A. Gullo (Ed)

A.P.I.C.E.

Anaesthesia Pain Intensive Care and Emergency Medicine

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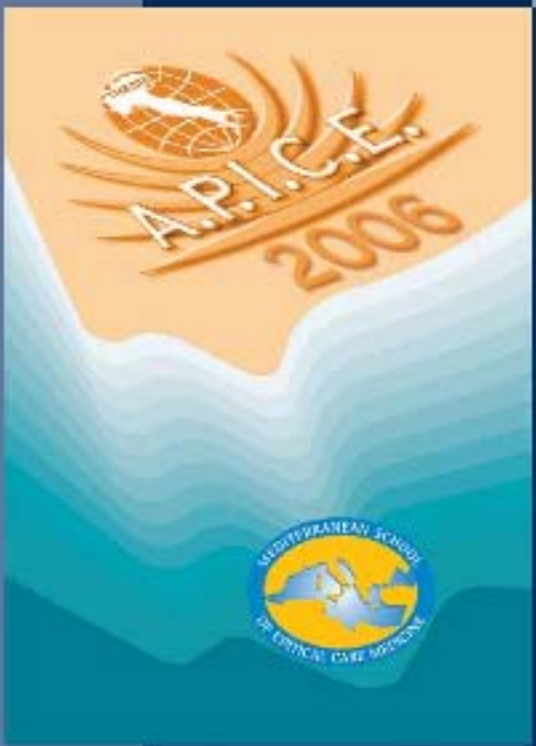

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Proceedings of the
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List of Abbreviations

ΔP	Driving Pressure
ΔP/ΔV	Elastance
ΔPoes	Changes in Oesophageal Pressure
ΔV	Change in the Volume
ΔV/ΔP	Compliance
ΔV’	Resistance
ACE	Angiotensin Converting Enzyme
ACGME	Accreditation Council of Graduate Medical Education
ADH	Antidiuretic Hormone
AG	Anion Gap
AGNB	Aerobic Gram-Negative Bacteria
AHA	American Heart Association
AHI	Apnoea/Hypopnoea Index
Aix	Augmentation Index
ALI	Acute Lung Injury
ANH	Acute Normovolaemic Haemodilution
AOP	Apnoea Of Prematurity
API	Application Interface
APTT	Activated Partial Thromboplastin Time
ARC	Australian Resuscitation Council
ARDS	Acute Respiratory Distress Syndrome
ARF	Acute Renal Failure
AS	Arterial Stiffness
ASA	American Society of Anesthesiologists
ASK1	Apoptosis-Signalling Kinase 1
ASRA	American Society of Regional Anesthesia
Asys	Area Under the Systolic Portion of the Pressure Wave
AT-III	Antithrombin-III
BAL	Bio Artificial Liver
BDZ	Benzodiazepines
BE	Base-Excess
BECAT	Taylor E. Booth Engineering Center for Advanced Technology
BiPAP	Bilevel Positive Airway Pressure
BIS	Bispectral Index

BP	Blood Pressure
C(p)	Compliance Corrected for Arterial Pressure
CAVH	Continuous Arterio-Venous Haemofiltration
CAVHD	Continuous Arterio-Venous Haemodiafiltration
CBF	Cerebral Blood Flow
CCE	Cardiac Cycle Efficiency
CFI	Cardiac Function Index
CHDF	Continuous Haemodiafiltration
CISV	Connecticut Institute for Supercomputing and Visualization
CNS	Central Nervous System
CO	Cardiac Output
COP	Colloid Oncotic Pressure
COPD	Chronic Obstructive Pulmonary Disease
CPAP	Continuous Positive Airway Pressure
CPFA	Coupled Plasmafiltration-Adsorption
CPNBs	Continuous Peripheral Nerve Blocks
CPP	Coronary Perfusion Pressure
CPR	Cardiopulmonary Resuscitation
CRM	Crew Resource Management
CRRT	Continuous Renal Replacement Therapy
CT	Computed Tomography
CVP	Central Venous Pressure
CVVH	Continuous Veno-Venous Haemofiltration
CVVHD	Continuous Veno-Venous Haemodiafiltration
DD	Death Domain
dDown	Delta Down
DI	Desaturation Index
DIC	Disseminated Intravascular Coagulopathy
DO_2	O_2-Delivery
dp/dt	Pressure Variations Over Time
DVT	Deep Vein Thrombosis
ECF	Extracellular Fluids
EELV	End Expiratory Lung Volume
EF%	Ejection Fraction
EFL	Expiratory Flow Limitation
ELAD	Extracorporeal Liver Assisted Device
ELBWI	Extremely Low Birth Weight Infants
EMS	Emergency Medical Services
ER	Endoplasmic Reticulum
ERC	European Resuscitation Council
ESRD	End Stage Renal Disease
EUO	Effective Urine Output

