulus for HPV. A decrease in cardiac output will also result in less blood flow to the collapsed lung because of higher pulmonary vascular resistance (PVR) present in that lung. These actions counter the direct depression of HPV. During thoracotomy, surgical manipulation of the

lung releases vasoactive substances (thromboxane, prostacyclin), which cause local vasodilation and blunting of HPV [5].

Choice of Anaesthetic

None of the inhalational anaesthetics offer any clinical advantage during OLV in terms of oxygenation [6, 7].

If HPV were clinically important then the depressive effects of the inhalational anaesthetics on HPV would be a disadvantage during OLV, and protective total intravenous anaesthesia (TIVA) techniques would be advantageous during thoracotomy. However, the clinical effects of intravenous versus inhalational anaesthetics on HPV and oxygenation are more theoretical than real. Comparison of oxygenation during OLV between patients receiving an inhalational anaesthetic compared with those have a TIVA anaesthetic show no clinical differences. In a study of 50 patients undergoing OLV for pulmonary resection one group received TIVA and the second group received an inhalation anaesthetic [8]. Blood pressure, heart rate and PaCO_2 levels were similar in both groups. As a group, the TIVA patients had slightly higher PaO_2 levels during OLV than those patients receiving inhalation anaesthesia, but both groups maintained adequate oxygenation.

As Conacher stated, “use of 100% O_2 , optimising dependent lung functional residual capacity (FRC), manipulating ventilatory parameters, and application of PEEP or continuous positive airway pressure (CPAP) are clinically far more important than the effects (or *lack of effects*) of anaesthetics on HPV” [9].

Mode of Ventilation

General anaesthesia decreases FRC. When a patient is in the lateral position intra-abdominal contents shift the diaphragm cephalad further reducing dependent lung FRC. During lateral thoracotomy the dependent ventilated lung may have areas of low V/Q and areas that are completely atelectatic.

The common practice during OLV is to ventilate with the same tidal volume (VT) as during two-lung ventilation, adjusting ventilator rate to keep PaCO_2 36–40 mm Hg. The dependent lung is ventilated with FiO_2 of 1.0 and a tidal volume of 10–12 ml/kg ideal body weight (IBW). This VT recruits dependent lung alveoli. Tidal volumes of < 8 ml/kg result in a further decrease in FRC with increased dependent lung atelectasis, while VTs > 15 ml/kg over-distend the alveoli and increase PVR in the dependent lung resulting in an increase in shunt to the non-dependent lung. Even with a shunt as high as 25%, a FiO_2 of 1.0 and large tidal ventilation usually results in a PaO_2 >150 mmHg during OLV.

Mechanical ventilation with a VT < 6 ml/kg IBW results in the reduction of systemic inflammatory markers and reduced mortality in critically ill patients with acute respiratory distress syndrome (ARDS) and acute lung injury (ALI) compared with patients ventilated with VT of 12 ml/kg. Even smaller VTs (4–5 ml/kg) have proven to be beneficial if plateau pressure is kept below 30 cm H_2O . Some anaesthe-

siologists suggest that these findings are applicable to patients undergoing thoracic operations with OLV. There is no scientific basis to support the use of small VT in OLV during thoracic surgery [10]. In contrast to patients with acute lung injury having continuing systemic inflammatory reaction, short-term mechanical ventilation in adults with healthy lungs does not induce a systemic inflammatory reaction. In one study, patients undergoing thoracic operations with OLV were divided into two groups. There were no differences in inflammatory markers (tumour necrosis factor, interleukin (IL)-1, IL-6, IL-8, IL-10 and IL-12) between patients ventilated with a VT of 10-15 ml/kg IBW with zero end-expiratory pressure (ZEEP) and those ventilated with a VT of 6 ml/kg IBW and 10 cm PEEP [11]. For previously uninjured normal lungs in patients undergoing major pulmonary surgery, mechanical ventilation with high VT and ZEEP does not increase pulmonary or systemic inflammatory response. Following OLV with re-expansion of the collapsed lung there is vascular injury, but not an inflammatory response, no matter which mode of ventilation has been applied [12].

Pressure-controlled ventilation has been suggested as an alternative to volume-controlled ventilation. Pressure-controlled ventilation is associated with lower peak airway pressure, lower shunt and higher PaO₂ than conventional volume-controlled ventilation during OLV [13]. Low VT ventilation and/or pressure-controlled ventilation can be used during OLV, but these ventilatory approaches result in atelectasis and hypercarbia.

Another technique experiencing renewed interest is high frequency ventilation (HFV). In one retrospective clinical study there were no differences in SaO₂ or end-tidal CO₂ between patients who had conventional OLV and those receiving HFV [14].

Optimising Oxygenation During OLV

If hypoxaemia occurs during OLV it is usually due to an inadequate FiO₂, alveolar hypoventilation from inadequate VT, or to a large alveolar-to-arterial O₂ tension gradient from continued perfusion of the deflated lung. The position of the double-lumen tube should be immediately re-confirmed to determine if the upper-lobe bronchus on the ventilated side is obstructed. Other mechanical problems (tube obstruction, bronchospasm) should be ruled out. Decreased perfusion of the ventilated lung due to haemodynamic causes (hypotension, arrhythmia) must also be considered.

Lower-lung PEEP

As mentioned, there is a reduction of FRC in the dependent lung during OLV in the lateral position. In the presence of decreased FRC, PEEP (5-10 cm H₂O) will recruit collapsed and under-inflated alveoli and improve oxygenation. Not all patients show an improvement with PEEP [15]. Pre-existing lung disease determines response. During mechanical ventilation some patients have expiratory gas

flow halted by the start of the next inspiration. This phenomenon (auto-PEEP, intrinsic-PEEP) increases FRC. Although there is a greater degree of auto-PEEP generated in patients with emphysema during OLV, it is also measurable in patients with normal lungs [16]. Applied PEEP may not improve oxygenation in these patients [17-18], and may even worsen oxygenation in patients who already have significant auto-PEEP and normal or high FRC. In such patients application of PEEP will increase alveolar airway pressure and dependent lung PVR, which in turn will divert blood flow to the non-ventilated lung worsening hypoxaemia. For a patient with chronic obstructive pulmonary disease (COPD) and a high level of auto-PEEP, addition of PEEP combined with large VT ventilation can lead to pulmonary hyperinflation and cardiopulmonary compromise.

Upper-lung CPAP

Passive insufflation with 100% O₂ to the non-ventilated lung is usually unsuccessful since O₂ fails to reach and recruit collapsed alveoli. If hypoxaemia does occur, the collapsed lung can be partially or fully re-expanded. A single breath to the operated lung will temporarily allow oxygenation of shunt blood. The lung will eventually re-collapse from absorption atelectasis and so it must be re-expanded periodically. This manoeuvre is impractical during thoracoscopy.

CPAP with 100% O₂ to the collapsed lung is the most effective means of correcting hypoxaemia during OLV [19]. CPAP maintains the patency of the non-ventilated alveoli with oxygen so unsaturated “shunted” blood becomes oxygenated. With CPAP the operated lung remains only partially distended without interfering with surgical exposure. Any increased airway pressure in the non-ventilated lung from CPAP may further increase PVR, which will divert blood flow to the ventilated lung.

CPAP is only effective when the distending pressure can reach the distal airways so there must be no major disruption or obstruction in that airway. CPAP is therefore not helpful with a bronchopleural fistula, during sleeve resection of the airway, during massive pulmonary haemorrhage or bronchopulmonary lavage, or with any obstruction from mucus, blood or tumour. The combination of PEEP applied to the ventilated lung and CPAP to the non-ventilated lung to maintain oxygenation is rarely, if ever, needed [20].

Manipulation of the Pulmonary Circulation

During pneumonectomy, ligation of the pulmonary artery completely eliminates shunt maximising dependent lung V/Q relationship. Although clamping the pulmonary artery during lobectomy will direct blood to the ventilated lung, this manoeuvre should be avoided because re-perfusion after total interruption of pulmonary artery flow may injure the lung.

If shunt is decreased, then V/Q in the ventilated lung will improve. In animal studies, direct infusion of prostaglandin F_{2a}, a potent pulmonary vasoconstrictor

into the pulmonary artery of the non-ventilated lung causes a significant decrease in shunt and an increase in PaO_2 . Phenylephrine has also been used as a non-specific pulmonary vasoconstrictor to improve oxygenation.

Another approach is to directly increase blood flow to the dependent lung. There has been considerable interest for nitric oxide (NO), a potent vascular smooth muscle vasodilator, in this role. NO produces more pronounced effects in well ventilated areas of the lung, where it promotes redistribution of pulmonary blood flow to regions with high V/Q ratio, thus decreasing pulmonary hypertension and improving oxygenation [21].

In one study, 60 patients undergoing pulmonary resection in the lateral position were divided into two groups [22]. If a patient became hypoxaemic during OLV, either inspired NO (iNO) 20 ppm or nitrogen was added to the inspired gas mixture. Eight patients in each group experienced hypoxaemia. Oxygenation improved in 2 patients in the iNO group and 2 patients in the control group. The majority (75%) of patients receiving iNO showed no benefit. The authors concluded that 20 ppm iNO was not superior to nitrogen in the treatment of hypoxaemia during OLV and that iNO was not a practical alternative to conventional management of hypoxaemia during OLV. Similarly, iNO (40 ppm) to the ventilated lung did not decrease mean pulmonary artery pressure (PAP) in patients with normal PVR [23]. Oxygenation was not improved since shunt remained unchanged. The effects of iNO are directly proportional to the degree of PVR present when it is administered, and most patients undergoing pulmonary resection have normal or only slightly elevated PVR.

For patients with increased PVR iNO in combination with another vasoactive agent can improve oxygenation. For example, aerosolized prostacyclin (PGI_2) improves gas exchange and pulmonary shunt by redistributing pulmonary blood flow from non-ventilated to aerosol-accessible ventilated lung regions. The combination of inhaled PGI_2 and iNO decreases elevated PAP. Intravenous PGI_2 and iNO resulted in a marked decrease in PAP with an increase in cardiac output and an improvement in PaO_2 in a patient with severe ARDS and pulmonary hypertension. Although potentially useful, the combination of iNO and PGI_2 has not yet been used during OLV. Administering iNO to increase perfusion to the ventilated lung and almitrine bismesylate (a potent pulmonary vasoconstrictor to decrease shunt) to the non-dependent ventilated lung has been shown to markedly increase oxygenation during OLV for video-assisted thoracoscopic surgery [24].

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Regional Anaesthesia for Thoracic Surgery

J.B. BRODSKY

Thoracic operations include a wide variety of different operative approaches. Most procedures are performed under general anaesthesia since controlled one-lung ventilation (OLV) is usually required. Analgesia strategies involving regional anaesthetic techniques are usually instituted prior to or during surgery in anticipation of postoperative pain. Different incisions are associated with varying degrees of postoperative pain. In general, the lateral thoracotomy incision is considered the most painful, median sternotomy less so, and video-assisted thoracoscopic surgery (VATS) the least painful. In addition to the skin incision, disruption of intercostal nerves, inflammation of the chest wall, diaphragm and pleura, and the number and sites of chest drainage tubes all influence pain. Patients also experience pain at non-incisional sites, particularly ipsilateral shoulder pain, which often follows thoracotomy and VATS procedures.

Each of the different types of pain following thoracic surgery can require different treatments. Since analgesic regimens are evaluated by a variety of criteria including (a) postoperative pulmonary function (spirometry, arterial blood gas values), (b) visual analogue pain scores (at rest and with cough and movement), (c) amount of supplemental opioid required, (d) length of hospital stay, and (e) overall patient satisfaction, no single technique or drug has been universally accepted as the “best” for thoracotomy [1-3].

Neuraxial Analgesia

Neuraxial (intrathecal, epidural) analgesia is probably the most popular current method for managing postthoracotomy pain. Epidural opioid analgesia, with or without local anaesthetic, when compared to intravenous (IV) opioids reduces pain, improves pulmonary function and oxygenation, and reduces post-thoracotomy complications [4].

Local anaesthetics given epidurally can supplement general anaesthesia during surgery, but postoperatively their addition may not significantly improve analgesia above the level achieved from epidural opioids only. Any concurrent hypotension and/or motor blockade from the local anaesthetic can limit the patient’s ability to ambulate. The addition of epinephrine and local anaesthetic may decrease the amount of epidural opioid needed for effective analgesia [5]. Single-shot intrathecal morphine produces analgesia for up to 24 hours. However, the epidural route is

usually preferred over the intrathecal route since placement of a catheter allows for continuous, prolonged drug administration. Patient-controlled epidural opioid analgesia is also possible.

Depending on the opioid selected, an epidural catheter placed at either a lumbar or thoracic level is effective for post-thoracotomy analgesia [6]. Lipophilic opioids (fentanyl, sufentanil) administered in the epidural space diffuse across into the cerebrospinal fluid (CSF), bind to spinal opiate receptors and produce a rapid onset of action. Lipophilic opioids are best administered at the thoracic level. Because they are rapidly absorbed into the systemic and cerebral circulations, severe postoperative respiratory depression may occur with the more potent lipophilic opioids [7]. Lipophilic agents provide satisfactory analgesia, but because of their relatively short duration of action they should always be administered by continuous epidural infusion. Hydrophilic agents (morphine, hydromorphone) diffuse more slowly into the CSF so onset of action is delayed. The longer duration of action for these opioids makes them the preferred agents when continuous infusion is not possible. Because of their low lipid solubility they can be administered either at a thoracic or lumbar level for effective post-thoracotomy analgesia.

Paravertebral Block (PVB)

The paravertebral space is a wedge-shaped area that lies to the side of the vertebral column and contains spinal (intercostal) nerves, dorsal rami, the rami communicantes and the sympathetic chain. As a spinal nerve emerges from the inter-vertebral foramen it lacks a fascial sheath and is composed of multiple nerve rootlets. Local anaesthetics can easily penetrate the nerve at this site to produce unilateral somatic and sympathetic blockade [8].

A PVB can be performed percutaneously (“blindly” or with a nerve stimulator), or intraoperatively under direct vision before the lung is re-expanded. Local anaesthetics in the paravertebral space produce analgesia in an identical fashion as continuous extrapleural intercostal nerve (ICN) block (see below) since the site of action for both is the paravertebral space [9].

Continuous thoracic paravertebral analgesia is as effective as epidural analgesia in managing post-thoracotomy incisional pain and is associated with fewer haemodynamic complications [10]. A meta-analysis of clinical trials of patients undergoing thoracic surgery confirmed these findings [11]. It found no difference in pain scores in studies comparing PVB and epidural analgesia. PVB was associated with fewer pulmonary complications, less nausea and vomiting, less hypotension, and fewer failed blocks than epidural analgesia. The advantages of PVB are that it effects only the operated side, is simple, safe and easy to learn, and has comparable analgesic effectiveness and a lower incidence of complications than epidural analgesia. Single-shot percutaneous PVB is effective for pain control after VATS for up to 48 hrs [12].

Intercostal Nerve (ICN) Blocks

Direct and Continuous ICN Blocks

ICN blocks can be performed intraoperatively with the lung collapsed, or percutaneously from outside the chest before or after surgery [13]. Studies have demonstrated improved analgesia, reduced opioid requirements and improved pulmonary function by combining an ICN block with patient-controlled IV analgesia (opioids, NSAIDs) when compared to IV opioids alone following thoracotomy [14]. Most studies find epidural analgesia superior to ICN [15]. Due to the relatively short action of local anaesthetics, continuous blocks are more practical than repeated individual blocks [16]. ICN blocks have minimal side effects. One study of 11,000 patients receiving percutaneous ICN blocks reported no systemic local anaesthetic toxicity [17], and infusions for up to 5 days were not associated with local anaesthetic complications [18].

Extrapleural Infusion

Continuous ICN blockade can be accomplished by placing several catheters in the intercostal grooves during surgery. A portion of the parietal pleura is lifted from the inner chest wall to create an extrapleural pocket. A catheter is then introduced percutaneously into the pocket under direct vision and the overlying pleura is closed. Local anaesthetics can then be infused through the indwelling catheters.

Intrapleural Infusion

Intrapleural analgesia can be achieved by injecting local anaesthetics into the thoracic cavity between the visceral and parietal pleura [19]. An epidural catheter can be placed through the chest wall while the thorax is still open and while the lung is collapsed. Catheter placement once the lung is re-expanded increases the risk of lung injury and the inability to confirm catheter position. Local anaesthetic can also be given directly through the chest drainage tube after the lung has been re-expanded at the completion of surgery. Clamping the chest tube for several minutes following anaesthetic administration increases the success rate since this manoeuvre prevents loss of local anaesthetic [20]. Most studies report incomplete pain relief when intrapleural analgesia is used alone. With intrapleural infusion local anaesthetic pools on the diaphragm respiratory function can be impaired [21]. Intrapleural local anaesthetics are particularly useful for post-VATS analgesia.

Cryoanalgesia

Freezing an intercostal nerve (-60°C for 35–60 seconds) damages its myelin sheath and interrupts conduction. This iatrogenic injury can reduce post-thoracotomy incisional pain. The ICN nerve at the incision and the two nerves above and below

are frozen [22]. Loss of sensory and motor function usually lasts 1-6 months [23]. Many patients experience painful neuralgias at the treatment sites [24]. Cryoanalgesia alone does not significantly improve pulmonary function, and although it may reduce the amount of IV opioid needed, it does not eliminate post-thoracotomy pain.

Transcutaneous Electric Nerve Stimulation (TENS)

Electrodes can be placed on either side of a thoracic incision and electrical stimulation applied [25]. TENS has not demonstrated a reduction in opioid requirements or an improvement in pulmonary function following lateral thoracotomy or median sternotomy, but it has shown a reduced requirement of NSAIDs following VATS procedures [26]. Long-term use of TENS may be more beneficial. One study found that TENS provided better pain relief and comfort compared to opioid patient-controlled analgesia from postoperative day 4 onwards, and the pain-reducing effect continued for at least 2 months postoperatively [27].

Ipsilateral Shoulder Pain

With reduction or elimination of incisional pain following thoracotomy, many patients complain of ipsilateral shoulder pain. The incidence of this pain has been reported as high as 75-85% in some series. Its aetiology remains unknown, although it may be referred pain from the diaphragm. This specific complaint is resistant to epidural analgesia [28], but its incidence may be decreased when NSAIDs are given preemptively [29]. Stellate ganglion block [30], phrenic nerve block [31, 32], and interscalene brachial plexus block [33] have been reported to be effective, while intrapleural local anaesthetics [34], and supra-scapular blocks [35] have failed to treat ipsilateral shoulder pain.

Conclusions

The most popular method to treat post-thoracotomy pain is epidural analgesia (thoracic or lumbar level, opioids +/- local anaesthetics). ICN blockade (by any method) can provide satisfactory to excellent analgesia, and remains a good alternative if an epidural is not performed. Cryoanalgesia and TENS probably have no current role since NSAIDs and low-dose ketamine can supplement IV opioids and regional nerve blocks.

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Why the Obese Patient is at Risk for Perioperative Complications

J.B. BRODSKY

Obesity has become a worldwide problem of epidemic proportions. Extreme obesity is associated with pathophysiologic changes in all organ systems, which in turn effect anaesthetic management. Since obese patients undergo all types of surgery, and not just weight loss operations, surgeons, anaesthesiologists and critical care physicians must be familiar with the special needs of the morbidly obese surgical patient.

Body mass index (BMI), an indirect measure of obesity, is calculated by weight (kg) divided by the square of height (m^2). By definition a BMI $\geq 30 \text{ kg}/m^2$ is obese, $\geq 40 \text{ kg}/m^2$ morbidly obese, and $\geq 50 \text{ kg}/m^2$ super-obese. Indices of weight are important because medication dosing is often based on weight. Normal weight ranges between $\pm 10\%$ of ideal body weight (IBW). IBW is estimated by the formula $IBW = (22)(\text{height } m^2)$ [1]. Lean body mass or weight (LBW), which includes muscles, bones, tendons, ligaments and body water, is equal to actual or total body weight (TBW) minus the weight of fat. In normal adults LBW is about 80% TBW (males) and 75% TBW (females). In morbid obesity LBW is increased and is 20-30% greater than IBW.

Cardiac output rises proportionally with increasing weight. Stroke volume also increases since a greater total blood volume (BV) is needed to perfuse added body fat. These changes lead to systemic hypertension and eventually ventricular dilation and cardiac hypertrophy [2]. Obese patients may not be physically active and can appear to be asymptomatic even in the presence of significant cardiovascular disease. Patients have increased pre-load and after-load, increased mean pulmonary artery pressure (PAP), and elevated right and left ventricular stroke work. Signs of pulmonary hypertension (exertional dyspnoea, fatigue, syncope) should be sought and echocardiography obtained in symptomatic patients. Right heart failure is common in older patients. Cardiac dysrhythmias are precipitated by chronic hypoxia (especially in patients with obstructive sleep apnoea, OSA), hypercapnia, electrolyte disturbances caused by diuretic therapy, fatty infiltration of the conduction system, and by ischaemic heart disease. Medications for chronic hypertension should be continued before surgery. An exception is the angiotensin-converting enzyme (ACE) inhibitors, which should be stopped preoperatively because they cause profound hypotension following induction of anaesthesia.

Work of breathing is increased since energy must be expended to carry additional body mass, while respiratory muscle performance is impaired. Oxygen

consumption and CO₂ production rise. The fatty chest and abdominal walls plus increased pulmonary BV contribute to reduced pulmonary compliance. Functional residual capacity (FRC) is reduced due to decreased expiratory reserve volume (ERV). Airways close during normal ventilation. Continued perfusion of non-ventilated alveoli results in a lower oxygen tension (PaO₂). All changes increase in direct proportion with increasing weight [3]. Sedatives should not be given preoperatively in order to avoid further depression of respiration.

Patient position during surgery is extremely important. Pressure points must be carefully padded to reduce the risk of pressure sores, neurologic injury, and rhabdomyolysis (RML). FRC is further reduced in the supine position. This causes increased ventilation/perfusion mismatch and increases in O₂ consumption, cardiac output, and PAP [4]. The Trendelenburg position (TP) and lithotomy position magnify these changes by further decreasing lung volumes. When possible, patients should be in the reverse-Trendelenburg position (RTP) since this “unloads” the diaphragm maximising FRC. An apnoeic obese patient’s haemoglobin will desaturate very rapidly because of reduced FRC and limited O₂ reserves [5]. Patients should be pre-oxygenated by mask, preferably in the RTP, for several minutes before induction of anaesthesia [6].

Bag and mask ventilation is often difficult due to altered anatomy including fat face and cheeks, limited range of motion of the head, neck and jaw, large neck, and excessive palatal and pharyngeal tissue, and reduced pulmonary compliance. Gastric insufflation during ineffective mask ventilation will increase the risk of regurgitation and acid aspiration.

Increasing weight is not a risk factor for difficult laryngoscopy [7]. The most reliable predictors of difficulty are high Mallampati score (III or IV) and large neck circumference [8]. The best strategy for successful laryngoscopy is to elevate the head, upper body and shoulders so that the patient’s ear is level with the sternum (head elevated laryngoscopy position, HELP) [9]. An assistant experienced with airway management should always be nearby and available to help. A laryngeal mask airway (LMA) can be used, even in morbidly obese patients, if tracheal intubation fails [10, 11].

During surgery obese patients should be ventilated with FiO₂ = 0.5–1.0 and tidal volume (VT) 12–15 ml/kg IBW, preferably in the RTP. A larger VT only marginally improves oxygenation and can injure the lung [12]. Positive end-expiratory pressure (PEEP) can be useful with pressure-controlled ventilation, but PEEP superimposed upon a large VT can actually worsen hypoxaemia by depressing cardiac output and therefore reducing O₂ delivery. Placement of sub-diaphragmatic packs or retractors or changing to lithotomy or TP will also impair ventilation.

Since the semi-recumbent and RTP positions maximize oxygenation, haemodynamically stable patients should also recover from surgery in one of these positions. General anaesthesia in morbidly obese patients results in a significant incidence of post-operative atelectasis [13], so supplemental O₂ should not be withheld in the recovery period. Restoration of normal pulmonary function after open abdominal surgery may take several days. Postoperative admission to an intensive care unit and/or mechanical ventilation is rarely needed. Factors that may



Fig. 1. The Head Elevated Laryngoscopy Position (HELP) significantly improves the view during direct laryngoscopy. The head, upper body and shoulders should be elevated so that the patient's ear is level with their sternum. When possible, the patient should also be in the reverse-Trendelenburg position (RTP) since this "unloads" the diaphragm maximising functional residual capacity (FRC).

necessitate ventilatory support include extremes of age, super-obesity, coexisting cardiac disease or pulmonary disease and CO_2 retention, fever or infection, and surgical complications [14].

Although obesity is an important risk factor for OSA, not every obese patient suffers from OSA [15]. A definitive diagnosis can only be made by polysomnography. OSA is characterized by frequent episodes of apnoea (> 10 second cessation of airflow despite continuous respiratory effort against a closed airway) and hypopnoea (50% reduction in airflow or reduction associated with a decrease in $\text{SpO}_2 > 4\%$). Patients maintain normal PaCO_2 during the day but have CO_2 retention, sleep disturbances, intermittent airway obstruction with hypoxaemia, pulmonary hypertension and cardiac arrhythmia at night. OSA leads to chronic hypoxaemia with secondary polycythaemia increasing the risk of cardiac and cerebral vascular disease. Airway management in OSA patients can be challenging. Sedatives and long duration opioids should be avoided and when possible, regional techniques or general anaesthesia with postoperative epidural analgesia should be used. Postoperatively, patients should be continuously monitored by pulse oximetry. If nasal CPAP or BiPAP are used at home, they will also be needed immediately following surgery. These devices allow alveolar recruitment during inspiration and prevent alveolar collapse during expiration.

A small number of extremely obese patients have "Obesity Hypoventilation Syndrome" (OHS) characterized by somnolence, cardiac enlargement, polycythaemia, hypoxaemia and hypercapnia. The most severe form of OHS is "Pickwickian Syndrome". Hypoventilation is central and independent of intrinsic lung disease, and is probably due to a progressive desensitization of the respiratory centre to hypercapnia from nocturnal sleep disturbances. Patients rely on a hypoxic ventilatory drive and hypoventilate or become apnoeic during emergence from general anaesthesia when given 100% O₂.

It remains controversial as to whether all morbidly obese patients are at increased risk for acid aspiration during anaesthetic induction. Risk factors include increased intra-abdominal pressure, high incidence of gastro-oesophageal reflux disease (GORD) and hiatus hernia, increased gastric volume (> 25 ml) and decreased gastric fluid pH (<2.5) [16]. Fasting obese patients may actually have a lower incidence of high-volume, low-pH gastric fluid than lean patients [17]. Patients at risk of acid aspiration may be those with GORD, diabetes and gastroparesis. Patients with previous restrictive weight loss surgery are at a particularly high risk of aspiration during induction of anaesthesia. For protection against acid aspiration a H₂-receptor antagonist or a proton-pump inhibitor can be given the night before and again on the morning of surgery with 30 ml of non-particulate antacid.

A complete medical history is essential since obesity is associated with many chronic medical problems which can influence perioperative morbidity and mortality. Co-morbidities such as cardiovascular disease, Type II diabetes, OSA and OHS must be recognized, and when possible optimized before surgery. Consultation with appropriate medical specialists may be indicated. Patients who have had previous bariatric surgery may experience metabolic changes which can include protein, vitamin, iron and calcium deficiencies.

Medication history is also important for revealing the use of diet drugs, since these can have significant side effects. The combination of phentermine and fenfluramine ("phen-fen") is associated with serious heart and lung problems. Sibutramine causes dysrhythmias and hypertension. Orlistat causes deficiencies in fat-soluble vitamins (A, D, E, K), and a reduction in vitamin K levels can increase the anticoagulation effects of coumadin.

Thromboembolism is a major cause of postoperative mortality. Prolonged immobilization can lead to phlebothrombosis. The risk of thrombosis is further increased because of greater BV and relative polycythaemia common in obese patients. Other risk factors include high fatty acid levels, hyper-cholesterolaemia and diabetes. In addition, morbidly obese patients demonstrate accelerated fibrin formation, fibrinogen-platelet interaction and platelet function. Anticoagulation or other prophylaxis measures should always be considered, even for patients with epidural catheters [18]. A vena cava umbrella is placed preoperatively in older and high-risk patients, and sequential compression boots are used during surgery. Early ambulation must be encouraged, so adequate postoperative analgesia is essential.

Pre-operative assessment of BV is important, especially for operations when significant haemorrhage and/or fluid translocation can occur. Intra-operative BV

deficits can lead to organ under-perfusion with reduced tissue oxygen delivery. If preoperative BV can be accurately estimated, then replacement crystalloid, colloid and blood therapy can be administered in a rational manner. Total circulating BV increases as BMI increases, but BV measured as mL/kg TBW actually decreases in a non-linear manner with increasing weight. Although 70 mL/kg is the accepted mean value in normal patients, this value grossly overestimates total BV in obese and morbidly obese patients [19].

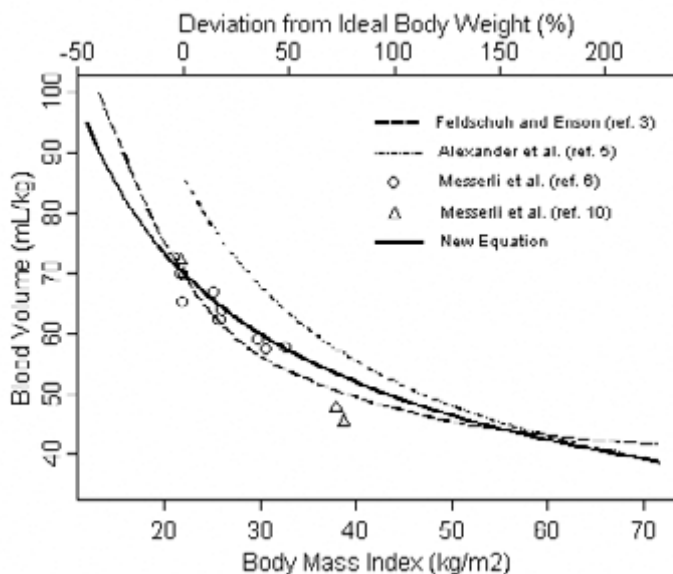


Fig. 2. Preoperative assessment of blood volume (BV) is important since replacement crystalloid, colloid and blood therapy can then be administered during the perioperative period in a rational manner. With increasing weight total circulating BV increases, but BV measured as mL/kg total body weight (TBW) decreases in a non-linear manner. Although 70 mL/kg is the accepted mean value in normal patients ($\text{BMI} = 22 \text{ kg/m}^2$), this value grossly overestimates total BV in obese and morbidly obese patients. A patient with a $\text{BMI} = 60 \text{ kg/m}^2$ will have a BV of about 40 mL/kg.

Appropriate amounts of intravenous fluid are needed to reduce postoperative complications [20]. Obese surgical patients develop RML from pressure injury to muscle. Long duration surgery is the major risk factor, while other factors include super-obesity, hypertension, diabetes and peripheral vascular disease [21]. When skeletal muscle is damaged, myoglobin is released into the systemic circulation where it is filtered by the kidneys. Very high concentrations overwhelm the kidneys causing acute renal failure (ARF). Disruption of the skeletal muscle membrane allows an influx of electrolytes and extra-cellular fluid into the damaged muscle. Intravascular fluid becomes sequestered in the oedematous muscle, and the fluid

shift results in hypovolaemia with haemodynamic instability. Chloride and calcium enter the injured cells causing serum hypocalcaemia and calcium retention in the skeletal muscles and renal tissue. Potassium leaves muscle cells producing hyperkalaemia, with dysrhythmias and possibly cardiac arrest. Metabolic acidosis ensues from release of lactic acid and other intracellular contents into the circulation.

Local signs and symptoms are non-specific and include muscle pain, numbness, tenderness, swelling, bruising and weakness. Aggressive pain management (as with epidural analgesia) may mask symptoms and delay diagnosis. The primary diagnostic indicator of RML is an elevated serum creatine phosphokinase (CPK) level. Any obese post-surgical patient who complains of buttock, hip, or shoulder pain and has a serum CPK level $> 1,000$ IU/L should be considered as having RML. Myoglobinuria is seen as "tea" or brown coloured urine. Important biochemical findings include metabolic acidosis, hyperkalaemia, hyperphosphataemia, hypocalcaemia, hyperuricaemia, and raised levels of muscle enzymes.

Prevention begins with intra-operative padding of all pressure points and close attention to patient positioning. Adequate perioperative hydration, and close postoperative monitoring are important. Therapy focuses on the prevention of ARF and the management of life-threatening metabolic complications. Large volumes of intravenous fluids will flush myoglobin from the kidneys. Diuretics such as mannitol or furosemide should also be given. Urine is alkalinized by infusion of sodium bicarbonate to increase the solubility of myoglobin. The target for aggressive hydration and diuresis is a urine output of > 1.5 ml/kg/h.

Hyperkalaemia is treated in the conventional manner. Persistent oliguria or anuria may require dialysis. Compartment syndrome is treated by fasciotomy. Thromboplastin and tissue plasminogen released from injured muscle make the patient susceptible to disseminated intravascular coagulation.

Obesity, per se, is not a risk factor for postoperative nausea and vomiting (PONV) [22]. However, many patients undergoing procedures are at high risk (female, receiving opioids, emetogenic surgery) for PONV. Intraoperative prophylaxis with several anti-emetic agents will reduce, but not eliminate, PONV. Dexamethasone (4-8 mg) should be part of the therapeutic regimen. Large volumes of intravenous fluids may reduce the incidence of nausea following bariatric surgery [23].

Finally, postoperative analgesia is extremely important since a comfortable patient will breath deeply, ambulate sooner, and thus have fewer respiratory and thromboembolic complications. Postoperative epidural analgesia with local anaesthetics and opioids is ideal for open abdominal and thoracic procedures. Intravenous patient-controlled analgesia with opioid dosing is also used. Large amounts of opioids, especially longer acting agents (morphine, demerol, hydromorphone) depress ventilation and should be avoided. Non-opioid analgesic adjuncts should be instituted early. Dexmedetomidine, which has no respiratory depressant effects, may become a useful alternative or supplement to opioids in obese patients, particularly those with OSA or OHS.

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Perioperative Care in Neurosurgery – Intraoperative Monitoring

C. ORI, M. MUNARI, S. VOLPIN

Intraoperative monitoring of neuronal function, cerebral haemodynamics and cerebral oxygenation provides information to guide anaesthetic and surgical procedures in individual patients. The aim of neuroanaesthesia is to provide optimal intracranial operating conditions, maintain cerebral perfusion pressure (CPP), protect against ischaemic insults and prevent postoperative complications. The anaesthetic techniques and the anaesthetics used in neuroanaesthesia are all geared to these objectives. A neurophysiologically monitored surgical approach can decrease neuronal injury and neurological deficit related to cerebral ischaemia and improve long-term neurological outcome. Traditionally, electrocardiography, arterial blood pressure, pulse oximetry, end-tidal CO₂ (ETCO₂), body temperature and urine output are monitored during neuroanaesthesia in the operating room.

Two German surveys [1] examined the practice of intraoperative monitoring in neurosurgery in 1991 and 1997. Central nervous system (CNS) monitoring was not a standard of practice in 1997. There was an increase in the use of electroencephalography and evoked potentials in 1997 compared with 1991, but both were still infrequently used. Compared with 1991, by 1997 standard monitoring had expanded to include the surveillance of systemic oxygenation, haemodynamics, ventilation and body temperature which were universally applied in adults and paediatric patients as recommended by the American Society of Anesthesiologists [2]. Because neurosurgical patients are at increased risk of secondary brain injury which is critical in determining neurological outcome, the adoption of standard monitors might have indicated that this has generally been recognized. Although new monitoring devices have been introduced into the operating theatre over the last decade, they have not been fully accepted as standard care in neurosurgery. There are great differences within and between countries, and even indications for something as simple as placing an arterial or a central venous line before craniotomy vary from one team to another.

Advances in neuromonitoring have provided insights into neurological function during anaesthesia. Despite the limitations and the necessary caution required to interpret neural function when using intraoperative monitors, these technologies have been definite steps in the right direction for assessing neural integrity. Changes in monitored parameters should reflect changes in the function of the CNS and/or in the blood supply of the part of the brain at risk during surgery. Because the extent and duration of secondary insults may have a significant impact on

unfavourable neurological outcome, timely detection and treatment of intraoperative complications is of special importance for patients undergoing neuroanaesthesia. The monitor should be used continuously if possible and the number of factors affecting the monitored parameters should be minimal.

General monitoring during intracranial surgery including ECG, invasive arterial pressure, ETCO_2 , inspiratory pressure, pulse oximetry, body temperature, head position, protection of the eyes, neuromuscular transmission and urine output is considered to be an absolute standard for monitoring [3]. Different specialized monitoring modalities used perioperatively during neurosurgery are able to detect intraoperative ischaemic insults, but are not yet fully accepted as standard care.

Neurological monitoring aims to detect changes in the main factors that affect CNS function. Under general anaesthesia, neuromonitoring can be performed through the assessment of cerebral haemodynamics, brain tissue oxygenation and electrophysiology.

Cerebral Haemodynamics

When neurological function fails, it is important to obtain information about the mechanism of CNS damage. One of the most common mechanisms of damage is inadequate blood flow. The intraoperative measurement of absolute values of cerebral blood flow (CBF), however, is still very difficult whereas monitoring of CBF changes is more accessible.

¹³³Xenon clearance is the only method available for measuring CBF in the operating room. CBF measurements using this well established technique are used mostly as a comparison tool to evaluate other monitoring techniques [4, 5]. In addition, the method is cumbersome and expensive and only provides discontinuous measures of brain perfusion.

An easy, direct and noninvasive monitor of CBF uses transcranial Doppler (TCD) ultrasound [6]. This technique enables the measurement of relative, not absolute, changes in CBF. TCD flow velocity measurements are most commonly and easily made in the middle cerebral artery (MCA) and internal carotid arteries, but may also be measured in other vessels.

A constant vessel diameter and an unchanged angle of insonation are the two main assumptions that govern the use of TCD as an indirect measure of CBF. Flow and flow velocity (FV) are directly related only if the diameter of the artery remains unchanged during the measurement period. Arterial carbon dioxide tension, blood pressure, anaesthetic agents and vasoactive drugs may all affect the diameter of vessels. Inhalational agents produce a dose-dependent increase in CBF which is dependent on the balance between the intrinsic vasodilatory action of the agent and the vasoconstriction secondary to flow-metabolism coupling. The intravenous agents do not affect the diameter of the conductance vessels and preserve flow-metabolism coupling. Thus CBF and MCA FV decrease in dose-dependent fashion [7]. During steady-state anaesthetic conditions, changes in blood FV can be interpreted to mean corresponding changes in cortical CBF.

TCD is the method of choice for detecting embolization, and continuous measurement of blood FV in the distribution area of the MCA may be helpful in differentiating intraoperative haemodynamic versus embolic neurological events [8]. Embolization as detected by TCD occurs in more than 90% of patients during carotid endarterectomy. Various studies have found an association between embolic rates and the risk of clinical neurological events and/or changes on brain imaging with CT/MRI [9, 10]. The presence of the emboli during initial dissection and wound closure appears to be more important in predicting adverse events than emboli during clamping or shunting, probably because of the different pathophysiology [9]. Emboli occurring during closure may be amenable to changes in surgical technique, as this may be a result of residual atheroma and early platelet aggregation. TCD may influence surgical and anaesthetic techniques and postoperative treatment, such as suggesting an anti-embolic therapy after the operation, with some reductions in thrombotic stroke rates [11].

In neurosurgery, TCD is able to test the intraoperative adequacy of CBF and also gives information about post-surgical blood FV, which may direct haemodynamic management after vascular surgery. The potential use of intraoperative TCD with arteriovenous malformation resection lies with estimating the completeness of resection and the diagnosis and treatment of the hyperperfusion syndrome, provided the feeding vessel can be monitored. The feeding vessels are characterized by high blood velocity, low pulsatility, low perfusion pressure and decreased CO₂ reactivity. In theory, in the presence of bilateral simultaneous monitoring the preoperative difference in velocity and in pulsatility between the two sides should progressively disappear [12]. A major risk associated with aneurysm surgery is the possibility of inadvertent occlusion or damage of the vascular branches from which the aneurysm arises, with the subsequent risk of stroke. In planning the surgical approach or in applying temporary clips the surgeon must consider collateral circulations. The functional integrity of these vessels frequently decides the patient's outcome. Doppler sonography has been advocated as a strategy to provide real-time assessment of vessel patency [13, 14]. However, determination of the degree of vessel stenosis so as to distinguish between robust and poor flow in a nonocclusive compromised vessel can be difficult. The microvascular ultrasonic flow probe holds significant advantages over microvascular Doppler studies, including the quantitative nature of the data obtained. The use of this device provides real-time feed-back concerning vessel patency. Blood flow measurements can be affected by blood pressure and arterial CO₂. To avoid false negative or positive values attention must be paid to assess flow measurements under stable settings. The relatively high incidence of detection of flow compromise, 31%, reflects the aneurysm locations and morphologies for which the probe was used. The highest incidence of flow reductions were seen in the basilar artery, MCA and anterior cerebral artery (ACA) locations and the utility of the flow probe measurements is likely to be highest for these aneurysms [15]. It is difficult to demonstrate the optimal threshold of flow reduction, but the available literature supports that a 25% or greater reduction in distal flow is correlated with ischaemia and even a subclinical degree of flow compromise may be important in the setting of a

ruptured aneurysm, where there is the potential for a subsequent spasm and further flow reduction [16]. Immediate, easy and quantitative measurements make this technique a useful addition for enhancing the safety of aneurysm surgery [15, 17].

Electrophysiological Activity

The goal of brain tumour surgery is to maximize the resection extent while minimizing the risk of permanent deficit. Neurophysiological monitoring measures spontaneous and evoked electrical activities of the nervous system with the purpose of preserving function and preventing injury at a time when clinical examination is not possible. The common techniques used in the surgical settings are recordings of electroencephalogram (EEG) and evoked potentials (EPs). An EP differs from the EEG in two main ways: (1) The EEG is a random, continuous signal, which arises from the ongoing activity of the outer layers of the cortex. An EP is the brain's response to a repetitive stimulus along a specific nerve pathway; and (2) EEG signals range from 10-200 mV. EPs are smaller in amplitude, thus requiring precise electrode positioning and special techniques (signal averaging) to extract the specific response from the underlying EEG "noise".

Many studies have demonstrated that these monitors are able to reveal the underlying neurophysiology with reasonable sensitivity and specificity [18-22]. Although not universally adopted, the growing body of literature provides strong evidence of the clinical utility of intraoperative monitoring (IOM) in a variety of cerebrovascular surgical and endovascular procedures. IOM is mandatory if neurological complications are expected on the basis of a known pathophysiological mechanism. IOM should be performed during surgery of supratentorial lesions in the central region and language-related cortex and brainstem lesions. In many cases, monitoring has become an integral part of the operating room, influencing and guiding surgical decisions.

Electroencephalography

Because the CNS is not commonly monitored during anaesthesia, episodes of hypoxia or hypoperfusion or of awareness do occasionally occur.

The EEG can be a useful tool for monitoring the brain when surgical procedures may potentially compromise cerebral perfusion or involve the cerebral cortex. During an anaesthetic state at a stable depth, EEG activity is stable as well and any EEG change may be a signal of cerebral ischaemia [23]. In the progression of acute cerebral ischaemia, a failure of electrical activity precedes the deterioration of ionic homeostasis; monitoring this activity can be important in predicting the development of cerebral ischaemia before irreversible damage occurs. A progressive CBF decrease gives rise to EEG attenuation and slowing frequencies. A variety of qualitative and quantitative EEG features have been proposed as thresholding criteria [24]. A decrease in fast activities is associated with a moderate CBF de-

crease, following changes in EEG amplitude with the appearance of delta rhythms [20, 24]. Some studies indicate that severe hypoperfusion is characterized by the disappearance of α and β and a predominance of δ frequencies [24, 25]. The type of alterations could also depend on the type of operation. Exploring the brain areas which are the most vulnerable to ischaemia is recommended, i.e. the frontal cortex which lies at the boundary between the ACA and MCA territories or the parieto-occipital cortex which is an area between the carotid artery and the basilar trunk [20].

Computer processed EEG provides frequency analysis and data reduction of the scalp EEG. Digital EEG includes various time intervals to map each waveform in relation to its frequency, amplitude and time of occurrence, thus making the interpretation of EEG more readily accessible. It offers a method for quantifying aspects of the EEG that have been routinely evaluated qualitatively. Utilizing this method it is now possible to calculate in real time the spectral amounts of the EEG, which are useful in a number of clinical settings. They provide continuous information of the onset, depth and duration of an anaesthetic on neuronal structures. They confirm satisfactory cerebral perfusion during neurosurgical operations and provide a continuous and objective record of sufficient cerebral oxygenation. They are immediately able to assess the effects of hypoperfusion and/or hypoxaemia on cortical structures and rapidly demonstrate the benefits of corrective measurements. For the assessment of brain hypoperfusion, many studies rely on the spectral edge frequency, defined as the highest frequency that can visually be identified on the “compressed spectral arrays” or “density modulated spectral arrays” [26]. The most relevant sign sufficient for diagnosing brain hypoperfusion is a power decrease of the α and/or β band powers associated with a power increase in the δ or θ band. However, quantitative threshold values for a significant CBF decrease are rarely reported in the literature, but one recent approach consists in considering the band power variability rather than the power values of the α and β bands [27]. Continuous EEG, however, remains the standard for recording when pattern recognition is required, such as during electrocorticography. In all cases, the monitoring technologist needs to be very familiar with anaesthetic agents and their effects on the EEG. Unfortunately, changes in EEG frequency and amplitudes may be caused by the administration of anaesthetic drugs as well as changes in anaesthetic depth. Deep anaesthesia and ischaemia produce similar EEG changes. In both cases, fast activity is replaced by slower, larger EEG waveforms. As anaesthesia is further deepened or ischaemia worsens, additional slowing occurs and the EEG amplitude decreases.

EEG monitoring provides information about the overall electrical functioning of the cerebral cortex but not much about the subcortical brain or cranial and peripheral nerves. The functioning of CNS sensory or motor pathways that may be at risk during surgical procedures is monitored by EPs.

Evoked Potentials

The range of application for EPs is growing, as demonstrated in several reviews [28-30]. EP monitoring indicates when something is wrong in the neural pathways, provided that the effect of anaesthetics, temperature and arterial pressure can be excluded as causes. The recording of EPs, such as EEG, can be substantially influenced by many anaesthetic agents commonly used in the operating room. Lipophilic anaesthetic drugs decrease the synaptic excitability in the central and peripheral nervous system, and can modify subcortical conductions by directly influencing the cortical generators or by decreasing the signal-to-noise ratio. Although intravenous and volatile anaesthetics affect EP characteristics, the significantly lower effect of propofol promote the use of this drug rather than inhalational agents when electrophysiological monitoring is required [31].

EPs during intracranial surgery serve the following main purposes:

1. Monitoring of the functional integrity of neuronal structures that may be at risk during neurosurgical procedures.
2. An indicator of cerebral hypoxia when the blood pressure is lowered for procedural requirements.
3. Monitoring the cerebral function during controlled hypothermia when the EEG becomes flat.
4. Monitoring of the effects of anaesthetic agents and other centrally active drugs, which apart from the cortex affect deeper neuronal structures.
5. An intraoperative warning device of unsuspected awareness during light anaesthesia when movement is abolished by muscle relaxants and cardiovascular responses are modified by vasoactive drugs.

Numerous studies have demonstrated a threshold relationship between regional CBF and cortical EPs. Although clinical function becomes abnormal at about 25 ml/min/100 g, electrical function generally remains normal when the CBF exceeds the "functional threshold" of about 22 ml/min/100 g. Below this level the EEG and somatosensory evoked potential (SEP) become abnormal. A CBF decrease gives rise to desynchronization of cortical neurones and/or a decrease in the number of functional neurones. This provokes an amplitude decrease or even the disappearance of some peaks. At lower levels, electrical activity is lost [32].

For the detection of brain ischaemia, most studies propose criteria based on an N20 amplitude decrease and/or a central conduction time (CCT) increase: significant values are considered a decrease larger than 50% in N20 amplitude and a CCT increase greater than 1 ms or more than 20% from normal values [20, 23]. The most sensitive cortical areas are the boundary zones between different perfusion areas, like the prerolandic area. The frontal N30, whose generator is likely to be close to the supplementary motor area, can evaluate the function of these areas, and it is interesting as a diagnostic criterion of brain hypoperfusion, especially of systemic origin [20]. Nevertheless, while the SEP alterations following a critical CBF decrease were clearly defined qualitatively, the definition of unequivocal quantitative criteria for an acceptable CBF decrease is still a matter of debate.

Surgery for vascular lesions of the brain may be complicated by ischaemia from

intentional temporary or permanent occlusion of major vessels with insufficient collateral supply, inadvertent occlusion of major artery branches or of minor perforating vessels, impaired microperfusion from inadequate retraction, and vasospasm induced by manipulation of vessels [33]. Continuous monitoring techniques, mainly recordings of EPs, are employed during this type of surgery. SEP monitoring is based on a correlation of SEP amplitude and latency with cortical cerebral perfusion. These parameters change when cortical perfusion is still above the critical level for ischaemia, where complete SEP loss occurs when infarction is impending. At the subcortical and brainstem levels SEP monitoring is not indicative of non-somatosensory pathways with sufficient reliability. Brainstem auditory evoked potentials (BAEPs), which correlate to a certain extent with brainstem perfusion, can help to decrease, but not to abolish, the risk of false negative monitoring results in this area. Motor evoked potential (MEP) monitoring has been established as a reliable monitor of the pyramidal tract during brain tumour surgery and recently has been applied during intracranial aneurysm surgery. It enables the detection of motor impairment, particularly from subcortical ischaemia [34].

Posterior frontal and anterior parietal lobes, as well as the dominant temporal lobe, are all suitable for intraoperative monitoring and/or mapping in order to localize the rolandic cortex, the descending motor pathways and the cortical site responsible for naming and reading and to achieve “radical” surgical removal. The motor cortex is identified by recording the phase reversal of SEP across the central sulcus. Although the cortical surface can often be distorted by a tumour mass, the central sulcus can still be identified with this technique in over 90% of cases [35]. Since this is a method for mapping the cortical surface, damaging the subcortical motor tract during removal of a deep-seated tumour is still possible. To overcome this issue, an electrical stimulation method is used to map out the subcortical motor pathways. Published data have shown a remarkably low incidence (%) of postoperative deficits among the high-risk patients [36].

The brainstem is a part of the nervous system where a high concentration of different nerve structures is found in a small space and even small incision injuries can result in severe neurological complications. Lesions involving these areas can be life threatening or have debilitating consequences. Classic intraoperative neurophysiological methods (SEP and BAEP) can evaluate only 20% of the brainstem. Continuous monitoring of the functional integrity of cranial motor nuclei and nerves is still unsatisfactory. The available techniques are based on the recording of the ongoing electromyographic (EMG) activity in the muscles innervated by cranial nerves [37]. However, the correlation between intraoperative EMG activity and outcome is still a matter of debate. An evaluation of the functional integrity of the structures of the brainstem is warranted only by the combined use of multiple monitoring techniques. While monitoring only BAEPs, only SEPs or only MEPs can be misleading, the integration of the data from all these modalities will provide the most reliable assessment of brain stem integrity. EP monitoring provides both specific information about a particular system (motor, sensory and auditory), and less specific information about the whole function of the brainstem.

One role of neurophysiological monitoring is to integrate the patterns with intraoperative clinical features to avoid false-positive or false-negative results and to warn the neurosurgeon before irreversible injury to the nervous system has occurred.

Cerebral Oxygenation

Maintenance of neuronal oxygenation is the final objective of all clinical procedures in neuroanaesthesia. Various physiological changes can affect brain oxygenation, as measured globally by jugular bulb oxygen saturation or measured regionally by near infrared spectroscopy.

Jugular venous bulb oxygen saturation ($SjvO_2$) has proved to be useful in neuroanaesthesia as an indirect assessment of global cerebral oxygen to guide physiological management decisions in a variety of clinical settings. When demand exceeds cerebral oxygen supply, the brain extracts more oxygen, resulting in decreased $SjvO_2$. In contrast, when cerebral oxygen supply exceeds demand, $SjvO_2$ is increased. It is widely accepted that this monitoring technique reflects the global balance between cerebral oxygen delivery and cerebral oxygen consumption [38].

Changes in $SjvO_2$ provide indirect information on the state of the cerebral metabolic rate of oxygen ($CMRO_2$) and because CBF is normally linked to $CMRO_2$, $SjvO_2$ provides indirect information on CBF as well. The intraoperative use of $SjvO_2$ in patients undergoing neurosurgical procedures may be beneficial both for detecting and treating cerebral venous desaturation and for calculating the cerebral arteriovenous oxygen content difference. Matta et al detected at least one episode of cerebral venous desaturation due to hyperventilation in approximately 50% of patients studied [39]. Monitoring of $SjvO_2$ is used during aneurysm surgery to control ischaemia. The use of temporary vessel occlusion enables the reduction of the pressure and size of the aneurysm during surgery. The safe limits for arterial occlusion and the benefits of reperfusion are yet to be determined. Monitoring $SjvO_2$ provides different data during anaesthesia, but cannot be used as a single source of information [40].

Near-infrared spectroscopy (NIRS) noninvasively and continuously measures regional changes in oxyhaemoglobin, deoxyhaemoglobin and cytochrome a₃ redox status and may be a sensitive indicator of cerebral hypoxia.

NIRS interrogates arterial, venous and capillary blood and the derived oxygen saturation is an average value for these three compartments. However, most of the NIRS signal is from the venous blood because it contributes to approximately 70% of the intracranial blood volume. The potential usefulness of NIRS is as a monitor of changes in cerebral oxygenation rather than an indicator of an absolute condition of the oxygenation in the mixed venous blood of the brain. It can be considered a promising method for detecting ischaemic events during neurovascular procedures, providing continuous and quantifiable information about brain oxygenation and haemodynamics in a noninvasive manner [41].

Brain tissue PO_2 monitoring as a method for determining oxygenation is of

increasing interest in neurosurgery, especially during aneurysm surgery in order to determine ischaemic events. Intraoperative monitoring of tissue O₂ has been performed by some authors through an intraparenchymal O₂ sensor probe, located deeply in the territory supplied by the artery carrying the aneurysm. This method seems to be accurate and has the advantage of providing real-time continuous data. This method still seems to be more important for the better understanding of focal brain ischaemia than for routine use in aneurysm surgery [42].

Neurosurgical patients are at increased risk of secondary injury and detection of intraoperative complications is very important for the neuroanaesthesiologist. The most important aims of neuroanaesthesia are to provide adequate CPP and CBF to meet the tissue demands of oxygen and glucose and to protect the brain should the supply decrease. Adverse outcome can be prevented with the use of better monitoring modalities, and the combination of monitors to provide information during surgical procedures is required to produce a better patient outcome.

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Incidents Provoked Specifically by Certain Drugs Used in Anaesthesia

M. KLIMEK, T.H. OTTENS, F. GRÜNE

One of the most frequent actions of an anaesthesiologist during the daily routine is the (intravenous) administration of drugs. This action alone offers many risks (e.g. wrong drug, wrong route, wrong dosage, wrong situation), but even when all these things are done right, there still remains the risk of incidents provoked by the drugs used. In this chapter, the term “incident” is used for any serious unwanted (and sometimes unexpected) effect of a drug, which is used with the best intentions for the patient’s health during anaesthesia and perioperative care. Of course, there is no drug without any theoretical side effect, so we will focus on relevant, preventable and/or treatable problems in the daily practice, where recent advances in evidence can be reported.

Hazards of Higher Oxygen Concentration

There is no mammalian life without oxygen, but at the same time, oxygen can be toxic, especially if hyperoxia is administered to patients treated with certain anti-neoplastic drugs like bleomycin, carmustine, busulfan and methotrexate [1]. This has been well known for more than 20 years, however this knowledge seems to be fading away and must be refreshed.

Two major risk factors for the development of bleomycin-induced pulmonary damage related to hyperoxia exposure are evidence of pre-existing pulmonary damage from bleomycin and prior exposure to bleomycin within a 1–2-month period. Other risk factors for bleomycin-induced pulmonary damage are total dose of bleomycin >450 mg and a creatinine clearance <35 mLmin⁻¹. Cisplatin, when used with bleomycin, can increase the lung toxicity of bleomycin because it is nephrotoxic and can delay renal clearance of bleomycin. The current recommendations are that patients with one or both major risk factors present should be maintained on the lowest FiO₂ to maintain SpO₂>90% [2–4].

Hyperchloraemic Acidosis Caused by Infusion of Too Much NaCl 0.9%

Next to oxygen, almost every patient undergoing anaesthesia will receive an IV-line with some crystalloid infusion. A solution of 0.9% NaCl is called a “physiological saline” solution, however, it contains 154 mmol/l of chloride, and is therefore not physiological at all. When performing blood gas analysis based on the theory of Stewart, it is evident that even smaller amounts (less than 2 litres) of this solution can induce severe hyperchloraemic acidosis due to shifts in the strong ion difference [5, 6]. Saline and saline based colloids are associated with a hyperchloraemic metabolic acidosis relative to Ringer’s lactate. There is some evidence that saline may alter renal function. Increasing awareness of the ‘Stewart hypothesis’ has led to relatively new ways of managing hyperchloraemic metabolic acidosis, whether or not associated with an adverse patient outcome [7].

Propofol Infusion Syndrome

Due to its favourable pharmacodynamics and -kinetics, propofol is commonly used in anaesthesia and Intensive Care. However, many adverse effects of this drug like asystole, myocardial failure, rhabdomyolysis and death are reported. Metabolic acidosis due to propofol seems to occur especially in children, but it has more recently been reported in adults as well [8]. In 1998 the term “propofol infusion syndrome (PRIS)” was introduced by Bray [9]. He described an acute refractory bradycardia eventually leading to death in children with the following risk factors: metabolic acidosis and/or rhabdomyolysis and/or hyperlipidaemia and/or an enlarged, fatty liver. Bray found the association between the occurrence of PRIS and administration of more than 4 mg/kg/h propofol for >48 hours. In the meantime, more than 60 cases have been published, including 20 paediatric deaths and 18 adult deaths. In addition, on some occasions the first signs of PRIS were able to be detected after much shorter periods than 48 hours, so that PRIS is not only a problem of the ICU, but a problem of the operating theatre as well. Patients undergoing long lasting neuroanaesthesia seem to be especially at risk and repeated lactate-checks are recommended as well as combining propofol with another drug for maintenance of anaesthesia (e.g. isoflurane) to avoid (too) high total doses of propofol. As soon as PRIS has developed, therapeutic options are very limited. Any kind of extracorporeal elimination (haemodialysis, haemofiltration) and cardio-respiratory support have turned out to be the most successful techniques [10].

Adrenocortical Suppression by Etomidate

Alongside propofol, etomidate has found its place as a standard drug for anaesthesia induction, especially in the patient with cardiac instability. However, etomidate is known to suppress adrenocortical hormone synthesis, not only when given over a prolonged period or in repeated doses, but even as a single dose like during

anaesthesia induction. Adrenocortical hormones play an important role in cases of haemodynamic instability in, for example, septic patients. There are some recent studies that may raise concern about the safety of etomidate in these patients [11]. Whilst some authors suggest to stop using etomidate in septic or other ICU patients, others discuss the indication to substitute the suppressed endogenous corticosteroids by injecting hormones next to etomidate when using it for anaesthesia induction in these patients [11-13].

Anaphylactic Reactions on Muscle Relaxants

Recently several surveys on the incidence of anaphylactic reactions during anaesthesia in adults and children have been published [14-17]. The common result of all these surveys is a high incidence of anaphylactic reactions on neuromuscular blocking agents, especially suxamethonium and rocuronium. These reactions are more severe than on latex and seem to occur more frequently in women than in men. Whilst suxamethonium still has its “always have it – never use it” limitations, rocuronium is to be used widely and probably without concern about this possible lethal side effect, although there are safer alternatives like cisatracurium [16], if rapid-sequence induction is not mandatory. This was also stressed by a warning letter of the Norwegian Health authorities, amongst others. However, there are some limitations in these surveys, which are due to reporting bias, local aspects in the countries observed, and especially due to the low power of the data provided considering the common use of neuromuscular blocking agents and the relatively low incidence of severe anaphylactic reactions. Lastly, it should be stressed that a negative skin-test for any neuromuscular blocking agents does not provide a 100% guarantee that an IV-administration will not produce severe anaphylaxis [15, 16].

Postoperative Agitation in Children After Sevoflurane

Sevoflurane seems to be the current agent of choice in paediatric anaesthesia, not only for inhalational induction but also for maintenance of anaesthesia [18]. For induction this is easy to understand, because the pharmacological and safety profile of sevoflurane is much better than that of halothane, leaving no real alternative. However, for maintenance of anaesthesia one should really think about alternatives. Unpleasant behavioural changes during emergence are extremely common (incidence up to more than 40%) after anaesthesia with sevoflurane maintenance, especially in children, and might be occurring together with EEG-changes [18-22]. Different measures have been taken to reduce the incidence (addition of nitrous oxide, premedication with benzodiazepines, early extubation, switching to other inhaled anaesthetics), but only the addition of propofol seems to be effective [18, 19, 22]. However, a more recent study also indicates that a switch to desflurane for maintenance after sevoflurane inhalation induction reduces the incidence of emergence agitation by 50 % [21]. One interesting study is a case-series on four cases of

delirium after sevoflurane, where the patients were able to report details of their postoperative experiences [23]. Not only does this case-series include one adult patient (24 years old), but it also clearly describes a paranoid delusion as a common feature of this state of agitation. The impact of these behavioural changes on morbidity and mortality seems to be low, but is nonetheless unknown. Due to the irritating impression such an emergence agitation might have on parents, information about this phenomenon should be given before the procedure. Finally, to avoid this problem, propofol maintenance after sevoflurane induction seems to be the best alternative.

Kidney Failure Due to Nonsteroidal Antiinflammatory Drugs

A multimodal approach including nonsteroidal antiinflammatory drugs (NSAIDs) must be considered to be the best postoperative pain treatment. However, there are some risks associated with the use of NSAIDs, and whilst a possible anticoagulatory effect is taken into consideration by almost everybody, a possible nephrotoxic effect is very often neglected.

NSAIDs affect the renal system by inhibition of the prostaglandin synthesis, which decreases distal tubular flow rate and sodium delivery, by reducing the glomerular filtration rate and increasing tubular sodium reabsorption. Additionally, there is a decline in aldosterone, which promotes potassium retention [24].

It should be clear that NSAIDs cause only a clinically unimportant transient reduction in renal function (up to 36% reduction in creatinine clearance) in the early postoperative period in patients with normal preoperative renal function. Therefore, they should not be withheld from adults with normal preoperative renal function because of concerns about postoperative renal impairment [24]. This is completely different in children and in patients with preoperative renal impairment (e.g. due to pre-existing renal insufficiency, reduced renal blood flow, hypovolaemia, or other nephrotoxic agents). In these patients, a too enthusiastic use of NSAIDs may cause severe nephrotoxic effects, that cannot be antagonized by any other measure, and acute renal failure including the need for renal replacement therapy [25, 26].

Myotoxicity of Local Anaesthetics

While the neurotoxicity of lidocaine has been an issue of concern for a long time, the myotoxic properties of the different local anaesthetic drugs in general are taken less seriously. However, there is clear evidence that acute and long-term administration of bupivacaine can induce more severe muscle cell damage than does ropivacaine [27-29]. It should be mentioned that all clinically used local anaesthetics are myotoxic, with a drug specific and dose-dependent rate of toxicity that worsens with serial or continuous administration [27]. There are some impressive case reports of myopathy or myonecrosis after continuous peripheral blocks,

infiltration of wound margins, trigger point injections and peribulbar blocks [29]. Despite the fact that the acute clinical effect of this myotoxicity is still controversial, the possible effects of long-term-administration, especially of bupivacaine, must be a point of concern before administering this drug via catheters to a patient for a longer period [28].

Systemic Toxicity of Local Anaesthetics and Treatment with Lipid Emulsion

Next to the local toxic effects of local anaesthetics, some recent developments in the field of systemic toxicity have taken place. Lipid emulsions have turned out to be suitable for resuscitation in patients after a systemic intoxication with local anaesthetic agents. The idea is that – due to their high lipophilicity – the injection of lipids will withdraw the local anaesthetic from the cardiac nerve fibres and bind the drug until elimination has taken place [30-32]. Since the first successful reports in animals in 2003, there have been three successful reports of resuscitation of patients who experienced the toxic side effects of different local anaesthetics. Of course, it is impossible to perform a clinical study on humans on this issue, but the encouraging reports, the convincing theoretical argumentation and the ease of application of these fat emulsions has lead to a policy in many hospitals that at the places where regional blocks are performed a bottle of lipids for infusion must be available. However, preventing intravascular injection by ultrasound-guided technique and not exceeding the toxic dose-limits still are the most important measures to keep the patient safe.

Central Anticholinergic Syndrome by Different Drugs and Use of Physostigmine

Central anticholinergic syndrome (CAS) can be provoked by almost every drug we use for general anaesthesia. Therefore, we, last but not least, want to draw the reader's attention to this common and relevant clinical phenomenon, which can easily be treated by the administration of physostigmine, if recognized by the anaesthesiologist [33-35]. The clinical signs can vary from apathy to agitation. Dilated pupils and a dry mouth are common, but not always present. CAS should be considered in all cases when the postoperative mental state does not recover to the preoperative level within an acceptable time. Physostigmine is the only treatment of choice. It has also demonstrated a positive effect on postoperative shivering and the duration of postoperative recovery [34]. The most relevant side effect is nausea.

Conclusions

Taking all these aspects together, the following must be concluded. Although we have made large steps forward in patient safety, commonly used drugs and techniques may still have dangerous side-effects. Every anaesthesiologist should keep his knowledge about these effects up to date and must be prepared to both recognize and treat these side-effects early and effectively in order to further improve safety in the operating theatre.

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Side Effects Induced by Anaesthetic Manipulation or by Surgical Operation

Y. LEYKIN, N. NOAL

All medical treatment could be associated with an injury or unexpected side-effects that can be added to the usual course of the disease, but which are not linked to the disease itself. Both mild and severe patient injuries may occur in response to anaesthesia.

Perioperative accidents and complications can be the result of:

- inadequate preoperative preparation;
- equipment failure;
- personal failure;
- inadequate postoperative care.

Mortality associated with anaesthesia and surgery is defined as the rate of deaths within the first 30 days from the surgical operation. Numerous studies evidence that the highest number of deaths takes place in the first 24 hours of the postoperative period.

Deaths can be the result of:

- the pathology for which the surgical operation is carried out;
- an elapsing pathology;
- anaesthesiological errors or complications;
- surgical errors or complications.

There are no concordant data on mortality associated with anaesthesia.

Since significant anaesthesia injury is a relatively rare occurrence, it is difficult to study prospectively or by retrospective medical record review. Therefore, many countries have performed a “closed claim project”, which is a reporting mechanism that provides an indirect assessment of the safety of anaesthesia practice in these countries.

Closed claim data can reveal important and previously unappreciated aspects of anaesthetic outcomes. Therefore, closed claims data do not provide a denominator for calculating the risk of anaesthetic injury; in fact, some injured patients do not file claims, whereas others without injury do file claims.

However, closed claims analysis is useful for generating hypotheses about the mechanism and prevention of anaesthetic injury. Although it cannot be used for testing of those hypotheses, the insights gained can be used for improving the quality of anaesthesia care, thus providing a tool for advancing patient safety and reducing liability exposure for the anaesthesiologists [1].

We must, however, emphasize that the technological progresses in surgery and

anaesthesia have substantially reduced mortality related to them. In fact, a report by Cheney et al shows that claims for death or brain damage decreased between 1975 and 2000 [2].

Patient Injuries in Response to Anaesthetic Procedures

Several studies have found that adverse respiratory events are the main source of injury and result in a high number of poor outcomes in healthy patients undergoing elective surgery, resulting in death or permanent injury, as compared with non respiratory accidents [3].

The most common events leading to injury were inadequate ventilation, oesophageal intubations and difficult tracheal intubation.

First of all, clinical assessment of the airways should be performed to identify any possible difficulties to intubate [4]. In fact, the most frequent occurrence with damaging respiratory events is undocumented airway assessment [5].

The highest rate of respiratory incidents occurs during emergency and general anaesthesia, mainly due to inappropriate anaesthesia management or lack of vigilance. Such incidents have often been judged as preventable events [6].

The formulation of standards including the use of pulse oximetry intraoperatively [7], the use of end tidal CO₂ for the verification of endotracheal intubation [3], and the use of pulse oximetry in postanaesthesia care units decreased the rate of respiratory related events between 1986 to 2000 [2].

The severity of injury during monitored anaesthesia care procedures is comparable to general anaesthesia, with 41% of the claims being for death or permanent brain damage. The delayed detection of respiratory depression as a result of over sedation was the most common mechanism of injury and could be preventable by the use of additional or improved monitoring [8, 9].

A comparison of adult and paediatric close claims revealed a large prevalence of respiratory related damaging events, most frequently related to inadequate ventilation.

Cyanosis and/or bradycardia often preceded cardiac arrest in paediatric claims related to inadequate ventilation, resulting in death or brain damage [10].

The main category of damaging events or mechanisms responsible for severe injuries related to respiratory events has changed over the time. The occurrence of respiratory system events has decreased primarily in claims for injuries due to inadequate ventilation or oesophageal intubation. Inadequate ventilation and oesophageal intubation were two of the three most common respiratory events before the use of pulse oximetry and capnography [1, 2]. However, the occurrence of difficult tracheal intubation would not be affected by better monitoring and it has remained relatively constant.

Difficulties or failure in airway management are still important factors in morbidity and mortality related to anaesthesia and intensive care. A patent and secure airway is essential to manage anaesthetized or critically ill patients. Oxygenation maintenance during tracheal intubation is the cornerstone of difficult

airway management and is always emphasized in guidelines.

The occurrence of adverse respiratory events has decreased in claims for injuries due to inadequate airway management mainly at induction of anaesthesia [11]. Nevertheless, claim reports emphasize that airway emergencies, tracheal extubation and/or recovery of anaesthesia phases are still associated with death or brain damage, indicating that additional educational support and management strategies to improve patient safety are required [12].

Other less common adverse respiratory events are:

- airway trauma associated with difficult intubation;
- pneumothorax, usually either needle-related or airway management related;
- upper airway obstruction;
- aspiration, usually occurring either during induction of general anaesthesia, or during maintenance of anaesthesia delivered via mask;
- bronchospasm, which tends to occur during induction of general anaesthesia in patients with a history of asthma or chronic pulmonary disease and/or smoking [4].

Even if a large number of guidelines regarding prophylaxis of aspiration do exist, the aspiration of gastric contents remains a problem, especially for patients undergoing urgent abdominal surgery, which has been shown to be the current most common situation in which aspiration occurs [13]. Respiratory incidents often result in death or permanent injury compared with other incidents.

The highest financial compensation was provided to patients for whom anaesthesia was complicated by prolonged perioperative hypotension or airway failure with secondary severe hypoxaemia [14]. Intraoperative hypotension and anaemia are the most important concerns associated with the occurrence of postoperative myocardial ischaemia and infarction. Perioperative hypotension is a side effect of anaesthetic drugs and in most cases cerebral autoregulation maintains a constant blood flow to the brain over a wide range of blood pressures. However, sometimes the critical level of hypotension, below which cerebral blood flow might be challenged, can be reached during anaesthesia and perioperative cerebral ischaemia may result.

In France, several deaths partially related to delayed or absent blood transfusion have been reported. In many cases, point-of-care monitoring of haemoglobin was not used to estimated blood loss. Blood loss associated with delayed or absent blood transfusion caused intraoperative hypotension and hypovolaemic shock, but also post operative myocardial infarction and ischaemia.

Central vascular catheters (CVCs) could also lead to injury, related to vascular access or catheter use or maintenance. The most common complications are wire or catheter embolus, cardiac tamponade, carotid artery puncture or cannulation, haemothorax or pneumothorax. Complications from a CVC are estimated to occur in more than 15% of patients in which CVCs are used. Claims related to CVCs have had a high severity of patient injury. Cardiac tamponade and haemothorax have had a higher incidence of death than all other CVC injuries.

In the 1990s, ultrasound guidance of central venous catheterization has been advocated as a mean to reduce mechanical complications and placement failure

compared with the landmark technique, especially in the presence of difficult central venous catheterization. Patient safety may also be improved by the use of waveform monitoring to prevent accidental arterial cannulation, and checking and acting on chest radiographs after central catheter placement [15].

Dental damage is a well-known complication during airway management. To reduce the number of injuries during airway management more training is required. Furthermore, studies suggest that errors in the use of medications are the leading cause of related anaesthetic events. Fortunately most of such errors are inconsequential [16]. It is worth noting that the number of drug errors in anaesthesia has been reduced significantly by the use of colour-coded labels for syringes and by improved education [17].

Adverse Events in Regional Anaesthesia

Regional anaesthesia (RA) is associated with numerous advantages and with very few complications. Although claims for death or brain damage are decreasing, nerve injuries may become the leading cause of anaesthesia-related injury for which a malpractice claim is made [18, 19].

The finding that most injuries to the ulnar nerve and brachial plexus seem to occur in the presence of adequate positioning and padding suggests that the mechanism of such injuries are not well known. Since preventive strategies for these nerve injuries are not apparent, no reduction in claims for these injuries may be expected. Therefore, the primary causes for financial compensation have been nerve lesions in response to regional anaesthesia. A surprising finding is that among claims for nerve damage in the 1990s, injuries to the spinal cord was the most frequent.

This seems to be related to neuraxial block in anticoagulated patients and blocks for chronic pain management. The complications of heart failure, neural injury and local anaesthetic toxicity are common to all regional anaesthesia techniques and each technique is associated with specific complications [20]. The incidence of cardiac arrest occurring during spinal blockade, often preceded by severe bradycardia, has been reported to be 6.4 per 10,000 patients, with many of these events being attributed partially or completely to the spinal anaesthetic [20].

In a 1988 survey, Caplan et al [21] analysed 14 cases of sudden cardiac arrest in healthy patients who had received spinal anaesthesia to determine whether there were recurring patterns of management that may have contributed to the occurrence or outcome of these anaesthetic accidents. They identified two patterns. The first was the intraoperative use of sedation which leads to unrecognized respiratory insufficiency. The second pattern appeared to be the inadequate appreciation of the interaction between sympathetic blockade during high spinal anaesthesia and the mechanism of cardiopulmonary resuscitation. Prompt increase of central venous filling, use of a potent alpha agonists such as epinephrine and positional change might have led to an improvement in organ perfusion, a shorter duration of cardiac arrest and lower degree of neurological damage.

However, patients may be refractory to treatment, even if it is immediate, because of the local anaesthetic intense sympathetic blockade which reduces circulating blood volume and may also cause a defective neuroendocrine response to stress. Therefore, even early administration of epinephrine may not guarantee a good outcome during neuraxial cardiac arrest.

A number of reports in the literature confirm the suddenness of the onset of bradycardia and hypotension during neuraxial block and the efficacy of early pharmacologic intervention. The incidence of cardiac arrest and neurological injury related with regional anaesthesia are very low, but it is significantly higher for spinal anaesthesia than for other regional techniques (1.4 per 10,000 anaesthetics; $p.05$) [22].

The most common causes of injury has been nerve lesion, infection, haematoma, headache or hearing loss following epidural, spinal anaesthesia or peripheral nerve blockade. The majority of patients developed a permanent nerve injury resulting in pain, incontinence of bladder or rectum or motor function impairment, and in a small number, paraplegia.

In a prospective study, Auroy et al showed that two-thirds of patients who developed neurological deficits had either suffered from paraesthesia during needle placement or pain on injection; these are dangerous signals of potential injury and must not be ignored. Seventy-five percent of the neurological deficits after spinal anaesthesia occurred in patients who had received hyperbaric lidocaine 5% [23].

Neurological complications during spinal anaesthesia occurred with a statistically different incidence regardless of whether lidocaine or bupivacaine had been used. The incidence of complications reported in this study is comparable with those found in other surveys. Complications caused by meningitis, abscesses or herniated discs usually had good recovery. Haematoma was the most common cause of neuraxial injuries and most these cases were associated with either intrinsic or iatrogenic coagulopathy. Sixty-eight percent of neuraxial haematomas were associated with impaired coagulation due to intrinsic coagulopathy, due to an anticoagulant often combined with other drugs which can also impair coagulation [24].

Even if the benefits of RA, particularly for vascular surgery, have been described in several reports and the frequency of epidural haematomas in RA for vascular surgery with intraoperative anticoagulation is very low, a careful risk-benefit assessment should be made preoperatively, and informed consent should be obtained.

In order to have a favourable outcome, monitoring of these patients should be improved so as to diagnose and treat the epidural haematoma as early as possible. The incidence of severe complication in regional anaesthesia is very low (0.1%), but further studies with larger numbers of patients are needed to assess the relative risk of physical status, type of surgery and local anaesthetic used.

Transient injuries can occur and are increasingly common (0.01-0.8%). Most neurological complications completely resolved within 8 postoperative days [19]. In contrast, the incidence of systemic toxicity to local anaesthetics has decreased in the last 30 years, from 0.02 to 0.1%. In addition, the incidence of postdural puncture headache has largely decreased from 37% thirty years ago to approximately

1%, because of advances in needle design. Backache is frequently related to central neural blockade, but other causes should be considered, such as the duration of surgery, patient position, use of lidocaine and irrespective anaesthetic technique. Urination disturbances are frequent in elderly male patients. Hypotension is the most common cardiovascular alteration associated with RA.

Neurological complications have also occurred after peripheral blocks. Even if the main reason to support the use of a nerve stimulator is the perceived reduction in the risk of nerve trauma, several complications have occurred despite its use.

Other factors may increase the risk of nerve injury during peripheral nerve blockade such as inadequate patient positioning, non cooperative patient or abnormal body status, insufficient physician experience, insufficient patient information on the procedure, excessive sedation or a non gentle technique.

Although many anaesthesiologists believe that it is necessary to obtain the lowest distance between the needle and the nerve for a successful blockade, this practice may lead to a higher number of nerve trauma [23]. At any rate, further studies are required to identify technical factors that could improve nerve injury during regional anaesthesia.

Nerve injury may occur due to inappropriate patient positioning during surgery. Various nerves or joints could be involved, but the most common injury has been lesions of the brachial plexus and ulnar nerve [25]. Although a few patients may have had a pre-existing unrecognized peripheral nerve lesion, the majority of patients who undergo surgery are healthy and without risk factors for developing neuropathies. Often, these lesions recover over time, but sometimes nerve injury due to patient positioning may lead to disability [26]. Therefore, it is important to prevent these lesions by ensuring a correct position of the patient in the surgery bed and using protective padding.

The Obstetrical Patient

Locoregional anaesthesia has become largely diffuse also in obstetrical patients. Spinal anaesthesia is the technique of choice in caesarean delivery both for elective and emergency surgery. Labour analgesia is generally carried out with the peridural technique, with numerous benefits.

The obstetrical patient is a particularly delicate category because of the physiological and anatomical modifications, due to pregnancy. The most common adverse outcomes in the obstetrical closed claim database was neonatal death, maternal death and complications resulting from RA [27].

Lee et al [20] showed that obstetrical patients usually present less severe complications due to RA, such as lombalgia, postdural puncture headache, paraesthesias and insufficient analgesic cover, than non obstetrical patients.

The leading cause of maternal death and brain damage has been a failure to secure a patient airway. The risk factors for adverse surgical outcomes were identified in an AANA study and included advance maternal age, ethnicity and obesity. Most complications occurred during emergency caesarean sections under general anaesthesia, due to aspiration and convulsion [28].

Perioperative Medicine

Advances in anaesthetic and surgical techniques and perioperative care have substantially reduced related mortality. The role of perioperative medicine becomes fundamental in preventing some of the complications due to anaesthesiological procedures, recognizing the patient at risk and reducing the final postoperative risk for the patient.

In the first instance, it is important to know the history and the clinical characteristics of patients undergoing surgery, so as to assign a determined anaesthesiological risk depending on their baseline conditions and on the kind of surgery [5]. The unanimously accepted classification is the American Society of Anesthesiologists (ASA). The ASA classification seems to be predictive for the risk of the postoperative complications.

Pedersen et al [29] have elaborated a model that identifies five significant preoperative predictive variables: age, chronic heart disease, renal disease, emergency surgery and type of operation. With this model it is possible to distinguish between patients with very different mortality risks. Advanced age is a significant risk factor for increased mortality [30].

Concomitant diseases further depress organ function, exacerbating risk. Additional risk factors in the elderly are emergency surgery, major surgical procedures, ASA III-IV and poor nutritional status. Decreasing perioperative risk in the elderly population requires rigorous preoperative assessment of organ function and reserve, good intraoperative control of concomitant disorders and vigilant postoperative monitoring and pain management.

Clinical and pharmacological anamnesis and laboratory data are useful in order to exclude eventual alterations of coagulation that contraindicate the ALR. A careful clinical airways assessment is fundamental, as seen above, in order to prevent a possible difficulty during intubation or incidents related to incorrect airway management.

As far as the management of the patients in the postoperative period is concerned, recently published data increasingly emphasize the importance and usefulness of a recovery room, where patients can be monitored for the first 12-24 hours, when adverse events are more frequent. The emergence from the drug-induced coma necessary during surgery is the most critical phase in the postoperative period. At present, 50% of deaths correlated with surgery occur in the first hours of recovery [31].

Patients need observation after all anaesthetic procedures. The level of monitoring may differ according to the type of surgery, the anaesthetic used, the patient's conditions and possible complications. The stay in the recovery room has the following goals:

- recovery from effects of anaesthetic drugs;
- stabilization of cardiopulmonary system and body temperature;
- control of hydroelectrolyte balance;
- intensive care support in case of acute complications;
- performing adequate postoperative analgesia;
- recovery of motor activity after regional anaesthesia [32].

Conclusions

We have shown that anaesthesia procedures are not without risk. The exact number of complications is unknown. Although errors and near-misses occur every day, most of these errors are fortunately inconsequential.

Because of the low frequency of occurrence of severe anaesthesia-related patient injuries, prospective studies of their incidence and strategies for their prevention require large numbers of patients. Therefore, these studies would have to be multi-centre in nature. In general, if the technique is used properly, if standard procedures are followed and equipment is provided with patient safety measures, most deaths can be potentially avoided.

Lack of knowledge of the equipment ought to be prevented by proper education. Having protocols and guidelines and using them is essential. Prudent anaesthetists should be very familiar with the contents of such documents.

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QUALITY OF CARE IN THE ICU

Quality Management in the ICU: Understanding the Process and Improving the Art

P. MURABITO, F. RUBULOTTA, A. GULLO

Recently clinicians, researchers, nursing-staff, economists and experts in the field of health system governance have stressed the importance of quality improvement for clinical management optimization. The advances made toward quality improvement have been marked by the ability of the team leader to ration resources and improve work through the development of guidelines and audit control. Evidence-based medicine is a modern approach for integrating current medical knowledge into clinical practice. It states that management of patients should be based on the rigorous assessment of the results of randomized controlled trials (RCTs) combined with evidence from other forms of research. This approach has merit. Variations in the management of patients can result in care of varying quality and varying mortality [1]. Critical care physicians and nurses are involved in the quality improvement process in accordance with the assumptions of Davidoff and Batalden: in contrast with the primary goals of science, which are to discover and disseminate new knowledge, the primary goal of improvement is to change performance [2]. The formal version of that cycle – the Plan-Do-Study-Act model – is now a key component of medical quality improvement [3] and also includes a “Publish” step. Indeed, the biologist Edward O. Wilson has gone so far as to state that: “One of the strictures of the scientific ethos is that a discovery does not exist until it is safely reviewed and in print” [4]. Unfortunately, publication in medical quality improvement has played a limited role to date. This lack of published reports has arguably deprived the health care system of rigorous scholarly evidence on work improvement and hence has slowed the development of the improvement process [5]. In fact, the previous mentioned gap demonstrates that medical quality improvement will not reach its full potential unless accurate and transparent reports of work improvement are published. With this as a starting point, specific goals need to be underlined. The first is to continue to improve accessibility to high quality clinical information, while the second is to raise the profile of medical information systems within the intensive care community in line with that which is already occurring in some medical schools [6].

Defining and Measuring ICU Performance

Quality of health care has in recent years become a national and international policy issue. Because of its characteristics, the intensive care unit (ICU) is a unique area of focus for quality improvement. Critically ill or injured patients are almost routinely admitted to the ICU where continuous monitoring and life support techniques are available and comprehensive treatment, as well as continuous care by trained physicians and nurses, can be provided. The ICU is a complex organization involving different disciplines, high technology, many diagnostic and therapeutic procedures, and it is burdened with high management costs. Patient outcome, which is not limited to survival but also related to residual disability and quality of life, as well as the effectiveness of treatment and efficiency of intensive care, have become policy issues.

The quality of care provided has a significant impact on these variables and continuous improvement in intensive care quality is the major challenge for the future. For this reason defining and measuring ICU performance are very complex tasks. To reach this goal, not only do scientific and medical theories need to be taken into account, but also ethical, economical, technical and sociological aspects. The American Institute of Medicine defines health care quality as “the degree to which health services for individuals and populations increase the likelihood of desired health outcomes and are consistent with current professional knowledge”[7]. Quality of health care can be measured from multiple domains, many of which are important to patients, providers, purchasers and insurers.

The Institute of Medicine report – *Crossing the Quality Chasm; A New Health System for the 21st Century* – identified 6 aims of health care: it should be safe, effective, patient centred, timely, efficient and equitable [8]. These aims provide a framework for considering the domains of quality and for evaluating the impact of quality improvement initiatives.

Quality improvement can be defined as the effort to improve the level of performance of key processes in the intensive care unit. It involves the establishment of variables to evaluate the level of current performance, finding ways to improve that performance and implementing new and better methods [9].

Although almost all researchers agree with these assertions, the best variables for measuring quality are still unclear. Curtis et al [10] have defined a good quality measure as one that is “important, valid, reliable, responsive, interpretable, and feasible”. A measure can be valid and reliable if data collection is not too burdensome and if results are really effective at improving performance.

For institutions to benchmark performance, data collection tools need to be standardized so that results can be compared with all ICUs. One of the more followed models in measuring ICU performance was developed by Donabedian [11], and includes three classic quality-of-care components: (1) structure; (2) process; and (3) outcome.

A. Structure

This is the first component of the quality of care model and can be defined as the way we organize care. Structurally, ICUs are quite heterogeneous, even within regions or countries. The main differences regard how the ICU is integrated into the hospital or health care system, the ICU size, the type and amount of technology available, and the number, roles and responsibilities of its staff [12]. An adequate organization is necessary to optimize the quality of care given [13]. This includes the presence of an appointed qualified medical and nursing director and the full time availability of intensive care physician and nurses.

Well-trained intensive care staff with full responsibility for patients has important implications for ICU performance [14]. There is a long list of working habits that are strictly linked to good performance: daily multidisciplinary meetings to discuss the clinical conditions of current patients, surveillance methods for avoiding or minimizing errors, structured meetings with other disciplines (surgery, radiology, cardiology etc.) as well as an optimal documentation of patient data and personnel allocation are all important quality issues.

It is essential that an ICU explicitly formulates the standards for its organization on the basis of data from the literature. Implementation requires an unambiguous consensus among all members of ICU staff. Moreover, a managerial approach to intensive care, including annual assessment of objectives in terms of type and volume of patients, economical management of resources and outcome prospects, are becoming increasingly important.

B. Processes

This term is used to indicate what we do, or we fail to do, for patients and their families during their stay in the ICU. A great number of processes are normally involved in ICU patient care ranging from individual care to general procedures such as admission and discharge and maintenance of equipment [15].

All these processes may be encumbered daily by different problems, with repercussions on performance. To solve these problems the “trouble shooting” method can be used. For example, we can take into consideration an unexpected increase in infectious complications or a sudden rise in costs.

A process can be started using some steps: identification of causes, implementation of solutions and monitoring of the effectiveness of changes. To reach the best result with the trouble shooting method the whole team must become involved, while to be effective a meticulous registration of infections, complications of procedures, near misses accidents and costs is required. There are some other approaches, like the systematic analysis of all processes in the ICU, but they will be analyzed in the following chapters.

We can assert that to obtain a high quality level of care in the ICU the combined effort of a large number of clinical and non-clinical processes is required. Just because data exist which show improved outcomes with specific interventions does not guarantee that these findings have been translated effectively into clinical practice [16-18].

C. outcome

This is the third component of the quality of care model and refers to the results we achieve. For this reason clinicians and researchers have spent a lot of time attempting to measure patient outcome. Although it is common to consider medical outcome with survival rate as the best parameter in evaluating ICU quality, to obtain more realistic information it is essential to take into account even different aspects of outcome as described in Table 1.

The classic outcome variable is mortality, but other are becoming more and more important. A good method for assessing outcome is the standardized mortality ratio (SMR) using an index of severity (APACHE, SAPS, MPM), provided that the model is well calibrated and customized. This measure is calculated as the observed mortality rate of an ICU cohort divided by the predicted mortality rate in the patient population. In short, it relates actual mortality to expected mortality [18]. The SMR performs reasonably well for patient cohorts.

Table 1. Different aspects of outcome

1.	MEDICAL OUTCOME: – Survival rate: ICU, hospital, long-term – Complication rate related to care – Medical errors – Adequacy of symptom control
2.	ECONOMIC OUTCOME: – Resource consumption: ICU, hospital, post-hospital – Cost-effectiveness of care
3.	PSYCHO-SOCIAL AND ETHICAL OUTCOME: – Long term functioning and quality of life – Patient satisfaction – Family satisfaction – Concordance of desired end-of-life decisions – Appropriateness of medical interventions provided
4.	INSTITUTIONAL OUTCOME: – Staff satisfaction and turnover rate – Effectiveness of ICU bed utilization – Efficiency of processes / procedures / functions involved in ICU care

The SMR is useful in examining overall performance among general and specific ICU populations on a retrospective basis and in benchmarking across ICUs and institutions. However, it cannot be used to make predictions in individual cases or to determine medical futility. Several severity-of-illness scores have been created to integrate the multiple complexities inherent in critically ill patients into a single predictive measure of mortality which can be used in the SMR.

The Acute Physiology And Chronic Health Evaluation in its third series (APACHE III) is a well known score routinely used in ICU practice. This system includes

points for 17 physiological variables, as well as age, admission, diagnosis and chronic health evaluation and it has been shown to be predictive of in-hospital mortality rate. It has performed equally well in community based and academic settings. The APACHE, like other scoring systems, presents some limitations. It is dependent on an operator and requires a long period of training to be used efficiently [19, 20]. The Simplified Acute Physiology Score (SAPS III) and the Mortality Probability Model (MPM) are two other predictive models used in the ICU [21]. They are equations derived from multivariable linear modelling of demographic and clinical data that predict outcome variables for each patient by comparison with the large inception cohort of ICU patients used to create the equations. Nonlinear models, such as neural networks, achieve similar predictive power. It has been demonstrated [22] by means of calibration analysis that these scoring systems often overestimate the risk of death in the studied population. Moreover, despite of the various differences among these scoring systems, there are no data available to assert that one approach is better than the others [23]. Length of stay (LOS) is a problematic outcome measure, even if it is often used to monitor the quality of care and resource utilization.

To avoid errors in the evaluation of the data collected about LOS it is important to choose a valid method for calculation. If we consider the number of days spent in the ICU we risk overestimating LOS. More accurate is the exact number of hours occupied or the number of days with midnight bed occupancy [24, 25].

If the arithmetic mean is used to calculate LOS in the ICU, it will often misrepresent the population, because LOS data are skewed by longer than typical stays and outliers. Reporting the median, mode, or geometric mean will more accurately reflect the central tendency of the data. Multivariate equations of APACHE III can determine a predicted LOS, which may be used as a quality benchmark. However, Marik and Hedman [26] showed LOS may not differ among survivors and nonsurvivors, although nonsurvivors have higher APACHE III scores. LOS in the ICU is influenced by many factors, such as the availability of a step-down unit, differences in discharge practices, and rates of mortality and hospital census. All affect LOS without necessarily reflecting quality of care practices. For example, although daily costs are reduced by transferring patients from the ICU to ward beds, premature transfers lead to worse outcomes [27].

Reductions in LOS and short-term mortality rates may merely reflect a shifting of the place of death with no real net improvements. As with mortality, whether LOS constitutes an appropriate measure for patient outcome is still under consideration by the Joint Commission on Accreditation of Healthcare Organizations.

Complication and error rates are often used as a measure of ICU performance. These are relevant because of the potential causal relationship of such adverse events with increased mortality, morbidity, or costs. However, not all adverse events lead to clinical consequences and not always is there a strict relationship between an error or complication and patient outcome. Symptom control and end-of-life decision making are important aspects of ICU care, but their use as a performance measure is limited by lack of training among physician and the paucity of tools to measure them.

For the assessment of ICU performance the evaluation of costs and resource consumption are the pillars for understanding the process of quality. The most used method, because of its simplicity and information content, is ICU LOS, in spite of all the limitations we have already analyzed. Another interesting method in the evaluation of severity of illness and related resource consumption is the therapeutic intervention scoring system (TISS). It enables the identification of: (a) the percentage of ICU beds utilized; (b) the classification of patients in relation to illness severity and optimal nurse/patient ratio; (c) the overall amount of care given during the day; and (d) comprehensive ICU care costs.

The TISS is a measure of ICU resource utilization that works well for cohorts. However, while spending a lot of money is justifiable if the benefits are really large, and even small expenditures which generate no benefits are wasted, resource use is most relevant in combination with the non economic outcomes in the table above.

Effective bed utilization is an important parameter because of the limited resources and the high costs of management. Kalb and Miller [28] developed a thoughtful framework for ICU triage in which they proposed that the use of critical care must be limited to clinical settings in which it has been demonstrated, or it is at least presumed, to be cost-effective.

Although the rate of adherence to written or published ICU admission and discharge standards is often used as a measure of the quality of ICU bed utilization, such standards have not been subjected to scientific validation and so they cannot be used for special purposes. There is also many data documenting the importance of patient and family satisfaction as measures of ICU performance [29-31].

A relative lack of communication between physicians and families is not a rare occurrence. This area of action has not yet been well developed because acquiring satisfaction data requires a great involvement of families by means of questionnaires or interviews which are unfamiliar and time-consuming to administer and analyze.

There are numerous potential dimensions to such surveys in ICU care, including satisfaction with the following: (a) level of care from physicians, nurses and other ancillary health care personnel; (b) involvement in decision regarding care; (c) amount and quality of communication with health care and administrative personnel; (d) outcomes of care; (e) administrative hospital functions such as admission, discharge and billing; (f) food; and (g) housekeeping. Although some have disputed the validity of the methods currently used, many tools have been created to measure these aspects in detail [32-36].

Furthermore, the importance of personal satisfaction also regards the workers of an ICU and it affects their performance. For example, job dissatisfaction produces a higher rate of staff turnover with some consequences: (1) training time and money are wasted; (2) staff morale is further degraded while stress on managers is increased; and (3) the ability of the ICU to perform as an experienced, highly functioning team is diminished, possibly leading to worse patient outcomes [37]. In conclusion, competencies are characteristics of a person that lead to superior performance [38]. However, performance measurement is not easy, particularly in

the health and public services where there is a wide range of stakeholders involved; Moullin addressed eight essentials of performance measurement (Table 2) [39]:

Table 2. Eight essentials of performance measurement

1.	use a balanced set of measures
2.	make sure you measure what matters to service users and other stakeholders
3.	involve staff in determining the measures
4.	include both perception measures and performance indicators
5.	use a combination of outcome and process measures
6.	take account of the cost of measuring performance
7.	have clear systems for translating feedback from measures into a strategy for action
8.	measurement systems need to be focused on continuous improvement, not a culture of blame

Improving ICU Performance

Stimulated by the reports and actions of the American Institute of Medicine, the Joint Commission on Accreditation of Healthcare Organizations and the National Quality Forum, there is now intense dialogue on the best way to implement quality improvement systems.

Much of the focus has been on a method of quality improvement pioneered by W. Edwards Deming and adopted from the business world called total quality management or continuous quality improvement (CQI). According to CQI, quality is a process that can be managed and requires ongoing evaluation and change. Most errors are not caused by individual inadequacies, instead they are a product of defects in the system of care. In traditional models of quality improvement, a seminal event is identified, root-cause analysis is performed, and changes are made within the institution to try to prevent a similar event in the future. In contrast to this reactive approach, the continuous quality improvement model calls for a proactive mechanism to identify possible areas for improvement across a health-care system.

In continuous quality improvement, all structures, processes, and clinical activities occurring in the critical care setting should be evaluated and considered for possible improvement initiatives [34]. Once target areas of improvement are found, a system of measuring the effectiveness of change is implemented [40]. There should be ongoing evaluation of the system and changes made when inadequacies are identified. Using this method, changes can be made over a range of areas and can be expanded across an institution, such as from one type of ICU to another.

The recent work of a Society of Critical Care Medicine task force provides a practical framework for initiating quality improvement in critical care units at an institutional level [16]. The suggested approach requires the participation of an

interdisciplinary ICU team. Initiating a new quality improvement programme or improving an existing programme requires a series of steps to ensure that the programme is successful. Tables 3 and 4 outline one approach to these steps [16].

Table 3. Key steps for initiating or improving a quality improvement programme

1.	Do background work: Identify motivation, support team work and develop strong leadership.
2.	Prioritize potential projects and choose the projects to begin.
3.	Prepare for the project by operationalizing the measures, building support for the project and developing a business plan.
4.	Do an environmental scan to understand the current situation (structure, process, or outcome), the potential barriers, opportunities, and resources for the project.
5.	Create a data collection system to provide accurate baseline data and document improvement.
6.	Create a data reporting system that will allow clinicians and other stakeholders to see and understand the problem and the improvement.
7.	Introduce strategies to change clinician behaviour and create the change that will produce improvement.

Table 4. Key steps for Evaluating and sustaining a quality improvement programme

1.	Determine whether the target is changing with ongoing observation, periodic data collection, and interpretation.
2.	Modify behaviour change strategies to improve, regain, or sustain improvements.
3.	Focus on sustaining interdisciplinary leadership and collaboration for the quality improvement programme.
4.	Develop and sustain support from the hospital leadership.

Quality improvement is an attitude and culture that should resonate through the entire ICU. As such, the foundation for a successful quality improvement programme is strong motivation, teamwork and leadership. Even though individual ICU clinicians may champion specific quality improvement projects, change is rarely achieved without strong leadership [41]. The first step for initiating and developing a quality improvement programme is to identify the opportunities and resources that might influence the choice of where to start.

The first project should be feasible and likely to be successful so that the team can build on its successes. Initially, the team should avoid ambitious projects that consume resources and discourage team members. Once the project has been identified, careful preparation is required. The initiation of a quality improvement project requires a project plan or business plan that includes a task list, budget considerations, and a timeline. The concept of a business plan is often intimidating to clinicians; however, it need not be extensive and can be helpful regardless of whether the quality improvement team is seeking additional funding for the project or not [42]. The plan should outline the project for team members and hospital administrators.

Without preliminary information on current quality of care and the barriers to a quality improvement project, it is difficult to design and launch a successful project. Therefore, performing an “environmental scan” is a fundamental step [43].

An initial scan may involve available clinical or administrative databases. The environmental scan may also include a measure of organizational culture. Several tools are now available for assessing the quality or safety culture of an ICU, such as the patient safety climate survey [44] and the safety climate scale [45].

Once the environmental scan is complete, the quality improvement team will have enough information to design an effective data collection system for baseline assessment. Without accurate baseline data, documenting improvements is impossible.

The target measure must be carefully defined using discrete, measurable components, and a specific improvement goal should be explicitly stated. Another important step regards the creation of a data reporting system which has to be transparent and informative [46]. The reason why a data reporting system is so important is that most critical care clinicians are too busy to analyze and interpret data themselves. In the absence of timely and useful data reporting, interest wanes and projects lose momentum. While all the steps analyzed are necessary, they are not sufficient to bring a quality improvement project to life; the necessary next step is to implement behaviour change strategies that are likely to produce the desired change [47].

The Cochrane Effective Practice and Organization of Care Review Group has published a summary of 41 systematic reviews of hundreds of original studies testing the effects of different behaviour-change strategies on clinician behaviour and patient outcomes [48].

Behaviour-change strategies can be simple or complex and vary in effectiveness [49]. For example, dissemination of mailed educational materials and conferences are least likely to change behaviour.

While audit and feedback of recent performance are the backbone of successful quality improvement initiatives, they are insufficient by themselves [50]. Informal discussions and formal presentations by local opinion leaders on the quality improvement team are crucial adjuncts to help change behaviour, but reminders and prompts (such as preprinted orders) along with periodic interactive educational interventions are most useful for inducing and sustaining change. The most powerful behaviour change strategies (and often the only strategies that are successful) are multifaceted rather than single approaches, are adapted to the local setting, and address documented barriers in the environment [51-55].

A key step in closing the loop on quality improvement initiatives is taking a scientific approach to evaluating whether the target measure is changing. In other words, the quality improvement programme itself should be subjected to a quality improvement process. Without formal evaluation of a quality improvement programme, it is impossible to judge whether it is successful and sustainable.

Although when compared with industry the quality revolution was late in coming to medicine, there can be no turning back. Improving quality and patient safety are vital to the practice of critical care medicine. Successful quality improvement programmes require interdisciplinary teamwork which is incremental and continuous. Although quality improvement may seem overwhelming at first, approaching a project in a step-wise manner as outlined here and beginning with a

single, concrete project can help to ensure that quality improvement becomes routine and integral to the ICU.

Quality improvement efforts require scientifically sound performance measures. Just as in clinical research, sufficient resources must be allocated to ensure a robust data collection, analysis, and reporting system. Leadership is crucial to the success of both the overall programme and each project within it. Individual quality improvement projects and the entire quality improvement programme should learn from its successes as well as failures. Models of care delivery utilized to meet the growing need for intensive care, such as the intensivist model, tele-medicine, or regionalization, must occur within the framework of the assessment and monitoring of outcomes.

The use of evidence-based protocols and care bundles will be increasingly used, despite some initial setbacks, as part of an electronic medical record in an integrated manner. Performance in accepted protocols will be widely reported and financial incentives provided to high performers. Large, multiple-centre collaborative efforts are setting new standards for the successful implementation of evidence-based practice in critical care and may be particularly successful when geographically based. Further research is needed to refine the methods and identify the most cost-effective means of improving the quality of health care received by critically ill patients and their families.

Clinical Governance

The term clinical governance was formulated to manage the quality of health care services in 1999 [56]. The importance of clinical governance is now internationally recognized, as the crucial need for strong relationships between medical, nursing and allied health staff and management to build a safety culture.

The UK government white paper – A First Class Service – defined clinical governance as “a framework through which NHS organizations are accountable for continuously improving the quality of their services and safeguarding high standards of care by creating an environment in which excellence in clinical care will flourish.”

The purpose of clinical governance is to ensure that patients receive the highest quality of NHS care possible. It covers the organization’s systems and processes for monitoring and improving services, such as reported in Table 5.

Table 5. Clinical Governance

-
- consultation and patient involvement
 - clinical risk management
 - clinical audit
 - research and effectiveness
 - staffing and staff management
 - education, training and continuous personal and professional development
 - the use of information to support clinical governance and health care delivery
-

Effective clinical governance should therefore ensure:

- continuous improvement of patient services and care
- a patient centred approach that includes treating patients courteously, involving them in decisions about their care and keeping them informed
- a commitment to quality, which ensures that health professionals are up to date in their practices and properly supervised where necessary
- a reduction of the risk from clinical errors and adverse events as well as a commitment to learn from mistakes and share that learning with others.

Clinical governance is the term applied to collecting all the activities that promote, review, measure and monitor the quality of patient care into a unified and coherent whole. In Western Australia, it has been defined as a systematic and integrated approach to assurance and review of clinical responsibility and accountability that improves quality and safety resulting in optimal patient outcomes [57].

The introduction of clinical governance is therefore aimed at improving the quality of clinical care at all levels of an organization by consolidating, codifying, and standardizing organizational policies and approaches, particularly clinical and corporate accountability [58]. Clinical governance gives the delivery of high quality health care its rightful status alongside service performance and financial control within each area of health service as well as throughout the whole health care system. The delivery of health care faces many challenges and changes, including an increase in demand for quality health services. Changing work patterns, while bringing important benefits, also brings additional responsibilities and risks. When operating in a complex and demanding environment the health system must acknowledge and respond to these clinical and social challenges. Clinical governance offers a way to achieve this target.

Risk Management and Patient Safety

Hospitals are complex systems, largely dependent on human performance, so improving hospital safety is not simple. Every change must be implemented with an understanding of human factors, engineering and safety science, and even good changes can create unexpected new hazards.

Increased safety precautions reduce preventable adverse events but generally impose both direct costs (to implement the safety precautions) and hidden costs (in the form of delays, new errors, or lost opportunities elsewhere). Perfect safety is not always possible and near-perfect-safety may impose unacceptably high costs.

The goal of minimizing the total cost of both accidents and accident-prevention requires information on both costs and effects of specific safety improvements. Such information is also needed to prioritize suggested safety improvements, when all cannot be implemented immediately. This evidence can best be produced during the economic evaluation loop, an iterative process involving routine, periodic assessment of costs and effects, and targeted original research where initial estimates may be characterized by uncertainty in key values [59].

Errors during medical practice are probably more frequent than we realize [60].

The increasing complexity of certain hospital environments, such as ICUs, probably makes them more prone to error than before. Fortunately, most errors in the ICU are detected early and corrected rapidly, usually without any long-term ill effects to the patients. Researchers have suggested that monitoring of errors should be an integrated part of the quality assurance of all medical practices [61].

Patient risk management can be defined as a structured procedure in a clinical unit with the aim to reduce harmful events. Nearly every patient admitted to an ICU suffers an adverse event. Data show: 5 million ICU admissions per years in the United States; 10% average mortality; ICUs account for 30% of hospitals costs; \$180 billion annually.

Clinical risk management considers how to identify and reduce or prevent adverse events for patients, and promotes learning from complaints, critical event audit (including near-misses) and identifying and dealing with poor professional performance.

Clinical risk management is a very important tool for making the medical health system safer. The first step is a cultural change: to err is human, thus all persons involved in the health system delivery are prone to making errors. To reduce the phenomenon, we have to learn from the error and start to take into account not who made the error but why the error occurs.

Errors must lose their ethical value (non blame culture) to become the starting point of a process which allows us to look into the mechanisms of the error, to detect the active or latent causes, to understand the weak points of our care delivering organization, and to plan the appropriate measures against the occurrence of new adverse events.

The reactive (from error to prevention) and proactive (before an adverse event occurs) approaches are the two methods mostly used when performing clinical risk management; the most useful tools for performing this kind of analysis are incident reporting, root cause analysis, clinical audit, and hospital failure mode, and they all critically effect analysis.

The intensive care unit is a hospital department that most of all needs to implement the culture of clinical risk management because of the use of ever new diagnostic and therapeutic tools, the importance of team work and of technical and clinical skill, and the complex case mix of patients.

The therapy and clinical diary sheet, as well as team organization, are some of the most important elements that we can improve even without specific skills in risk management. The use of check lists and diagnostic and therapeutic flow-charts is useful in helping less skilled physicians to manage critically ill patients. Clinical risk management is an approach to improving the quality and safe delivery of health.

In the previous chapters the concepts of the critical illness, quality of care, and patient safety were introduced and approaches were reviewed to identify the safety concerns of patients, measure quality of care, and improve care through the modification of caregivers behaviour.

Three aspects emerged: care of the critically ill is fraught with potential hazards for patients; error of omission (i.e. failure to provide contemporary, evidence-

based care) might be a greater threat to patient safety than errors of commission; and improvement of care needs the appropriate cultural milieu, a system-wide commitment, active engagement of all relevant stakeholders, and constant measurement and feedback [62].

Professional Development and Management

The job of weighing and balancing the evidence on particular topics (knowledge management) has been made much easier for clinicians through a range of organizations, and the various national and international bodies producing evidence-based guidelines.

Professional education and development includes credentials (recognizing the adequacy of individuals' training and experience for their scope of work) and performance appraisal.

Regular review of professional practice is an important aspect of clinical governance and implies that education and professional development are recognized and supported.

Applying the principles of corporate governance to clinical practice offers a way to address patients, clinicians and public concerns in a transparent and coherent way. However, it is important to recognize that while patient benefit is an aim to be pursued immediately, system-wide quality improvement has a long-term outcome and financial benefits will only be realized gradually. Clinical governance, education in developing behavioural changes policies and clinical leadership are important vehicles in driving the health system towards a new era.

Promoting a Culture of Safety and Learning

Pronovost et al outline key steps for establishing a culture of safety and learning [63]. They argue that we must embrace a systems approach to error, rather than simply blaming those unlucky individuals involved in a preventable adverse event. However, the tremendous barriers to culture change should not be understated. It is not easy to step forward when your actions contribute to harming a patient. Few health care professionals have been educated to expose and discuss their mistakes. The fear of professional and legal consequences cannot be underestimated as a deterrent to personal and organizational changes. Learning and improvement can proceed without the spectre of blame and punishment.

Although we need to move toward a system that encourages reporting of adverse events, the information derived from the many near misses occurring daily offers an immediate database to identify care processes that need to be redesigned.

A culture of safety also requires leadership that promotes system changes. There is no value in reporting errors and near misses if there is no response to these reports. Responsiveness requires well-trained staff with the time to investigate near misses, and implement changes to improve the safety of the system.

Advances in organization and patient management in the ICU have led to

reductions in the morbidity and mortality suffered by critically ill patients. Quality of health care, especially within the ICU, has become an issue of great relevance.

Practice patterns and the quality of medical care vary widely and health care providers are increasingly interested in having objective information about their performance [64].

Most ICU physicians have a sophisticated understanding of pathophysiology and pharmacokinetics, but only few clinicians or researchers possess formal training in systems emphasizing quality improvement techniques, or concepts regarding a change in physician behaviour and practice [65-69]. Medical errors and hospital complications are prevalent, often leading to disability, resulting in large costs and 27,000 to 98,000 deaths per year [70-73]. Optimizing safety in the ICUs requires the improvement of communication between all staff. This involves improving the structure in the healthcare organization, identifying problem areas and systemizing and implementing tools, standards, protocols, and guidelines for safe practice for both patients and medical staff [57].

- *Communication:* Poor communication, teamwork, and problem solving among ICU staff are common, and are perceived as being more prevalent and important for ICU nurses and physicians [74-78]. For this reason, to improve quality the most important step is to establish dialogue with your ICU partners in care, hospital administrators and colleagues [70]. Communication is essential in identifying factors that might contribute to patient harm (change in culture). Much effort has to be made to create an environment that encourages ICU workers to communicate matters regarding patient safety without consequences.
- *Standardization:* Another problem is the variability in practice and outcome not explained by patient or illness characteristics. Improving ICU care can be accomplished by standardizing care through the use of practice guidelines, parameters and protocols to help to reduce errors and improve quality patient care. Moreover, there is not an adherence to established standards of care being related to poor outcomes [79]. Indeed, only 50 to 70% of Americans receive the care that is recommended for their situations [75] and 20 to 30% receive inappropriate medical interventions [80].

The Joint Commission on Accreditation of Healthcare Organizations is developing care quality measures to be used in all hospitals [81].

The Veterans Health Administration and the Institute for Healthcare Improvement have a joint project underway to bring together 15 ICUs to collaborate in the design of the ideal intensive care unit [82, 83]. Both the Federal Agency Healthcare Research and Quality in its report on patient safety, and the National Quality Forum identified ICU staffing as an important opportunity to improve care [84].

A national employer health care coalition, known as the Leapfrog Group, is also working to improve the value and safety of health care for its employees [85]. One area of focus is the development of new purchasing specifications for ICU care. Among those specifications there are ICU staffing requirements for intensivists.

The critical care setting is a complex and highly technical environment where coordination becomes crucial to effectively treat critically ill patients. It takes a

qualified team to care for the critically ill, one with patient safety as its highest priority. For these reason the Society of Critical Care Medicine has developed a brochure which provides ideas on how to inspire positive change:

- *Education and Training*
- a. Personnel training to understand and prevent common errors: although certification is not mandatory to practice critical care, it validates knowledge, experience and clinical judgment.
- b. Implementing the ability to use knowledge effectively and readily in order to perform a task and to make decisions consistently, accurately, and independently is essential. Management of the ICU patient can be challenging, particularly for practitioners not specifically trained in the treatment of the critically ill [82-84].
- c. Create a better atmosphere: the critical care unit must be an environment that is safe, efficient, well-managed, functional and comfortable for patients and staff [81].
- d. Implement a Multiprofessional Team with speciality training or equivalent qualifications in critical care medicine. In order to provide high quality care to critically ill patients, ICUs must successfully integrate the skills of physicians, nurses, pharmacists, respiratory therapists, and nutritionists, as well as other professionals [85].

These data demonstrate that ICU care is important, expensive, and problematic. Therefore, vigorous efforts are needed to critically examine and improve ICUs.

Table 6. Johns Hopkins programme to improve quality in ICU

STEP 1: Conduct a cultural survey
STEP 2: Educate staff on the science of safety
STEP 3: Identify staff's safety concerns (through a safety survey)
STEP 4: Analyze event
STEP 5: Implement improvements
STEP 6: Document results
STEP 7: Share stories and disseminate results
STEP 8: Resurvey staff – cultural survey

The critical care setting is a complex and highly technical environment where coordination becomes crucial to effectively treat critically ill patients. It takes a qualified team to care for the critically ill, one with patient safety as its highest priority in accordance with the Johns Hopkins programme (Table 6).

Audit System

ICUs are a vital component of modern health care. Improving ICU performance requires a shift from a paradigm that concentrates on individual performance to a different paradigm that emphasizes the need to assess and improve ICU systems and processes [23].

Improving ICU performance involves the following sequential steps: measuring indices of ICU performance relevant to the topic or area of interest; making interventions aimed at improving those measures; and then re-measuring the indices to document the effect of the intervention [40].

The 1997 White Paper 'The New NHS Modern Dependable' introduced the issues of clinical governance and a duty of quality into NHS organizations, with the clinical audit as a cornerstone. The definition of clinical audit endorsed by the National Institute of Clinical Excellence and the Healthcare Commission is "the systematic and critical analysis of the quality of clinical care. This includes the procedures used for diagnosis and treatment, the associated use of resources and the effect of care on the outcome and quality of life for the patient and involves a quality-improvement process that seeks to improve patient care and outcomes through the systematic review of care against explicit criteria and the implementation of change [86, 87]. The Health Care commission has developed a National Clinical Audit Programme to improve quality of care and patient safety. This is usually achieved by setting standards, measuring current performance against those standards, identifying shortfalls and putting in place any necessary action. As standards change, re-audit will become necessary. Also the Royal College of Anaesthetists has published a document which recommends carrying out audits for many roles, functions and situations: "Raising the Standard: A Compendium of Audit Recipes (second edition Feb. 2006)" [88].

The audit system forms a core part of clinical governance [89]; it is a powerful tool that allows healthcare organizations and professionals to accurately evaluate their clinical performance and to target actions appropriately. It therefore represents the formal process whereby clinicians and other healthcare professionals are required to ensure continuing improvement of clinical standards, a process that enables them to look at the quality of care being delivered to their patients and helps to identify substandard care and consequently to institute changes. Auditing is a cycle process that requires standards to be set and practice to be compared against these standards. The quality audit is a systematic and independent examination to determine whether quality activities and related results comply with planned arrangements and whether these arrangements are implemented effectively and are suitable to achieve objectives.

The audit system forms a cycle:

- setting of standards
- measurement of current practice
- comparison of current practice with standards
- change (or reinforcement) of practice
- re-auditing [90].

Setting standards. Standards improve patient outcome and are related to the structure, process or outcomes of patient care.

The structure of patient care relates to the setting in which the care is delivered.

The process of patient care relates to the manner in which care is delivered. The importance of auditing the process of patient care increases as the evidence supporting the most appropriate processes increases.

Outcomes of patient care – many different patient outcomes can be measured, but hospital mortality is the most commonly used for ICU patients. Although functional capacity and quality of life would provide valuable information, practicalities preclude their measurement for all patients.

Measurement of current practice – data collection and analysis for an audit should be carried out as rigorously as for clinical research. Audits and clinical research require complete, accurate, and high-quality data, which have been analyzed correctly, if valid conclusions are to be drawn.

Changing practice – the findings of an audit may suggest that change is necessary at an individual, team, or service level.

The three broad questions that clinical audit and outcomes monitoring seek to answer can be summarized as:

- are patients being given the best of care?
- are they better?
- do they feel better?

The Effective Practice and Organization of Care Group of the Cochrane Collaboration (a worldwide venture dedicated to preparing, maintaining and disseminating systematic reviews of the effects of healthcare) has produced two reviews of the effectiveness of audit and feedback. The first [91] examines the effect of audit and feedback on the performance of healthcare professionals and on patient outcomes. The reviewers concluded that audit and feedback can sometimes be effective in improving the practice of healthcare professionals and although the effects are limited, they are potentially worthwhile.

The second review [92] examines trials where audit and feedback have been compared with other interventions, for example, local consensus processes. The utility of real time safety auditing during routine clinical work was determined by counting the number of errors detected as well as any unit policy or guideline changes prompted by information gained from the audits.

The feasibility of auditing was determined by the completion of auditing and staff disclosure of errors each day audits were attempted. Safety audits have the potential to increase safety awareness of clinical staff while providing prompt feedback regarding team performance in critical patient safety domains. The audit is useful for identifying weaknesses in the process and for distinguishing the elements that can be integrated into the system from those that are likely to disrupt it [93].

Audit has become a familiar part of clinical practice. Since its introduction into mainstream clinical care, the importance of the audit in identifying the current standards of practice and endeavouring to make improvements has become clear as one looks at an increasing number of areas. Over the years, we have learnt a number of lessons from auditing, some of them not entirely welcome [94]. Auditing is an essential management tool for monitoring and improving quality in the ICU.

Quality Improving Management in the ICU Patients – Last Minutes Reports

Various circumstances hinder the clinical examination of a patient in an ICU. Nevertheless, clinical assessment is crucial for the formulation of a diagnostic and therapeutic plan. History and clinical examination need to be performed timely and efficiently. They are best done in a structured manner, so that no important details are missed. The physician should follow the concept of “A B C”, in which “A” stand for airways, “B” for breathing and “C” for circulation.

It is essential that some pathological findings in the clinical examination prompt immediate therapeutic interventions to avoid further deterioration. Clinical assessment is normally performed at the time of patient admission to the ICU. However, part of history and clinical examination may still be missed. It is therefore crucial to obtain this information as soon as possible as it may help with the management of the patient. Clinical examination is repeated at the daily ward rounds as well as at any time that the patient’s condition changes. Result of tests and data collected from monitoring equipment should be viewed as an addition to the patient’s clinical assessment and must not distract the clinician from the patient’s clinical condition. Precise documentation of the findings is vital to allow comparison of the patient’s progress on a daily basis and to provide quality and continuity of care.

Abdominal Compartment Syndrome. Abdominal compartment syndrome (ACS) is a life threatening disorder in critically ill patients caused by rapidly decreasing intra-abdominal pressure (IAP) >12 mmHg, which may result in multiple organ dysfunctions with a possibly fatal outcome. The various causes for the development of an ACS include first and foremost pelvic trauma, volume resuscitation after severe haemorrhage and reperfusion after aortic aneurysm repair as well as intra-abdominal packing. An elevated body mass index is a risk factor for ACS. In addition, excessive volume requirement and significantly increasing airway pressures within the first 24 h after admission in the ICU are indicators of an impending ACS.

Increased IAP causes venous stasis and arterial malperfusion of all intra- and extra-abdominal organs, thus resulting in ischaemia, hypoxia and necrosis. In parallel, respiratory, cardiocirculatory, renal, intestinal and cerebral decompensation can occur. Final multiorgan failure has a mortality around 60-70%. Timely diagnosis of ACS can still be difficult in spite of clinical indicators such as increased airway pressure, hypoxia, oliguria, shock and acidosis. For the early recognition of intra-abdominal hypertension repetitive measurement of the intra-bladder pressure (>20 mmHg) can be helpful. Besides intensive care treatment with artificial ventilation, circulatory support with volume and catecholamines, the decision for a prompt abdominal decompression and open abdominal treatment is life-saving and can preserve further functional damage to vital organ systems [95].

Antibiotic Novel Approach for Bacterial Infections. Antibiotics are one of the pillars of modern medicine. However, bacterial resistance emerges in a very small

proportion of patients when an antimicrobial agent is introduced on the market or just after its introduction [96].

There is a huge variation in the time for emergence of resistance, which varies among organisms and antibiotics. For example, penicillin resistance in *Staphylococcus spp* emerged rapidly, whereas penicillin resistance among *Streptococcus pneumonia* took several decades. Eventually, resistance rises to such a high level that it reduces efficacy of the drug in a human population. At this point, a new antibiotic is required, which is active against resistant bacteria. In response to bacterial resistance, the pharmaceutical industry has produced a remarkable range of antibiotics [97]. In the future the genomic revolution will be a possible new way of discovering novel antibiotics [98].

Acute Coronary Syndrome. Coronary artery disease remains a major cause of death in developed countries. Epidemiology of acute coronary syndrome (ACS) encompasses the study of trends of mortality, incidence and case fatality. Methodology includes data from populational and hospital registries of ACS. Significant improvement in ACS mortality and hospital case fatality were registered from 1997 to 2002. Sudden cardiac death continues to be a major health concern due to problems of prevention. Prehospital management is also a major source of health inequalities and this merits further analysis of those disparities. Recent data have shown large improvement in acute coronary care but the relatively high rates of ACS incidence stress the need to promote primary prevention and the screening of minor atherosclerosis lesions [99]. In the study, treatment pathways for ACS patients were developed and country-specific resource use was multiplied by unit costs. The countries examined were the United Kingdom (UK), France, Germany, Italy and Spain. Patients with unstable angina and acute myocardial infarction (ST-segment elevation and non-ST-segment elevation with/without Q-wave) were considered.

The study models the incidence of ACS, 1-year mortality, investigations, revascularization, pharmaceutical use and medical management. Economic outcomes were direct healthcare costs (in 2004 Euros), including total cost, cost per patient with ACS and cost per capita. The estimated number of deaths in the first year following ACS diagnosis ranged from around 22,500 in Spain to over 90,000 in Germany. The largest contributors to total costs are hospital stay and revascularization procedures. Pharmaceuticals were estimated at 14-25% of ACS total cost. The total cost of ACS in the UK is estimated around 1.9 billion Euros, compared with 1.3 billion Euros in France, 3.3 billion Euros in Germany, 3.1 billion Euros in Italy and 1.0 billion Euros in Spain. The cost per ACS patient ranges from 7,009 Euros (UK) to 12,086 Euros (Italy).

In conclusion, countries with higher expenditure on ACS patients tended to have lower case-fatality rates, and countries with the lowest incidence of ACS also had the lowest cost per capita. The costs of ACS constitute a large proportion of total healthcare expenditure of Western European economies [100].

The clinical benefit of the combination of aspirin plus clopidogrel over aspirin alone to prevent recurrent events after acute coronary syndrome is obviously a key

step of the past few years in the management of coronary artery disease. The extended benefit of this combination among patients undergoing stent implantation is another key message for clinicians. The consistent benefit of dual oral antiplatelet therapy in all clinical trials is reassuring for clinicians. However, all well designed clinical trials generate new hypotheses and unsolved clinical issues. What the loading dose of clopidogrel should be and whether we should monitor the biological response to clopidogrel in order to improve its clinical benefit are the next clinical challenges for clinicians dealing with ACS. Providing adequate answers to these relevant clinical issues should improve the clinical benefit of clopidogrel [101].

Age is an important determinant of outcomes for patients with ACS. However, community practice reveals a disproportionately lower use of cardiovascular medications and invasive treatment even among elderly patients who would stand to benefit. Limited trial data are available to guide the care of older adults, which results in uncertainty about benefits and risks, particularly with newer medications or invasive treatments and in the setting of advanced age and complex health status.

Part II of the American Heart Association scientific statement summarizes evidence on the presentation and treatment of ST-segment-elevation myocardial infarction in relation to age (<65-74, 75-84, and ≥ 85 years). The purpose of this statement is to identify areas in which the evidence is sufficient to guide practice in the elderly and to highlight areas that warrant further study. Treatment-related benefits should rise in an elderly population, yet data to confirm these benefits are limited, and the heterogeneity of older populations increases treatment-associated risks. Elderly patients with ST-segment-elevation myocardial infarction more often have relative and absolute contraindications to reperfusion, so eligibility for reperfusion declines with age, and yet elderly patients are less likely to receive reperfusion even if eligible. Data support a benefit from reperfusion in elderly subgroups up to 85 years of age. The selection of the reperfusion strategy is determined more by availability, time from presentation, shock, and comorbidity than by age. Additional data are needed on selection and dosing of adjunctive therapies and on complications in the elderly. A "one-size-fits-all" approach to care in the most elderly is not feasible, and ethical issues will remain even in the presence of adequate evidence. Nevertheless, if the contributors to treatment benefits and risks are understood, guideline-recommended care may be applied in a patient-centred manner in the oldest subset of patients. In conclusion, few trials have adequately described treatment effects in older patients with ST-segment-elevation myocardial infarction. In the future, absolute and relative risks for efficacy and safety in age subgroups should be reported, and trials should make efforts to enrol the elderly in proportion to their prevalence among the treated population. Outcomes of particular relevance to the older adult, such as quality of life, physical function, and independence, should also be evaluated, and geriatric conditions unique to this age group, such as frailty and cognitive impairment, should be considered for their influence on care and outcomes. With these efforts, treatment risks can be minimized, and benefits can be placed within the health context of the elderly patient [102].

Non-ST-segment elevation myocardial infarction (NSTEMI) is a major cause of cardiovascular morbidity and mortality in the United States. It makes up the highest risk category of non-ST-segment elevation acute coronary syndromes (NSTEMI), for which timely diagnosis and appropriate therapy are paramount to improve outcomes. Evidence-based treatment, with combination of antiplatelet and anticoagulant therapy, and with serious consideration of early coronary angiography and revascularization along with anti-ischaemic medical therapy, is the mainstay of management for NSTEMI. Aggressive risk-factor control after the acute event is imperative for secondary prevention of cardiovascular events. The practical application of the American College of Cardiology/American Heart Association (ACC/AHA) guideline recommendations results in improved outcomes [103]. In addition, there is the data and insights from a national quality improvement initiative known as Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation (CRUSADE) proposed by the ACC/AHA guidelines, for managing non-ST-segment elevation ACS, as well as the findings and implications of the Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY), a study of bivalirudin with or without a glycoprotein (GP) IIb/IIIa inhibitor in patients with non-ST-segment elevation ACS who were undergoing an invasive intervention, and the results of two recent studies of clopidogrel in patients with ST-segment elevation myocardial infarction (MI) that are not reflected in current ACC/AHA guidelines for managing ST-segment elevation MI. Data from the CRUSADE registry suggest that there is room for improvement in the use of GP IIb/IIIa inhibitors and clopidogrel during the first 24 hours of hospitalization in patients with non-ST-segment elevation ACS who undergo early invasive cardiac procedures, and in the prescribing of angiotensin converting enzyme (ACE) inhibitors at the time of discharge. Adherence to ACC/AHA guidelines for non-ST-segment elevation ACS has improved over time but further improvement is needed. Failure to reduce the dose of a GP IIb/IIIa for patients with renal insufficiency resulting in excessive dosing of GP IIb/IIIa inhibitors increases the risk of major bleeding and is particularly common among the elderly, women, and patients with renal insufficiency. The ACUITY study suggests that bivalirudin plus a GP IIb/IIIa inhibitor is a suitable alternative to standard therapy for moderate- to high-risk patients with non-ST-segment elevation ACS who are undergoing early invasive intervention, and bivalirudin alone may be preferred because of a lower risk of major bleeding. However, interpretation of the ACUITY results is complicated by numerous methodological concerns, so the role of bivalirudin in managing non-ST-segment elevation ACS is still evolving. In patients with ST-segment elevation, clopidogrel provides an early benefit in reopening occluded coronary arteries and a late benefit in reducing cardiovascular mortality and morbidity without increasing the risk of bleeding. Clopidogrel treatment is warranted before as well as after percutaneous coronary intervention in patients with ST-segment elevation MI who receive fibrinolytic therapy. Adding clopidogrel to fibrinolytic therapy and other standard therapy reduces mortality without increasing the risk of bleeding. In conclusion, evidence-based guidelines provide recommendations for the management of ACS, but the pace of clinical research is rapid and current

guidelines do not reflect the latest research findings. Pharmacists need to stay abreast of new developments and ensure that clinical practice reflects these developments [104].

Nesiritide, recombinant human β -type natriuretic peptide (hBNP), is a potent vasodilator that rapidly reduces cardiac filling pressures and improves dyspnoea in patient with acute decompensated congestive heart failure. Two multianalyses suggest that nesiritide is associated with worsening renal function and increased mortality. Importantly, nesiritide should be used only in hospitalized patients with acutely decompensated congestive heart failure who have dyspnoea at rest.

Ongoing trials will determine whether nesiritide improves clinically significant end point, such as death or rehospitalization, compared with levosimendan in patients suffering advanced chronic heart failure awaiting cardiac transplantation [105-107]. The treatment of cardiogenic shock complicating the acute coronary syndromes consists of medical therapy, percutaneous revascularization procedures, cardiac surgery, and the implantation of devices. Medical therapy is limited to different positive inotropic and vasoactive drugs, without any firm evidence of survival benefit using these drugs. Several new pharmacological compounds are at different stages of clinical research, but are not yet routinely approved for the treatment of cardiogenic shock. The only evidence-based therapy with proven survival benefit is timely revascularization. Intra-aortic balloon pump counterpulsation maintains its central role as supportive treatment in cardiogenic shock patients. Anecdotal evidence is available about the use of ventricular assist devices, cardiac resynchronization therapy, and emergent heart transplantation [108].

Artificial Ventilatory Support. Chronic obstructive pulmonary disease (COPD) is one of the major causes of chronic morbidity and mortality throughout the world, while acute exacerbation of COPD (AECOPD) is one of the important causes of patient hospitalization.

As COPD is a disease state characterized by irreversible airflow limitation and dynamic pulmonary hyperinflation, the mechanical ventilation strategy for AECOPD is different from other diseases. To improve the clinical result of mechanical ventilation for AECOPD, the Chinese Society of Critical Care Medicine of the Chinese Medical Association held a consensus conference to draft guidelines by categorizing all the information gathered from the literature into five grades from A to E, with A being the highest, according to a modified Delphi criterion.

The main recommendations were as follows: (1) Noninvasive positive pressure ventilation (NPPV) should be the routine option for AECOPD patients, particularly in hospitalized patients with mild to moderate exacerbations ($7.25 < \text{pH} < 7.35$) with obvious dyspnoea (with use of accessory respiratory muscles). Appropriate choice of nose or nose-and-mouth mask, careful monitoring and staff training play important roles in the successful use of NPPV; (2) Invasive positive pressure ventilation is used in serious respiratory failure to ensure the effective ventilation and airway toilet; (3) Proper selection of ventilation mode, together with the careful adjustment of tidal volume, respiratory rate, inspiratory flow rate and positive end-expiratory pressure are important in order to avoid dynamic pulmonary

hyperinflation; (4) Sequential ventilation (early extubation following by NPPV) is recommended as a weaning strategy for intubated patients; (5) For those in whom exacerbation is due to pulmonary infection, NPPV should be initiated with pulmonary infection control as the window to decrease the duration of invasive ventilation, the risk of ventilator associated pneumonia, and hospital mortality [109].

Most children who undergo congenital heart surgery require postoperative mechanical ventilation. Failed extubation (FE) may result in physiological instability, delay, or set back of the weaning process. FE is statistically associated with prolonged mechanical ventilation. Harrison et al [110] sought to identify frequency, pathogenesis, and risk factors for FE after congenital heart surgery in young children ≤ 36 months of age who underwent congenital heart surgery in the period between January 1998 and July 1999 at their centre. They performed a retrospective chart review and defined reintubation within 24 h as an FE. Demographic, preoperative, intraoperative, and postoperative data were collected. A modified version of logistic regression, which accounts for lack of independence in data with multiple records per subject, was used to assess the impact of risk factors for FE. A forward selection process was used with $p < 0.05$ as the criterion for entry into the model. Estimated odds ratios (EORs) were reported with 95% confidence intervals (CI). The predictive ability of the final model was assessed by using the area under the receiver operating characteristic curve. A total of 212 children ≤ 36 months of age underwent 230 congenital heart operations. Eleven children (5.2%) died perioperatively. After excluding patients who died, there were 219 surgeries among 202 patients; 25.9% (51 of 197), 51.8% (102 of 197), and 72.6% (143 of 197) of patients were successfully extubated by 12, 24, and 48 h, respectively. There were 22 cases in which an initial attempt at extubation failed at a median of 67.8 hrs (range, 2.4-335.5 h). Five patients failed a subsequent attempt at extubation at a median of 189.5 h (range, 115.8-602.5 h). The most common causes of initial FE were cardiac dysfunction ($n = 6$), lung disease ($n = 6$), and airway oedema ($n = 3$). Risk factors for FE included pulmonary hypertension (EOR, 38.7; 95% CI, 2.9-25.8; $p < 0.001$), Down syndrome (EOR, 4.6; 95% CI, 1.8-11.8; $p = 0.002$), and deep hypothermic circulatory arrest (EOR, 4.5; 95% CI, 1.3-17.5; $p = 0.018$). All were independent predictors of FE (area under the curve, 0.837). The strongest predictor was pulmonary hypertension, which when used alone to predict FE provided a sensitivity of 0.83 (95% CI, 0.59-0.94) and a specificity of 0.75 (95% CI, 0.68-0.80). Harrison et al concluded that extubation fails after approximately 10% of congenital heart surgery in young patients. Causes of FE are diverse, with preoperative pulmonary hypertension, presence of a congenital syndrome, and intraoperative circulatory arrest being risk factors for FE. Prospective validation of the predictive model with larger numbers and at multiple institutions would improve its utility [110].

Weaning from mechanical ventilation is one of the main challenges facing ICU physicians. Difficult weaning affects about 25% of critical patients undergoing mechanical ventilation. Its duration correlates on the one hand with pathophysiological aspects of the underlying disease and, on the other hand, with other factors such as the development of neuromyopathy of the critically ill patient, prolonged use of sedative-hypnotic drugs and, most of all, physician reluctance to identify the

correct timing of therapeutic steps for weaning and subsequent extubation. The goal of adopting weaning protocols is to overcome problems due to an exclusively clinical opinion. Protocols have to be used together with daily clinical evaluation of the patient and the procedure must be carried out by an ICU team of both medical and nursing staff. Attempts to wean a patient from a ventilator and extubate him should be made through a spontaneous breathing trial (SBT) with T-tube or pressure support ventilation (PSV) with pressure support of $7\text{--}8\text{ cmH}_2\text{O} \pm \text{PEEP} \geq 4\text{ cmH}_2\text{O}$. Proper recourse to noninvasive mechanical ventilation and an accurate timing for tracheostomy are effective tools which can be used by physicians to facilitate weaning and to improve patient outcomes [111].

Matić et al [112] compared T-tube and PSV as two methods of mechanical ventilation weaning of patients with COPD after failed extubation. They conducted a prospective randomized trial at their multidisciplinary ICU over 2 years and included 136 patients with COPD who required mechanical ventilation longer than 24 h. The patients who could be weaned from mechanical ventilation were randomized to either a T-tube or PSV 2-h spontaneous breathing trial. The patients in whom the 2-h trial was successful were extubated and excluded from further research. Patients in whom the 2-h trial failed had mechanical ventilation reinstated and underwent the same weaning procedure after 24 h in the event they fulfilled the weaning criteria. The weaning outcome was assessed according to the following parameters: extubation success, mechanical ventilation duration, time spent in ICU, reintubation rate, and mortality rate. The authors reported that the 2-h trial failed in 31 patients in T-tube and 32 patients in the PSV group, of whom 17 and 23, respectively, were successfully extubated ($p < 0.001$, chi-square test). Mechanical ventilation lasted significantly longer in the T-tube than in the PSV group (187 h vs 163 h, respectively, $p < 0.001$, Mann-Whitney test). In addition, patients in the T-tube group spent significantly more time in the ICU than patients in the PSV group (241 hours (interquartile range 211–268) vs 210 hours (211–268), respectively, $p < 0.001$, Mann-Whitney test). Reintubation was required in 8 and 6 patients in the T-tube and PSV group, respectively, and death occurred in 4 and 2 patients, respectively, during ICU stay. Matić et al concluded that patients with COPD who failed the 2-h spontaneous breathing trial had a more favourable outcome when the PSV rather than the T-tube method was used for weaning from mechanical ventilation [112].

Wolthuis et al [113] compared the effects of mechanical ventilation with a lower tidal volume (VT) strategy versus those of greater VT in patients with or without acute lung injury (ALI)/acute respiratory distress syndrome (ARDS) on the use of opioids and sedatives. Theirs was a secondary analysis of a previously conducted before/after intervention study, which consisted of feedback and education on lung protective mechanical ventilation using lower VT. The study evaluated the effects of this intervention on medication prescriptions from days 0 to 28 after admission to the multidisciplinary ICU. Medication prescriptions in 23 patients before and 38 patients after intervention were studied. Of these patients, 10 (44%) and 15 (40%) suffered from ALI/ARDS. The VT of ALI/ARDS patients declined from 9.7 ml/kg predicted body weight (PBW) before to 7.8 ml/kg PBW after the intervention

($p=0.007$). For patients who did not have ALI/ARDS there was a trend toward a decline from 10.2 ml/kg PBW to 8.6 ml/kg PBW ($p=0.073$). Arterial carbon dioxide tension was significantly greater after the intervention in ALI/ARDS patients. Neither the proportion of patients receiving opioids or sedatives, nor prescriptions at individual time points differed between pre-intervention and post-intervention. In addition, there were no statistically significant differences in doses of sedatives and opioids. Findings were no different between non-ALI/ARDS patients and ALI/ARDS patients. The study concluded that concerns regarding sedation requirements with the use of lower VT are unfounded and should not preclude its use in patients with ALI/ARDS [113].

Petrucci and Iacovelli [114] reported data on ARDS complicated by ventilator-induced lung injury. They confirmed that lung-protective ventilation strategies may lead to improved survival. Their aim was to assess the effects of ventilation with lower VT on morbidity and mortality in patients aged 16 years or older affected by ARDS and ALI. A secondary objective was to determine whether the comparison between low and conventional VT was different if a plateau airway pressure of greater than 30 to 35 cm H₂O was used. The authors searched databases of intensive care journals and conference proceedings, reference lists and 'grey literature' from 2003 to 2006. The paper included randomized controlled trials comparing ventilation using either lower VT or low airway driving pressure (plateau pressure 30 cm H₂O or less), resulting in VT of 7 ml/kg or less versus ventilation that uses VT in the range of 10 to 15 ml/kg, in adults (16 years old or older). Trial quality was individually assessed and data were extracted. Wherever appropriate, results were pooled. Furthermore, fixed- and random-effects models were applied. The authors found one new study in this update for a total of six trials, involving 1,297 patients, which were eligible for inclusion. Mortality at day 28 was significantly reduced by lung-protective ventilation: relative risk (RR) 0.74 (95% CI 0.61-0.88); hospital mortality was reduced: RR 0.80 (95% CI 0.69-0.92); overall mortality was not significantly different if a plateau pressure less than or equal to 31 cm H₂O in control group was used: RR 1.13 (95% CI 0.88-1.45). There was insufficient evidence about morbidity and long term outcomes. The authors stressed the concept that clinical heterogeneity, such as different lengths of follow up and higher plateau pressure in control arms in two trials, make the interpretation of the combined results difficult. Mortality is significantly reduced at day 28 and at the end of hospital stay. The effects on long-term mortality are unknown, although the possibility of a clinically relevant benefit cannot be excluded [114].

In conclusion, comparison from ARDS network data and conventional ventilation evidence such as in a 70 Kg patient with ARDS showed that conventional ventilation at a VT of 10-12 ml/kg of body weight and an end-expiratory pressure of 0 cm of water can lead to alveolar overdistension (at peak inflation) and collapse (at the end of expiration). Protective ventilation at VT of 6 ml/Kg limits overinflation and end-expiratory collapse by providing a low VT and an adequate positive end-expiratory pressure [115-117].

Cardiopulmonary Resuscitation. In order to evaluate the quality of cardiopulmonary resuscitation (CPR) performed by a physician-manned ambulance, and assess whether it changed with time influenced by developing scientific evidence and guideline changes, a retrospective observational study was performed of all cardiac arrest patients (except trauma) older than 18 years treated between May 2003 and December 2006 by the physician-manned ambulance in Oslo. CPR quality was assessed from continuous electronic recordings from the defibrillators (LIFEPAK 12, Physio-Control or a modified Heartstart 4000, Philips Medical Systems). Ventilations were assessed from changes in transthoracic impedance, chest compressions from transthoracic impedance for LIFEPAK 12 and from an accelerometer for Heartstart 4000 (nine patients). Values were given as mean $\pm$ SD and differences analysed with ANOVA and unpaired Student's t-test with Bonferroni correction. Forty-eight of 169 consecutive cases were excluded from CPR quality analysis, 47 due to missing defibrillator data and one due to a short arrest time (<1 min). Hands-off intervals (fraction of time without spontaneous circulation where no chest compressions are given) were reduced from 0.18 ± 0.11 in 2003 to 0.10 ± 0.06 in 2006 ($p=0.03$). Compression and ventilation rates were significantly reduced from 122 ± 12 and 16 ± 3 min $^{-1}$, respectively in 2003 to 111 ± 10 and 12 ± 3 in 2006 ($p<0.0001$ and $p=0.001$). In 2003-2004 10% were discharged alive versus 16% in 2005-2006 ($p=0.3$, Chi-square test). High quality CPR is achievable out-of-hospital, and the improvement with time could reflect developing scientific evidence focusing on reducing hands-off intervals and hyperventilation [118, 119].

Cerebral Resuscitation. Ischaemic/hypoxic insults to the brain during surgery and anaesthesia can result in long-term disability or death. Advances in resuscitation science encourage progress in clinical management of these problems. However, current practice remains largely founded on extrapolation from animal studies and limited clinical investigation. A major step was made with the demonstration that rapid induction of mild sustained hypothermia in comatose survivors of out-of-hospital ventricular fibrillation cardiac arrest reduces death and neurological morbidity with negligible adverse events. This provides the first irrefutable evidence that outcome can be favourably altered in humans with widely applicable neuroprotection protocols. How far hypothermic protection can be extended to global ischaemia of other aetiologies, however, remains to be determined. All available evidence suggests an adverse response to hyperthermia in the ischaemic or post-ischaemic brain.

Management of other physiological values can have dramatic effects in experimental injury models and this is largely supported by available clinical data. Hyperoxaemia may be beneficial in transient focal ischaemia but deleterious in global ischaemia. Hyperglycaemia causes exacerbation of most forms of cerebral ischaemia and this can be abated by restoration of normoglycaemia. Studies indicate little, if any, role for hyperventilation. There is little evidence in humans that pharmacological intervention is advantageous. Anaesthetics consistently and meaningfully improve outcome from experimental cerebral ischaemia, but only if present during the ischaemic insult. Emerging experimental data portend clinical

breakthroughs in neuroprotection. In the interim, organized large-scale clinical trials could serve to better define limitations and efficacy of already available methods of intervention, aimed primarily at regulation of physiological homeostasis.

No neuroprotective drug has been shown to be beneficial in improving the outcome of severe traumatic brain injury (TBI), nor has any prophylactically induced moderate hypothermia shown any beneficial effect on outcome in severe TBI, despite the optimism generated by preclinical studies. This contrasts with the paradox that hypothermia still is the most powerful neuroprotective method in experimental models because of its ability to influence the multiple biochemical cascades that are set in motion after TBI. The aim of this short review is to highlight the most recent developments concerning the pathophysiology of severe TBI, to review new data on thermoregulation and induced hypothermia, the regulation of core and brain temperature in mammals and the multiplicity of effects of hypothermia in the pathophysiology of TBI. Many experimental studies in the last decade have again confirmed that moderate hypothermia confers protection against ischaemic and nonischaemic brain hypoxia, traumatic brain injury, anoxic injury following resuscitation after cardiac arrest and other neurological insults.

Many post-traumatic adverse events that occur in the injured brain at a cellular and molecular level are highly temperature-sensitive and are thus a good target for induced hypothermia. The basic mechanisms through which hypothermia protects the brain are clearly multifactorial and include at least the following: reduction in brain metabolic rate, effects on cerebral blood flow, reduction of the critical threshold for oxygen delivery, blockade of excitotoxic mechanisms, calcium antagonism, preservation of protein synthesis, reduction of brain thermo-pooling, a decrease in oedema formation, modulation of the inflammatory response, neuroprotection of the white matter and modulation of apoptotic cell death. The new developments discussed in this review indicate that by targeting many of the abnormal neurochemical cascades initiated after TBI, induced hypothermia may modulate neurotoxicity and, consequently, may play a unique role in opening up new therapeutic avenues for treating severe TBI and improving its devastating effects. Furthermore, greater understanding of the pathophysiology of TBI, new data from both basic and clinical research, the good clinical results obtained in randomized clinical trials in cardiac arrest and better and more reliable cooling methods have given hypothermia a second chance in treating TBI patients. A critical evaluation of hypothermia is therefore mandatory to elucidate the reasons for previous failures and to design further multicentre randomized clinical trials that would definitively confirm or refute the potential of this therapeutic modality in the management of severe traumatic brain injuries [120-122].

Brain hypothermia therapy has been expected to lead to good neurological outcome in acute brain insults. There have been a few positive results which have been proven by multicentre randomized clinical trials (RCT) in the cardiopulmonary arrest (CPA) in patients with ventricular fibrillation. Among these clinical trials, early application of hypothermia, maintenance of cerebral blood flow during hypothermia therapy and prevention of quick re-warming have shown to produce

good outcome from clinical experiences. For brain hypothermia therapy to become an effective method for acute brain insults, indications, brain oriented intensive care and biomarkers for the therapy must be established. RCT in acute brain insults beside CPA victims are needed in the near future.

Coagulation Pathway. The blood clotting system or coagulation pathway, like the complement system, is a proteolytic cascade (Fig. 1). Each enzyme of the pathway is present in the plasma as a zymogen (inactive form), which on activation undergoes proteolytic cleavage to release the active factor from the precursor molecule. The coagulation pathway functions as a series of positive and negative feedback loops which control the activation process. The ultimate goal of the pathway is to produce thrombin, which can then convert soluble fibrinogen into fibrin, which forms a clot. The generation of thrombin can be divided into three phases, the intrinsic and extrinsic pathways, which provide alternative routes for the generation of factor X, and the final common pathway, which results in thrombin formation.

Severe sepsis is associated with an exacerbated procoagulant state with a protein-C system impairment. In contrast, the inflammatory and coagulation status of non-septic organ failure patients is less documented.

Soluble thrombomodulin levels have been shown to be higher in septic patients than in healthy controls, while protein C, protein S and soluble EPCR levels are lower. Similar results have been obtained in non-septic patients with organ failure.

Monocyte thrombomodulin overexpression, along with increased circulating levels of activated protein C, suggest that the capacity for protein C activation is at least partly preserved in both settings. No difference in the inflammatory profile has been found between septic and non-septic patients.

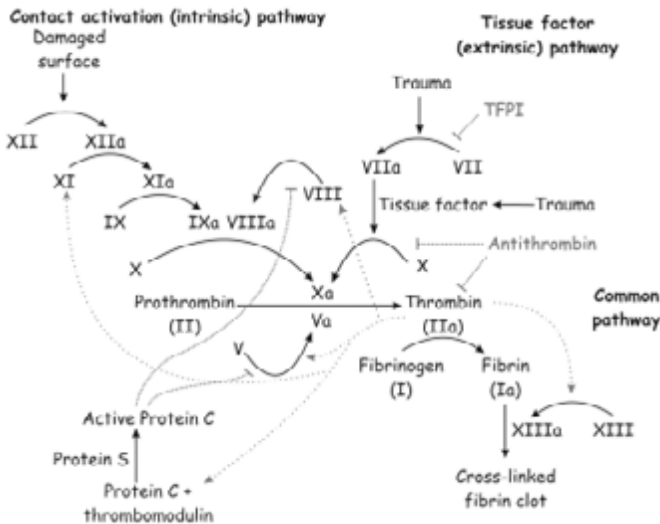


Fig. 1. Coagulation process

In conclusion, the pathogenesis of organ failure in critical-care patients is therefore characterized by an overwhelming systemic inflammatory response and by exacerbated coagulation activation, independently of whether or not infection is the triggering event [123].

CRRT Technology and Logistics. Implementing continuous renal replacement therapy (CRRT) in an ICU is a somewhat difficult issue and quite different from starting a new ventilation mode or a new haemodynamic device. It may indeed require an on-call medical emergency CRRT team as expertise in this field is really a key issue to success. Education for the nursing team is another key point, especially as ongoing or continuous education is changing very quickly.

Uniformity of the type of device used is another crucial part in the organization process with regard to CRRT implementation in the ICU. Involvement of both the ICU and nephrology teams is another key to success especially when different modes and higher exchange rates are used. Appropriate antimicrobial therapy poses one of the greatest challenges during the management of a septic patient in the ICU.

Acute renal failure (ARF) is a common complication of sepsis and often occurs as a component of multiple organ dysfunction syndrome. CRRT is increasingly used as an effective extracorporeal blood purification therapy in this critically ill patient population. Available data demonstrate that sepsis, ARF and different modalities of CRRT may have profound effects on the pharmacokinetics and pharmacodynamics of various antimicrobial agents used in the ICU.

Guidelines for antimicrobial prescription which will fit the individual patient undergoing a particular method of treatment are still unavailable. Understanding the principles of drug removal by CRRT and pharmacokinetics of various agents can help to modify the drug dosage and dosing intervals for individualized therapy. Meanwhile, monitoring the drug serum concentration is still mandatory whenever clinically feasible [124].

Endocrine Interventions in the ICU. Patients with critical illness, particularly those who depend on intensive care for a prolonged period of time, have a high morbidity and mortality. The acute and chronic phases of critical illness are associated with distinct endocrine alterations.

Acute endocrine adaptations to the severe stress of critical illness, comprising an activated anterior pituitary function, have been selected by nature and can, as such, be considered as beneficial for survival. These adaptations disappear or wane during the prolonged phase of critical illness. In this phase there is a reduced pulsatile secretion of different anterior pituitary hormones and the so-called “wasting syndrome” occurs. This prolonged endocrine/metabolic stress response is quite different from the acute response and may, to some extent, no longer be adaptive. Intervention within the endocrine system, however, remains highly controversial, as it is difficult to differentiate between beneficial adaptations and harmful abnormalities and to outline strategies for therapy.

Insulin infusion titrated to maintain normoglycaemia may be a notable excep-

tion, as this intervention has been proven to increase survival and reduce morbidity of surgical intensive care patients. Treatment of “relative adrenal failure” with hydrocortisone also appears to improve the outcome of patients with septic shock, but diagnostic and dosing issues still remain unresolved. Although extensive research has shown that infusion of hypothalamic-releasing peptides is able to restore physiological hormonal patterns within the somatotrophic, thyrotrophic, and gonadal axes and, thereby, to generate a controlled anabolic response, further research is needed to investigate whether such interventions actually improve the outcome of critical illness.

The neuroendocrine response to critical illness is complex and dynamic. The implications for the EP in managing these patients are unclear and evolving. There seems to be a role for steroids in selected critically ill ED patients and glycaemic control may yet be shown to be important as well [125].

Hyperglycaemia and insulin resistance are common in severe illness and are associated with a worse outcome. In 2001, a randomized, single-centre, prospective un-blinded trial of surgical patients compared intensive-glycaemic control (serum glucose 4.4–6.1 mmol·L⁻¹) with more liberal glucose management (serum glucose 10–12 mmol·L⁻¹) [126]. Significant decreases in mortality and morbidity were observed in the intensively treated group. In addition, a pronounced mortality benefit was demonstrated for patients who required ICU therapy for three or more days.

For patients staying in the ICU longer than three days, maintaining blood glucose concentrations between 4.4–6.1 mmol·L⁻¹ during ICU admission is associated with reduced in-hospital mortality, but also with more frequent hypoglycaemic events. Intensive insulin therapy significantly reduced morbidity, but not mortality amongst all medical ICU patients. It had been appreciated for over a century that severe illness is associated with hyperglycaemia. However, for most of that time “stress-hyperglycaemia” had been either largely ignored, or assumed adaptive.

It is now well established that both the degree and duration of hyperglycaemia are independent risk factors for adverse outcome: whether for patients following severe brain-injury, severe paediatric burns, critical-illness polyneuropathy, trauma, myocardial infarction, stroke, as well as for a heterogeneous group of ICU patients whether previously diagnosed diabetic or not [125–129]. What remains to be determined is whether or not therapeutic euglycaemia is associated with improved outcome. The study by Van den Berghe et al [125] provides important new information to help resolve this question.

The previous work of this group involving surgical and trauma ICU patients [126] has influenced clinical practice, and heightened our awareness regarding seemingly mundane interventions such as glycaemic control. Notably, for many, ‘tight’ glycaemic control has since become an indicator of quality of care in the ICU. It also helped to emphasize a new paradigm where resuscitation advances well beyond the concept of simple insertion of “lines and tubes”. This study will influence our approach to the care of medical ICU patients. However, in the context of the current literature, intensive-insulin therapy is not beneficial for all; nor is it innocuous.

Prior to the study by Van den Berghe et al [125] many clinicians made the

specious assumption that therapeutic interventions for surgical ICU patients might freely translate to medical ICU patients. An important lesson from this study is to remind clinicians of the heterogeneity of our patient populations. In contrast, specialties such as cardiology have made great advances by being able to study more homogeneous populations, subsequently streamlining care. Nonetheless, most ICU physicians are familiar with the work on relative adrenal insufficiency; perhaps another endocrinopathy has been added to our constellation of ICU diseases. So, what should we do? Options include waiting for data from additional trials: whether from a multicentre trial (e.g. the NICE-SUGAR trial) or one with lower control-group mortality. However, evidence that acute hyperglycaemia is more acutely toxic in the critically ill than either healthy or diabetic individuals argues against inaction. Alternatively, the option of treating all medical and surgical patients exists, given the likelihood that more will benefit than by treating none. However, this study illustrates that ICU treatment should be individualized.

An interim suggestion is to avoid marked hyperglycaemia (serum glucose $8 \text{ mmol}\cdot\text{L}^{-1}$) for medical ICU patients during the first three days of their admission. If critical illness persists, then subsequent normoglycaemia ($4.4\text{--}6.1 \text{ mmol}\cdot\text{L}^{-1}$) becomes justified [130–132].

Van den Berghe et al [125] provide important new information for the care of medical ICU patients, while at the same time raising additional questions. For those expecting a simple resolution of the question of glycaemic control in the critically ill, they will be surprised. For those eager to better characterize the metabolic abnormalities of critical illness, the story has just become more fascinating. Hyperglycaemia and hyperinsulinaemia are common in ICU patients and relates to illness severity. Intensive insulin therapy (IIT) to maintain normoglycaemia reduces morbidity and mortality. Blood glucose control explains this benefit, as a high insulin dose is associated with adverse outcome. Mitogenic insulin effects could theoretically explain this link.

Normoglycaemia can be maintained in ICU patients without a sustained further elevation of insulinaemia. Together with the increased adiponectin levels, this finding suggests that IIT may improve insulin sensitivity. Skeletal muscle, but not liver, revealed an increased metabolic insulin signal. The therapy did not impose mitogenic risk in these tissues [133].

Ethical Aspects of Withdrawing and Withholding Treatment. Decisions about withdrawing and withholding treatment are common in health care. During almost every encounter between health professionals and patients a decision needs to be made about treatment options. In most cases these choices do not pose any difficulty, for example, starting antibiotics when a patient has an infection. However, decisions not to treat, or to stop treating, raise fundamental questions about the nature and purpose of nursing and the ethics of end-of-life care. Nurses need to be proactive in deciding what nursing care is and what treatment is. An ethical distinction is drawn between acts and omissions.

How this distinction relates to withdrawing and withholding treatment will be considered. Further ethical issues discussed relate to judgement about the futility

of treatment, patients autonomy and nurses' duty of care to patients at the end of life, and the importance of the decision to refuse treatment [134, 135].

Infection Control Manoeuvres and Microbiological Surveillance. Hospital infections are important because of the increased risk of morbidity and mortality and their economic burden and are most commonly seen in the ICU. It is mandatory to document the characteristics of patients at an ICU, obtain bacteriological samples, and determine the distribution of the isolated microorganisms. The most commonly isolated microorganism are *E. coli*, *S. Aureus*, *S. aeruginosa*, *Acinetobacter* and MRSA. Hospital infections pose a serious problem in an ICU setting. Surveillance studies comprise the basis for treatment of ICU infections. A multidisciplinary approach is required for a better quality of care and the achievement of therapy [136, 137].

Informed Consent. Informed consent is a process by which a person authorizes medical treatment after discussion with clinicians regarding the nature, indications, benefits and risks of treatment [138]. In the past, physicians did not routinely seek permission from patients and/or proxies to provide medical treatment, even when such treatments involved invasive procedures with significant risk [139]. However, in current practice, such physician sovereignty has been replaced with an emphasis on patient autonomy [140].

At present, physicians are obliged to expect and encourage patient participation in decisions regarding care. The process of obtaining informed consent can improve patient satisfaction and health outcomes as well as engender trust in the physician compliance with treatment recommendations [141]. Patients receiving care in the ICU make up a highly vulnerable population with regard to informed consent. While many invasive procedures often accompany the provision of life support in the ICU and are frequently required for diagnostic or therapeutics purposes, critically ill patients are often not capable of participating in the consent process. This is the result of the common incidence of delirium complicating critical illness, related to both underlying illnesses and the use of sedatives and analgesics to treat anxiety and pain [142, 143]. Because of this, proxies are often required to provide health decisions for impaired patients [144]. The education of clinicians, patients, and proxies regarding the process of informed consent can improve this process in critically ill patients. Furthermore, by providing physicians and nurses with a standard consent form and encouraging routine distribution of this form to patients and/or proxies at the admission to the medical ICU can significantly increase the frequency with which informed consent may be obtained for invasive procedures [145].

A recent study by Clark [146] examines the informed consent process from the perspective of intensive care patients. Using the largest single-method database of patient-derived information in the United States, the author systematically outlined and tested several key factors that influence patient evaluations of the ICU informed consent process. Measures of information, understanding, and decision-making involvement were found to predict overall patient satisfaction and patient

loyalty intentions. Specific actions supportive of ICU informed consent, such as giving patients information on advance directives, patient's rights, and organ donation, resulted in significantly higher patient evaluation scores with large effect sizes. This research suggests that the effectiveness of the informed consent process in the ICU from the patient's perspective can be measured and evaluated and that ICU patients place a high value on the elements of the informed consent process. Conducting emergency research in the out-of-hospital and emergency department setting is a challenge because of the inability of patients to provide informed consent in many situations. Salzman et al [147] reported a brief overview of the history of the exception from informed consent for emergency research and summarized the methods they recently used to successfully complete community consultation and public disclosure for a trial evaluating 2 devices used during cardiopulmonary resuscitation in a large metropolitan area.

Liver. There is currently no ideal real-time and bedside technique for assessing liver function in critically ill patients. Although they are unable to differentiate between liver blood flow and cell function, dynamic tests – i.e. indocyanine green plasma disappearance rate and lidocaine metabolism (monoethylglycinexylidide test) – are nonetheless superior to static tests. Recently, the indocyanine green plasma disappearance rate, which nowadays can be measured reliably by a transcutaneous system in critically ill patients, was confirmed to correlate well with indocyanine green clearance.

In general, the indocyanine green plasma disappearance rate is superior to bilirubin, which is still used as a marker of liver function, and comparable or even superior to complex intensive care scoring systems in terms of outcome prediction. Furthermore, indocyanine green plasma disappearance rate is more sensitive than serum enzyme tests for assessing liver dysfunction and early improvement in the indocyanine green plasma disappearance rate after onset of septic shock is associated with better outcome. Since no ideal tool is currently available, dynamic tests such as indocyanine green plasma disappearance rate and monoethylglycinexylidide test may be recommended for assessing liver function in critically ill patients. The indocyanine green plasma disappearance rate has the advantage, however, of being measurable noninvasively at the bedside and providing results within a few minutes [148].

Stadlbauer and Jalan [149] summarized the therapeutic approach to patients with acute liver failure with the main focus on bioartificial and artificial liver support. They also described specific and general therapeutic approaches based on recent advances in the understanding of the pathophysiology of acute liver failure. One recent finding is that bioartificial liver support systems use hepatocytes in an extracorporeal device connected to the patient's circulation. Artificial liver support is intended to remove protein-bound toxins and water-soluble toxins without providing synthetic function. Both systems improve clinical and biochemical parameters and can be applied safely to patients. Although bioartificial liver-assist devices have not been shown to improve the survival of patients with acute liver failure, further development is underway.

Artificial liver support systems have been shown to alter several pathophysiological mechanisms involved in the development of acute liver failure, but survival data are still limited. Mortality in patients with acute liver failure is still unacceptably high. The most effective treatment, liver transplantation, is a limited resource and so other therapeutic options to bridge patients to recovery or stabilization have to be considered. Better understanding of the pathophysiology of acute liver failure and device development is necessary to achieve the elusive goal of effective extra-corporeal liver assistance [149].

Liver transplantation has revolutionized the management of acute or fulminant liver failure. Overall success rates of liver transplantation are satisfactory, although not as high as for elective transplantation. Although the bulk of liver transplants use standard whole grafts, interesting data are emerging on auxiliary liver grafts and donations from living donors. Liver transplantation is an integral part of management protocols complementing the sophisticated critical care protocols that have contributed significantly to the overall improved outcomes seen in acute liver failure. The potential for liver support devices to have an impact on the need for liver transplantation and outcomes after transplantation remains exciting [150].

Metabolism and Nutrition. The metabolism of critical illness is characterized by a combination of starvation and stress. There is increased production of cortisol, catecholamines, glucagon and growth hormone and increased insulin-like growth factor-binding protein-1. Phagocytic, epithelial and endothelial cells elaborate reactive oxygen and nitrogen species, chemokines, pro-inflammatory cytokines and lipid mediators, and antioxidant depletion ensues.

There is hyperglycaemia, hyperinsulinaemia, hyperlactataemia, increased gluconeogenesis and decreased glycogen production. Insulin resistance, particularly in relation to the liver, is marked. The purpose of nutritional support is primarily to save lives and secondarily to speed recovery by reducing neuropathy and maintaining muscle mass and function. There is debate about the optimal timing of nutritional support for the patient in the ICU. It is generally agreed that the enteral route is preferable if possible, but the dangers of the parenteral route, a route of feeding that remains important in the context of critical illness, may have been overemphasized. Control of hyperglycaemia is beneficial, and avoidance of overfeeding is emphasized. Growth hormone is harmful.

The refeeding syndrome needs to be considered, although it has been little studied in the context of critical illness. Achieving energy balance may not be necessary in the early stages of critical illness, particularly in patients who are overweight or obese. Protein turnover is increased and N balance is often negative in the face of normal nutrient intake; optimal N intakes are the subject of some debate. Supplementation of particular amino acids able to support or regulate the immune response, such as glutamine, may have a role not only for their potential metabolic effect but also for their potential antioxidant role. Doubt remains in relation to arginine supplementation. High-dose mineral and vitamin antioxidant therapy may have a place [151].

Molecular Biology. Studies have demonstrated that biomarkers can reliably differentiate diseases in which the clinical symptoms are ambiguous; natriuretic peptides (NPs), such as brain natriuretic peptide (BNP), can be used as noninvasive markers of heart failure, but their use in ICU patients is complicated by other known stimulators of their release, such as hypoxia and right ventricular strain due to lung disease itself.

Jefic et al [152] found that neither BNP nor N-terminal pro-BNP could differentiate between high- and low- pulmonary artery wedge pressure respiratory failure, but that levels of these markers did inversely correlate with indices of cardiac contractility. C-reactive protein is a general indicator of infection [153] and a potential indicator of ventilated associated pneumonia (VAP) resolution [154].

Procalcitonin seems to hold promise for identifying cases of bacterial infection such as in VAP, in which persistently elevated levels were strong predictors of an unfavourable outcome [155]. It remains to be seen whether procalcitonin should be used to guide antibiotic therapy in VAP [156].

Ye et al [157] found that the pre-B-cell colony-enhancing factor (PBEF) has the potential to be a novel marker of acute lung injury, finding significantly increased PBEF levels in both the lungs and serum of animals and human with ALI and a nearly eightfold higher risk of ALI when subjects had certain PBEF single-nucleotide polymorphisms.

Acute renal failure (ARF) is typically diagnosed by measuring serum creatinine, which is an unreliable indicator during acute changes in kidney function. Mishra et al [158] found that urine and serum level of neutrophil gelatinase-associated lipocalin are sensitive, specific, and highly predictive early markers for acute ischaemic renal injury in children after cardiac surgery. Broader use of this marker for early recognition and treatment of ARF awaits validation in a larger population in whom additional mechanisms of renal injury might be involved. Early growth response factor-1 (EGR1), a nuclear transcription factor, was discovered about 15 years ago and belongs to a larger family of early response genes. It appears to function as a convergence point for many signalling pathways, including those involved in inflammation and apoptosis, and its expression is rapidly induced by a variety of stimuli. The induced EGR1 protein is thought to couple external stimuli to intracellular events, by altering the expression of EGR1 target genes such as tissue factor, vascular endothelial growth factor, and intercellular adhesion molecule 1 (CD54), human rhinovirus receptor, proteins that are common in organ injury. Because EGR1 appears to mediate responses to sepsis and reperfusion injury, as well as intensifying inflammatory responses, it may be important in the pathogenesis of critical illness. This perspective aims to summarize the current state of knowledge of the effects and mechanisms of EGR1 in acute illness states such as inflammation and ALI [159].

Impairment of the ability to mount an inflammatory response is associated with death from adult critical illness. This phenomenon, characterized by reduced monocyte production of pro-inflammatory mediators such as tumour necrosis factor alpha (TNF- α), is poorly understood in children. Hall et al [160] hypothesized that differential expression of inflammation-related genes would be seen in mo-

nocytes from children with adverse outcomes from multiple organ dysfunction syndrome (MODS). Ex vivo lipopolysaccharide-induced TNF- α production and plasma cytokines were prospectively measured biweekly in children with dysfunction of two or more organs.

Concomitantly, monocyte expression of 28 pro- and anti-inflammatory genes (cytokines, Toll-like receptor (TLR)/nuclear factor kappa B signalling pathway factors, inflammasome elements) was measured. Thirty children (22 survivors, eight nonsurvivors) were evaluated. High mRNA levels for interleukin (IL)-10, IL-1 receptor-associated kinase (IRAK-M) and the putative inflammasome inhibitor pyrin were associated with death ($p \leq 0.02$). Plasma IL-10 levels were higher and ex vivo TNF- α production was lower in nonsurvivors ($p < 0.05$). Among survivors, high mRNA levels for IL-10, IRAK-M, pyrin, IRAK1, or TLR4 were associated with longer durations of paediatric intensive care unit stay and mechanical ventilation ($p \leq 0.02$). These data suggest that adverse outcomes from paediatric MODS are associated with an anti-inflammatory monocyte mRNA phenotype. Future studies are warranted to explore mechanisms of immunodepression in paediatric critical illness.

Neurocritical Care. Over the past 20 years, neurointensive care units have evolved from neurosurgical units focused primarily on postoperative monitoring to units that provide comprehensive medical and specialized neurological support for patients with life-threatening neurological diseases. In addition to standard interventions, areas of expertise unique to neurocritical care include management of intracranial pressure, haemodynamic augmentation to improve cerebral blood flow, therapeutic hypothermia, and advanced neuromonitoring (i.e. continuous electroencephalography, brain-tissue oxygen, and microdialysis). Neurointensivists defragment care by focusing on the interplay between the brain and other systems, and by integrating all aspects of neurological and medical management into a single care plan.

Outcomes research has established that victims of traumatic brain injury and haemorrhagic stroke experience reduced mortality, better functional outcomes, and reduced length of stay when cared for by neurointensivists in a dedicated neurointensive care unit. In the United States a national system for accrediting training programmes and certifying intensivists with special qualifications in neurocritical care is currently being established by the United Council of Neurologic Subspecialties. Neurocritical care is one of the newest subspecialties of medicine and is at the forefront of bringing effective new therapies to patients with life-threatening neurological diseases [161].

In the neurointensive care unit, neurological monitoring is depended upon to signal the onset of neurological decline. Many monitoring techniques such as intracranial pressure monitoring, cerebral perfusion pressure measurement, jugular venous oxygen saturation, transcranial Doppler ultrasound and continuous electroencephalogram are commonly practiced. Newer methods of monitoring include quantitative EEG, direct cerebral blood flow measurements, cerebral microdialysis, brain tissue oxygenation and cerebral near-infrared spectroscopy.

When used in combination, as in multimodal monitoring, the goal is to overcome some of the disadvantages of each technique and to achieve a higher degree of accuracy in detecting secondary brain insults. However, such a large amount of data can be generated that the combinations have to be chosen carefully, or the monitoring data will not be able to be acted upon quickly enough to be of benefit to the patient [162].

Nursing Workload Management System. In recent decades, the healthcare system has experienced enormous pressure to improve quality and reduce costs, and the competition for patients among health care providers has become intense.

Hence the quality of patients care has become a vital concern and the continual improvement in health care delivery and cost containment has become an absolute priority. Since nursing consumes the largest portion of a hospital personnel budget (40% as a whole), administrators tend to focus their cost containment efforts on nursing departments. Nursing budgeting and staffing decisions depend on accurate assessment of nurse workload. This in turn depends on the quality and consistency of workload distribution and balancing among nurses. Consistently balanced workloads help nursing managers predict required staffing levels and identify over-staffed units more easily. Furthermore, distributing work fairly among nurses is essential for optimal quality of care.

The expected outcomes of a nursing workload management project are to help nursing administration to appropriately allocate staff to the patient classification, increase patient safety standards, minimize staff wastage and optimize the allocation of staff, thus enhancing staff job satisfaction through the fair distribution of tasks among nursing personnel, and increasing administrative human resources planning skills [163].

For over 30 years, in an attempt to demonstrate the cost-benefit ratio of the ICU, a variety of tools have been developed to measure not only the severity of illness of the patient but also to capture the true cost of nursing workload. In this context, the nursing activities score (NAS) was developed as a result of modifications to the therapeutic interventions scoring system-28 (TISS-28). The NAS is a tool to measure nursing workload in the ICU and it has been shown to be twice as effective in measuring how nurses spend their time caring for critically ill patients as the TISS-28. Gonçalves et al [164] reported the introduction of the NAS into everyday use in an intensive care unit in Brazil, highlighting the challenges of standardization of operational definitions, training requirements and accurate completion of the documentation when using such a tool. They also outlined the rationale and steps undertaken to achieve this and highlighted the benefits of such a process.

Point of Care. Ultrasound provides a diagnostic modality that allows a whole-body approach at the bedside of a critically ill patient in the search for infectious foci. Both common sites of infection, such as the lung and pleura, central veins, and maxillary sinuses, and also less common sites, such as gastrointestinal perforation, sepsis due to mesenteric ischaemia, or even meningitis, provide characteristic ultrasound patterns. Optimal use of ultrasound also combines bedside diagnosis

with subsequent interventional procedures that can decrease the need for transfer to other imaging and interventional suites. Experience has shown that fevers of unknown origin in the critical care unit often have ultrasound equivalents. Therefore, if a comprehensive ultrasound examination is negative, it is now appropriate to speak of fever of unknown sonographic origin.

Lung ultrasound can be routinely performed at the bedside by intensive care unit physicians and may provide accurate information on lung status with diagnostic and therapeutic relevance. Bouhemad et al [165] review the performance of bedside lung ultrasound for diagnosing pleural effusion, pneumothorax, alveolar-interstitial syndrome, lung consolidation, pulmonary abscess and lung recruitment/derecruitment in critically ill patients with acute lung injury.

Emergency ultrasound is suggested to be an important tool in critical care medicine. Time-dependent scenarios occur during preresuscitation care, during cardiopulmonary resuscitation, and in post-resuscitation care. Suspected myocardial insufficiency due to acute global, left, or right heart failure, pericardial tamponade, and hypovolaemia should be identified. These diagnoses cannot be made with standard physical examination or the electrocardiogram. Furthermore, the differential diagnosis of pulseless electrical activity is best elucidated with echocardiography. Therefore, an algorithm of focused echocardiographic evaluation in resuscitation management was developed, a structured process of an advanced life support-conformed transthoracic echocardiography protocol to be applied to point-of-care diagnosis.

The new 2005 American Heart Association/European Resuscitation Council/International Liaison Committee on Resuscitation guidelines recommended high-quality cardiopulmonary resuscitation with minimal interruptions to reduce the no-flow intervals. However, they also recommended identification and treatment of reversible causes or complicating factors. Therefore, clinicians must be trained to use echocardiography within the brief interruptions of advanced life support, taking into account practical and theoretical considerations. Focused echocardiographic evaluation in resuscitation management was evaluated by emergency physicians with respect to incorporation into the cardiopulmonary resuscitation process, performance, and physicians' ability to recognize characteristic pathology. The aim of the focused echocardiographic evaluation in resuscitation management examination is to improve the outcomes of cardiopulmonary resuscitation [166].

Pulmonary embolism remains a great diagnostic challenge. The value of different ultrasound methods is presented in a review by Mathis [167]. With regard to the accuracy of echocardiography, it shows a sensitivity of 41-50% and a specificity of 90% for unselected patients with suspicion of pulmonary embolism as a result. On the other hand, the sensitivity of echocardiography in cases of haemodynamically unstable patients is very high. In a recent multicentre trial of thoracic ultrasound in the diagnosis of pulmonary embolism on 352 patients sensitivity was 74%, specificity 95%, positive predictive value 95%, negative predictive value 75% and accuracy 84%. Colour Doppler sonography with compression is a safe modality ensuring the source of embolism in deep vein thrombosis. With suspicion of deep

vein thrombosis the mean sensitivity was 95 % (38-100%) and mean specificity was 97% (81-100%). The combination of chest sonography, echocardiography and compression sonography of leg vein thrombosis enhances the sensitivity of sonography to 92 %, while this accuracy cannot be reached with any other method [167].

Intra-abdominal pathology, either primary or secondary, may frequently be found in critically ill patients. Without early diagnosis and treatment, the patient's condition may deteriorate and even progress to death. Wan and Chen [168] provide a current review of the literature regarding liver, biliary, pancreatic, and splenic problems in critically ill patients and describe common ultrasound findings, including the appearance of free intraperitoneal air. According to the liver surface, edge, echostructure, and echogenicity, either diffuse liver diseases or focal liver diseases can be detected on ultrasound. By scanning the biliary tree and gallbladder, many right upper quadrant diseases can be diagnosed. The role of ultrasound for acute pancreatic pathology is to identify any lesions and to evaluate the severity of the diseases. Similarly, the spleen can be evaluated for relevant pathology in the critical care setting [168].

Trauma. The World Health Organization (WHO) estimates that by 2020 trauma will be the first or second cause of lost years of life for the entire world population, including both the developing nations and the most industrialized countries [169]. In 1996 the American National Academy of Sciences published "Accidental Death and Disability; The Neglected Disease of Modern Society" [170]. The study focuses attention on morbidity and mortality due to trauma. Even today these two elements are so epidemiologically relevant as to warrant a renewal of the line of approach. The overriding aim is to achieve faster access, improved quality of treatment, and reduced indices of disability and premature mortality.

The aim of improving care of trauma victims requires close interaction between the services operating in the hospital, in particular in the emergency department, and the prehospital system of care [171] with the aim of guaranteeing an effective and integrated system of care. This simple statement has deep roots in modern medicine: a great number of organizations, often voluntary organizations, and academic community have contributed to planning the functions of first aid and emergency medicine with the aim of optimizing preventive measures of trauma treatment.

The key points of the integrated system of trauma care include the institution of emergency departments, the definition of standards for prehospital interventions, the definition of the requisites of different hospitals in relation to the different level of specialization (the trauma team), the training of personnel [172] and the importance of certificate courses such as Advanced Trauma Life Support.

In the last 20 years there have been a large number of disasters which have endangered the lives of approximately 800 million people and caused the death of over 3 million individuals throughout the world. Such events are often unforeseeable in their extent and severity, and they exceed the ability of a community, a region or a country to adequately tackle the health needs of the population and in particular of the victims [173, 174].

Following the recent terrorist attacks in the United States, the potential extent of such catastrophic events has become clear. A state of alarm has spread throughout the world, and the possible developments of similar terrorist attacks in the future could seriously endanger the existence of humanity. Disasters and mass accidents require exceptional health intervention measures to be put into action. They require an impressive organizational apparatus and the implementation of precise strategies and closely connected and interdependent special civil protection and health measures.

These events can be divided into the following categories:

1. cataclysm – both natural (earthquakes, monsoons, tornadoes) and man-made (nuclear accidents, accidental release of chemicals, aircraft crash, structural collapse of stadium)
2. armed conflicts – both on a large scale between nations and more insidious types of civil war within a nation
3. terrorist attacks – often linked to some of the abovementioned situations (release of chemicals or bacteriological agents or attacks on board aeroplanes or by means of aircraft destined to strike a certain target or indiscriminately strike the population).

These situations are not always foreseeable and are often difficult to identify. In the most recognized academic communities a crucial role is played by careful planning the health intervention and the use of models capable of reproducing the various disaster scenes for the simulation and implementation of the various strategies via the aid of information systems which are also useful for training and the assessment of the level and quality of learning. Research, analysis and data collection are the final aim to provide precise indications for improving the interventions of prevention and treatment of trauma patients. The delivery of effective trauma care requires a complex system needing trained practitioners with specific expertise and skills, availability of diagnostic and therapeutic resources, and readily available specialty care [175].

Rusnak et al [176] reported relations between health outcomes and implementation of individual recommendations of the guidelines in trauma patients (405 patients included from 5 available Austrian hospitals). The analysis focused on the compliance of treatment modalities to TBI guidelines recommendations. Compliance was evaluated based on scores developed specifically for this purpose. To evaluate the relations between the TBI guidelines compliance and outcomes, the estimation of odds ratios was computed using multiple as well as logistic regression with age, ISS and initial GCS used to control confounding.

The study produced the following results. The option on prehospital resuscitation was followed in 84%, the guideline on early resuscitation was followed in 79%. The guideline on intracranial pressure treatment threshold was the most closely followed one (89%). The option on cerebral perfusion pressure was followed in less than 30% of patients. Only the scores on resuscitation of blood pressure and oxygenation and on cerebral perfusion pressure were positively and statistically significantly related to ICU survival.

Positive relations were also found for adherence to the recommendations on

the type of monitoring, hyperventilation (guideline), prophylactic use of anti-seizure drugs, and the total of scores. The other recommendations were negatively related to ICU survival, but computed odds ratios were statistically not significant. Analysis of relations between compliance scores and length of ICU and hospital stay in survivors showed that adherence to the recommendations on type of monitoring was related to a reduction in length of stay in the ICU and hospital, adherence to the hyperventilation guideline was related to shortened ICU stay, but increased hospital stay, and adherence to the guideline on mannitol was related to reduced days in hospital, but not to days in the ICU. Implementing the standard on corticosteroid use was related to a reduction in days both in hospital and the ICU. Using the standard on prophylactic use of anti-seizure drugs was related to a reduction in ICU days. If all the recommendations were closely followed an increase of days in ICU would be observed, while the length of stay in hospital would be reduced.

The authors concluded that the relatively strong relation between initial resuscitation in the hospital and ICU survival provides a firm basis for future efforts of emergency teams. The positive influence of some of the recommendations on reduction in ICU or hospital days may provide economic incentives to promote guidelines implementation [176].

Severe brain injuries, most often occurring in young subjects, are a major source of lost work years. These injuries are medical and surgical emergencies. Prehospital management of severe brain injuries requires intubation and mechanical ventilation aimed at normal arterial carbon dioxide pressure.

Signs of transtentorial herniation include uni- or bilateral mydriasis and require immediate perfusion of 20% mannitol or hypertonic sodium chloride. Neurological disorders after head injury justify emergency cerebral computed tomography. The presence of a mass syndrome or signs of transtentorial herniation are in principle indications for surgery. Specialized hospital management is essential.

In the case of refractory intracranial hypertension, the cerebral perfusion pressure and osmotherapy should be adapted to the volume of the cerebral contusion. The use of deep hypothermia and barbiturates should be minimized as much as possible. Magnetic resonance imaging makes it possible to identify the cerebral lesions [177].

Radiology Resources. Chest radiographs are frequently obtained as a complement to physical examination of critically ill patients. There are two different options regarding the utility of chest radiograph in the ICU: chest radiographs should be requested based on indication only, specifically there is a sound reason to obtain a film, a so-called 'on demand'; alternatively, chest radiographs should be obtained routinely everyday without any specific reason to do so (a so-called 'daily routine'). Favouring the latter strategy produces the high prevalence of pathological findings on chest radiographs in ICU patients [178].

Presently, the consensus of the American College of Radiology Expert Panel is that daily routine radiographs are indicated in patients with acute cardiopulmonary dysfunction and those receiving mechanical ventilation [179]. Graat et al [180]

demonstrate that daily routine chest radiograph hardly ever reveal potential abnormalities and seldom result in a change in therapy.

Neuroimaging is essential in the treatment of cerebral nervous system disorders or in patients in the ICU with deterioration of their neurological function. Leading clinical symptoms are acute neurological deficits with different stages of hemisymptomatology, primary or progressing loss of consciousness or vigilance deficit, focal or generalized seizures, sometimes combined with an acute respiratory or circulatory insufficiency. The resulting questions can be summarized in those of intracranial-space-occupying haemorrhage, acute infarction; and signs for reduced cerebral blood flow, cerebrovascular vasospasm, or intracranial mass. Recent evolutions in imaging have contributed to an increase in diagnostic sensitivity and specificity along with reduced side effects. Müller-Forell and Engelhard illustrate typical and atypical differential diagnoses, with some emphasis on traumatic brain injury [181].

Rapid Response Team (RRT): An Old Concept vs a New Challenge. Rapid response teams (RRTs) are becoming prevalent in healthcare organizations across the world due to a large campaign by the Institute for Health Care Improvement. Numerous hospitals are working with critical care teams to quickly implement an RRT to improve patient safety and clinical outcome [182].

RRT positions ICU nurses to be the clinical experts that are called to the patient's bedside to collaborate and confirm the deteriorating condition of the patient. Floor nurses are encouraged to utilize the expertise of ICU nurses without the threat of disrespect or embarrassment. This type of collaboration may bring a positive culture change between floor and ICU nursing. Attitudes, staffing issues and financial constraints within the ICU may impact start-up implementation of an RRT.

On many occasions staff reported more than one reason for activating an RRT: staff concerned about patients (50%); change in respiratory status (45%); change in mental status (24%); change in heart rate/rhythm (14%); and change in blood pressure (12%). A summary of benefits include: improved patient safety, decreased length of stay, decreased code blue (equivalent of code red in the Italian health system), decreased transfers to the ICU, increased nurse awareness and identification of signs and symptoms leading to patient deterioration, decreased mortality and morbidity, increased physician satisfaction with nurses, increased patient satisfaction, and increased nurse job satisfaction.

Jones et al [182] assessed the characteristics of patients who died in a teaching hospital and the role of the medical emergency team (MET) in their end-of-life care. This was a retrospective analysis of 105 deaths over the month of May 2005 by a blinded investigator, who documented patient age, parent hospital unit, comorbidities, presence and timing of not-for-resuscitation (NFR) designation, and presence and timing of first MET review.

The authors analysed differences between medical versus surgical patients, NFR versus non-NFR patients, and MET-reviewed versus non-MET-reviewed patients. Of the 105 patients who died, 80 were medical patients and 25 were surgical

patients. Five patients were not designated NFR at the time of death, and three of these had antecedent MET criteria in the 24 hours before death. Of the 100 patients who were designated NFR at the time of death, 35 received a MET call during their admission. Of the 35 MET calls, 10 occurred on the same day as the patient's death, and 12 on the same day as the NFR designation. Documentation of NFR status occurred later in the admission for patients who received a MET call than for those who did not receive a MET call (mean $\pm$ SD, 13.3 $\pm$ 16.1 versus 5.3 $\pm$ 10.8 days after admission; $p=0.003$). Hypotension, hypoxia and tachypnoea were the most common MET triggers, and pulmonary oedema, pneumonia and acute coronary syndromes were the most common reasons for the deterioration in the patient's condition. Following the MET review, patients were admitted to the ICU and newly classified as NFR in 15 and nine of the 35 MET calls, respectively.

Jones et al [182] concluded that most patients who died were designated NFR at the time of death. A third of these patients were seen by the MET before death. In about 10% of cases, the MET participated in the decision to designate the patient NFR.

Sedation and analgesia in intensive care. Sedative, analgesic and/or neuromuscular blocking agents are commonly used in critical care. In one study, physicians prescribed up to 23 different agents, and nurses typically administered fewer than half the prescribed dosage [183]. Prescription and administration patterns may differ primarily because of the difficulty in differentiating anxiety, pain and delirium in intubated patients who are also cognitively impaired. The stress response to critical illness can have many deleterious effects.

Appropriate use of sedation and analgesia can attenuate the stress response, alleviate pain and anxiety, and improve compliance with care. Agitation responds best to anxiolytic drugs; pain is best relieved by analgesics [184]. Although clinical guidelines commonly assist decision making, improve quality of care, assist in quality assurance programmes, and control health care costs, clinical guidelines are not without controversy and are often disregarded by clinicians [185].

A combination of these drugs can act synergistically, because most analgesics provide some degree of sedation. In select cases, neuromuscular blocking agents are required, but they should not be used without concomitant sedation and analgesia. Use of agents needs to be tailored to the needs of individual patients; indications, anticipated length of need, and underlying organ system derangements are important considerations. It is clear that much remains to be learned about optimizing sedation and analgesia in critically ill patients. Better methods for assessing patients for adequacy of sedation and analgesia are needed.

Objective monitors such as the bispectral index may prove to be useful, although more data are needed before widespread use of devices such as these can be recommended. Newer drugs with lesser tendencies toward accumulation (e.g. remifentanyl, dexmedetomidine) may also find a place if evidence of improvements in patient outcomes is demonstrated. Perhaps more importantly, however, improvements in strategies for administering sedatives and analgesics must be investigated. Sedation protocols such as nursing-directed protocols or daily sedative

interruption must be further studied so that improvements of such existing protocols, as well as development of new sedation strategies, can take place.

Payen et al [186] conducted a patient-based survey of practices to fully describe the assessment and the management of pain and sedation of a large cohort of mechanically ventilated patients during their first week of ICU stay. A total of 1,381 adult patients were included in a prospective, observational study in 44 ICUs in France. Pain and sedation assessment, analgesic and sedative use, and analgesic management during procedural pain were collected on days 2, 4, and 6 of the ICU stay. The observed rates of assessment on day 2 for sedation (43%) and analgesia (42%) were significantly lower than that of use of sedatives (72%) and opioids (90%), also noted on days 4 and 6. The use of protocols/guidelines for sedation/analgesia in the ICU reduced the proportion of patients who were treated, although not evaluated. A large proportion of assessed patients were in a deep state of sedation (40-50%). Minor changes in the dosages of the main prescribed agents for sedation (midazolam, propofol) and analgesia (sufentanil, fentanyl, morphine, remifentanil) were found across 6 days of the patient's ICU stay. Procedural pain was specifically managed for less than 25% of patients; during those procedures, the proportion of patients with pain significantly increased from the baseline pain evaluation.

The authors concluded that excessively deep states of sedation and a lack of analgesia during painful procedures must be prevented. To facilitate systematic pain and sedation assessment and to adjust daily drug dosages accordingly, it seems crucial to promote educational programmes and the elaboration of protocols/guidelines in the ICU.

Sedation of the critically ill patient has several components including hypnosis and analgesia. Hypnotic-based sedation (HBS), where midazolam and/or propofol are used, with morphine or another analgesic added as needed, has been common. The advent of remifentanil has allowed greater use of analgesia-based sedation (ABS) where relief of discomfort from the tracheal tube or pain are the important objectives, and hypnosis is given as necessary.

Parker et al [187] compared HBS and ABS (remifentanil-based sedation) within a general ICU. During the first study period of 12 weeks, 111 patients received HBS. After the development of new guidelines for the use of remifentanil in the ICU, a second 12 week study period used an analgesia-based regimen, with hypnotics added only if needed. In the study results 96 patients received ABS, and 79 received remifentanil. It was possible to manage 29 (37%) of the patients receiving remifentanil without the use of supplementary hypnotic agents. In the remaining 63% the use of remifentanil was associated with a reduction in the amount and duration of propofol used. Significantly more patients receiving ABS had satisfactory levels of sedation during synchronized intermittent mandatory ventilation (19 [2.55] vs 50 [14.83], $p < 0.001$). Parker et al [187] concluded that the use of ABS allowed patients to be managed more comfortably, either without a hypnotic drug or with less hypnotic drug, than using conventional HBS.

Sepsis Definitions, EGDT, Implementations of Bundles and Quality of Indicators. Consensus on definitions of infections that can be used in clinical trials in patients with sepsis remains a critical point. Infection is a key component of the definitions of sepsis, yet there is currently no agreement on the definitions that should be used to identify specific infections in patients with sepsis. Agreeing on a set of valid definitions that can be easily implemented as part of a clinical trial protocol would facilitate patient selection, help classify patients into prospectively defined infection categories, and therefore greatly reduce variability between treatment groups.

Consensus definitions of infection were developed for the six most frequent causes of infections in septic patients: pneumonia, blood stream infections (including infective endocarditis), intravascular catheter-related sepsis, intra-abdominal infections, urosepsis, and surgical wound infections. Definitions of the common sites of infection associated with sepsis in critically ill patients represent a gold standard. Use of these definitions in clinical trials should help improve the quality of clinical research in this field [188].

Sepsis as a disease has received renewed interests since recent publications of a revised clinical definition and crucial clinical trials showing the benefits of early goal-directed resuscitation, recombinant human activated protein C, and low-dose corticosteroids. The epidemiology of sepsis has also been further examined. Management guidelines and international quality improvement efforts have been developed targeting increased disease identification, clinician education, and optimal patient care with the result of decreasing patient mortality. The evidence suggests that early recognition and early intervention are most important in affecting outcome.

The rationale for therapeutic targets in sepsis has arisen from the concept of pathogenesis. In a review of the management of sepsis, Cinel and Dellinger [189] focus on recent advances in pathogenesis of sepsis that can aid in management of sepsis patients. Recent findings show that cellular survival in sepsis is related to the magnitude of the stimulus, the stage of the cell cycle and the type of microbe. While phenotypic modification of the endothelium (pro-coagulant and pro-adhesive properties, increased endothelial permeability, endothelial apoptosis and changes in vasomotor properties) leads to vasoplegia as a direct correlate to septic shock mortality, phenotypic changes in the epithelium cause activation of the virulence of the opportunistic pathogens and loss of mucosal barrier function, the latter causing a vicious circle in severe sepsis. Early identification of sepsis with protocolized screening, triggering evidence-based protocolized care, is anticipated to reduce sepsis morbidity and mortality.

Current treatment of sepsis includes early antibiotic therapy, early aggressive goal-directed resuscitation targeting tissue hypoperfusion, steroids (for refractory shock), activated protein C (for high risk of death) and maintaining support of organ systems. A better understanding of the pathogenesis of sepsis has led to specific proven management tools that are likely to improve clinical outcome once incorporated into protocolized care [189].

Early goal-directed therapy (EGDT) was successful in reducing mortality from septic shock in a single-centre trial. However, implementation of EGDT faces

several barriers, including perceived costs and logistic difficulties. Huang et al [190] conducted a decision analysis to explore the potential costs and consequences of EGDT implementation. Estimates of effectiveness and resource use were based on data from the original trial and published sources. Implementation costs and lifetime projections were modelled from published sources and tested in sensitivity analyses. The hospital team generate incremental cost-effectiveness ratios from the hospital (short-term) and US societal (lifetime) perspectives, excluding non health-care costs, and by applying a 3% annual discount. The study simulated an average US emergency department, with a total of 1,000 simulation cohorts ($n=263$ for each cohort) of adult patients with severe sepsis/septic shock. The interventions included EGDT under three alternative implementation strategies: emergency department-based, mobile ICU team, and ICU-based (after emergency department transfer).

For an average emergency department, the authors estimated 91 cases per year, start-up costs from \$12,973 (ICU-based) to \$26,952 (emergency department-based), and annual outlay of \$100,113. EGDT reduced length of stay such that net hospital costs fell approximately 22.9% (\$8,413–\$8,978). EGDT implementation had a 99.4% to 99.8% probability of being dominant (saved lives and costs) from the hospital perspective, and cost from \$2,749 (intensive care unit-based) to \$7,019 (emergency department-based) per quality-adjusted life-year with 96.7% to 97.7% probability of being <\$20,000 per quality-adjusted life-year from the societal perspective. The ICU-based strategy was the least expensive, because of lower start-up costs, but also the least effective, because of implementation delay, and all three strategies had similar cost-effectiveness ratios. Sensitivity analyses showed these estimates to be particularly sensitive to the effect of EGDT on mortality and intensive care unit length of stay, but insensitive to other variables.

Huang et al concluded that EGDT has important start-up costs, and modest delivery costs, but assuming LOS and mortality are reduced, EGDT can be cost-saving to the hospital and associated with favourable lifetime cost-effectiveness projections [190].

Despite abundant experimental studies of biomarker patterns in early severe sepsis and septic shock, human data are few. Furthermore, the impact of the severity of global tissue hypoxia resulting from resuscitative strategies on these early biomarker patterns remains unknown. The temporal patterns of IL-1 receptor antagonist, intercellular adhesion molecule-1, TNF- α , caspase-3, and IL-8 were serially examined over the first 72 h of hospitalization after early haemodynamic optimization strategies of early goal-directed vs. standard therapy for severe sepsis and septic shock patients. The relationship of these biomarker patterns to each haemodynamic optimization strategy, severity of global tissue hypoxia (reflected by lactate and central venous oxygen saturation), organ dysfunction, and mortality were examined.

Abnormal biomarker levels were present upon hospital presentation and modulated to distinct patterns within 3 h based on the haemodynamic optimization strategy. The temporal expression of these patterns over 72 h was significantly associated with the severity of global tissue hypoxia, organ dysfunction, and mortality.

Rivers et al conclude that in early severe sepsis and septic shock, within the first 3 h of hospital presentation, distinct biomarker patterns emerge in response to haemodynamic optimization strategies. A significant association exists between temporal biomarker patterns in the first 72 h, severity of global tissue hypoxia, organ dysfunction, and mortality. These findings identify global tissue hypoxia as an important contributor to the early inflammatory response and support the role of haemodynamic optimization in supplementing other established therapies during this diagnostic and therapeutic “window of opportunity” [191].

Nguyen et al [192] examined the outcome implications of implementing a severe sepsis bundle in a clinical governance emergency department as a quality indicator set with feedback to modify physician behaviour related to the early management of severe sepsis and septic shock. A two-year prospective observational cohort study was conducted in a university hospital. The study enrolled 330 patients presenting to the emergency department who met the criteria for severe sepsis or septic shock.

Five quality indicators comprised the bundle for severe sepsis management in the emergency department: (a) initiate central venous pressure (CVP)/central venous oxygen saturation (SCVO₂) monitoring within 2 h; (b) administer broad-spectrum antibiotics within 4 h; (c) complete early goal-directed therapy at 6 h; (d) administer corticosteroids if the patient is on vasopressor or if adrenal insufficiency is suspected; and (e) monitor for lactate clearance. Patients had a mean age of 63.8±18.5 years, APACHE II score 29.6±10.6, emergency department length of stay 8.5±4.4 h, hospital length of stay 11.3±12.9 days, and in-hospital mortality 35.2%. Bundle compliance increased from zero to 51.2% at the end of the study period. During the emergency department stay, patients with the bundle completed received more CVP/SCVO₂ monitoring (100.0 vs. 64.8%, $p<0.01$), more antibiotics (100.0 vs. 89.7%, $p=0.04$), and more corticosteroid (29.9 vs. 16.2%, $p=0.01$) compared with patients with the bundle not completed.

In a multivariate regression analysis including the five quality indicators, completion of early goal-directed therapy was significantly associated with decreased mortality (odds ratio, 0.36; 95% CI, 0.17–0.79; $p=0.01$). In-hospital mortality was less in patients with the bundle completed compared with patients with the bundle not completed (20.8 vs. 39.5%, $p<0.01$). Nguyen et al concluded that implementation of a severe sepsis bundle using a quality improvement feedback to modify physician behaviour in the emergency department setting was feasible and was associated with decreased in-hospital mortality [192].

Sepsis is associated with increased morbidity, mortality, and costs of care. Although several therapies improve outcomes in patients with sepsis, rigorously developed measures to evaluate quality of sepsis care in the ICU are lacking.

Berenholtz et al [193] selected an initial set of candidate measures, and in 2003–2004 an interdisciplinary panel reviewed the literature and used a modified nominal group technique to identify interventions that improve outcomes of patients with sepsis in the ICU. Design specifications or explicit definitions for each candidate measure were developed. Ten potential measures were identified: vancomycin administration, time to vancomycin initiation, broad-spectrum antibiotic

administration, time to broad-spectrum antibiotic initiation, blood culture collection, steroid administration, corticotropin stimulation test administration, activated protein C eligibility assessment, activated protein C administration, and vancomycin discontinuation. The authors [193] concluded that the identification of potential measures of quality of care for patients with sepsis can help caregivers to focus on evidence-based interventions which improve mortality and help to evaluate their current performance. Further work is needed to evaluate the feasibility and validity of the measures.

Steroids and Adrenal Insufficiency. Adrenal insufficiency is being diagnosed with increasing frequency in critically ill patients. There exists, however, much controversy in the literature as to the nature of this entity, including its pathophysiology, epidemiology, diagnosis and treatment. A review performed by Marik [194] summarizes our current understanding of the causes and consequences of adrenal insufficiency in critically ill patients.

Activation of the hypothalamic-pituitary-adrenal axis with the production of cortisol is a fundamental component of the stress response and is essential for survival of the host. Dysfunction of the hypothalamic-pituitary-adrenal axis with decreased glucocorticoid activity is being increasingly recognized in critically ill patients, particularly those with sepsis. This condition is best referred to as 'critical illness-related corticosteroid insufficiency'. Critical illness-related corticosteroid insufficiency may occur due to dysfunction at any point in the hypothalamic-pituitary-adrenal axis including tissue glucocorticoid resistance. Critical illness-related corticosteroid insufficiency leads to an exaggerated proinflammatory response with increased tissue injury and organ dysfunction. Marik [194] concluded that critical illness-related corticosteroid insufficiency is common in critically ill patients, particularly those with sepsis. Supplemental corticosteroids may restore the balance between the pro- and anti-inflammatory mediators in patients with severe sepsis, septic shock and ARDS, and thereby improve the outcome of patients with these conditions.

Opert et al [195] reported that low-dose hydrocortisone infusion (about 300 mg/day) improves shock reversal and reduces IL-6 levels, with the haemodynamic effects, but not the immune effects, being more pronounced in non-responders to the 250- μ g short adrenocorticotrophic hormone stimulation test. Siraux et al [196] showed that low-dose (1 μ g) adrenocorticotrophic hormone stimulation test could identify a subgroup of septic shock patients with inadequate adrenal reserve who have worse outcome and would have been missed by the high-dose (250 μ g) test. In conclusion, the current evidence shows improved mortality with steroid use in non-responders to the high-dose test. It remains to be seen whether the subgroup identified by the low-dose test will also see improved mortality with steroids.

Selective Digestive Decontamination (SDD). SDD is the only evidence-based manoeuvre that prevents infection and mortality in the critically ill. The target microorganisms of SDD include the "normal" PPMs including *Streptococcus pneumoniae* and Methicillin-sensitive *Staphylococcus aureus* (MSSA) and the "abnor-

mal” AGNB, including *Klebsiella*, *Acinetobacter*, and *Pseudomonas* species. Methicillin-resistant *S. aureus* (MRSA), by design, is not covered by the original protocol of SDD, and hence, seven randomized trials conducted in an ICU where MRSA was endemic at the time of the study, showed a trend towards higher MRSA infection rates in patients receiving SDD [197]. These observations suggest that the parenteral and enteral antimicrobials of the SDD protocol, i.e. cefotaxime, polymyxin, tobramycin, and amphotericin B, select and promote MRSA. Under these circumstances, SDD requires the addition of oropharyngeal and intestinal vancomycin. Two RCTs show that the addition of vancomycin to SDD is an effective and safe manoeuvre [198].

The Cochrane Library meta-analysis [199] – the only one that includes the first RCT on antimicrobial resistance [200] – reports that SDD does not lead to resistance amongst AGNB but, even better, the addition of enteral polymyxin/tobramycin to the parenteral antimicrobials reduces resistance compared with the parenteral antibiotics only. This is in line with previous RCTs demonstrating that enteral antimicrobials control extended spectrum β -lactamases producing *Klebsiella* [201]. Reports claiming resistance are invariably of low evidence including before-after studies [202]. SDD implemented in two American ICUs with endemic vancomycin resistant enterococci (VRE) did not lead to an increased number of VRE infections [203]. VRE did not emerge in any of the RCTs using enteral vancomycin [204].

Antimicrobial resistance, being a long-term issue, has been evaluated in eight SDD studies monitoring antimicrobial resistance between 2 and 7 years, and bacterial resistance with SDD has not been a clinical problem [205].

In agreement with original experience [206, 207], updating reports [208-210] have confirmed that SDD is a prophylactic strategy whose objective is to reduce the incidence of infections, mainly mechanical ventilation associated pneumonia in patients who require intensive care, preventing or eradicating the oropharyngeal and gastrointestinal carrier state of potentially pathogenic microorganisms.

Taylor et al [211] reviewed 54 RCTs and nine meta-analyses evaluating SDD. Thirty eight RCTs showed a significant reduction in the infections and four in mortality. All the meta-analyses show a significant reduction of the infections and five out of the nine meta-analyses report a significant reduction in mortality. Thus, five patients from the ICU with SDD must be treated to prevent pneumonia and 12 patients from the ICU should be treated to prevent one death. The data that show benefit of the SDD on mortality have an evidence grade 1 or recommendation grade A (supported by at least two level 1 investigations). The aim of the review was to explain the pathogenesis of infections in critical patients, describe selective digestive decontamination, analyze the evidence available on its efficacy and the potential adverse effects and discuss the reasons published by the experts who advise against the use of SDD, even though it is recognized as the best intervention evaluated in ICUs to reduce morbidity and mortality of the infections [211].

Remarks and conclusions

Improving care is a real challenge in the ICU. Critical care has always been a horizontal specialty in a vertical world [212].

Many in healthcare today are interested in defining “quality improvement”. Batalden and Davidoff [213] proposed defining it as the combined and unceasing efforts of everyone – healthcare professionals, patients and their families, researchers, payers, planners and educators – to make the changes that will lead to better patient outcomes (health), better system performance (care) and better professional development. This definition arises from their conviction that healthcare will not realize its full potential unless change making becomes an intrinsic part of everyone’s job, every day, in all parts of the system. Defined in this way, improvement involves a substantial shift in our idea of the work of healthcare, a challenging task that can benefit from the use of a wide variety of tools and methods.

Performance, patient safety, risk management and audit are the central pillars for increasing the quality of care in ICU patients. Communication is the platform for reaching a consensus in a very crowded and unique multidisciplinary and multi-professional environment so as to improve quality of care, patient satisfaction and ultimately patient survival.

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