EVLW	Extra-Vascular Lung Water
FDA	American Food and Drug Administration
FiO_2	Fraction of Inspired Oxygen
FOT	Forced Oscillation Technique
FRC	Functional Residual Capacity
GABA	Gamma-Amino Butyric Acid
GEDV	Global End-Diastolic Volume
GFR	Glomerular Filtration Rate
GIVITI	Gruppo Italiano per la Valutazione degli Interventi in Terapia Intensiva
GP	General Practitioner
HD	Haemodialysis
HES	Hydroxyethyl Starch
HIT	Heparin-Induced Thrombocytopenia
HIV	Human Immunodeficiency Virus
HR	Heart Rate
HREs	Hypoxia-Responsive Elements
HS	Hyperosmolar Syndromes
HSFC	Heart and Stroke Foundation of Canada
IC	Invasive Candidiasis
ICF	Intracellular Fluids
ICH	Intracerebral Haemorrhage
ICP	Intracranial Pressure
ICU	Intensive Care Unit
IHCA	In-hospital cardiac arrest
IHD	Intermittent Haemodialysis
IL-1R	Interleukin-1 Receptor
ILCOR	International Liaison Committee on Resuscitation
INR	International Normalised Ratio
IRAKs	IL-1R-Associated Protein Kinases
IRES	Internal Ribosomal Entry Sites
ISS	Interstitial Space
ITBV	Intrathoracic Blood Volume
ITEB	Information Technology Engineering Building
IVS	Intravascular Space
JTTR	Joint Trauma Theatre Registry
KIA	Killed In Action
LIP	Lower Inflexion Point
LMWH	Low-Molecular Weight Heparin
LOD	Logistic Organ Dysfunction
LPS	Lipopolysaccharide
LV	Left Ventricle
MA	Metabolic Acidosis

MAPK	Mitogen-Activated Protein Kinase
MARS	Molecular Absorbent Recirculating System
MAS	Meconium Aspiration Syndrome
MDRD	Modification of Diet in Renal Disease
MEFV	Maximal Expiratory Flow-Volume
MET	Medical Emergency Team
$MgSO_4$	Magnesium Sulphate
MIF	Migration Inhibitory Factor
MLAC	Minimum Local Anaesthetic Concentration
MMPs	Matrix Metalloproteinases
MO	Morbid Obesity
MOCA	Maintenance of Continued Accreditation
MODS	Multiple Organ Dysfunction Syndrome
MOF	Multiple Organ Failure
MOSF	Multiple Organ System Failure
MRDH	Modified Rapid Deployment Hemostat
MRI	Magnetic Resonance Imaging
MRSA	Methicillin-Resistant Staphilococcus Aureus
MSSA	Methicillin-Sensitive Staphilococcus Aureus
MVT	Monomorphic Ventricular Tachycardia
NAC	N-Acetylcysteine
NEP	Negative Expiratory Pressure
NFL	Non Flow-Limited
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
NMDA	N-Methyl-D-Aspartatic acid
NPE	Neurogenic Pulmonary Oedema
NRCPR	National Registry of Cardiopulmonary Resuscitation
NRP	Neonatal Resuscitation Program
NS	Normal Saline
NSG	Naso-Gastric Suction
OG	Osmolal Gap
OHCA	Out-of-Hospital Cardiac Arrest
OPS	Orthogonal Polarisation Spectral
OSAS	Obstructive Sleep Apnoea Syndromes
P	Pressure
PA	Pulmonary Artery
PAC	Pulmonary Artery Catheter
PAN	Polyacrylnitrile
PaO	Pressure at the Airway Opening
PaO_2	Partial Oxygen Pressure In Arterial Blood
PAOP	Pulmonary Artery Occlusion Pressure

PAP	Plasma Adsorption Perfusion
PARs	Proteinase-Activated Receptors
PBEF	Pre–B-Cell Colony-Enhancing Factor
PCD	Programmed Cell Death
PCM	Pulse Contour Method
PCO_2	Carbon Dioxide Tension
PCWP	Pulmonary Capillary Wedge Pressure
PD	Peritoneal Dialysis
PEA	Pulseless Electrical Activity
PEEP	Positive End-Expiratory Pressure
PEEPi	Intrinsic Positive End-Expiratory Pressure
PERK	Protein Endoplasmic Reticulum Kinase
pHi	Intramucosal pH
PICU	Paediatric Intensive Care Units
Poes	Oesophageal Pressure
Posm calc	Calculated Osmolality
Posm meas	Measured Osmolality
Posm	Plasma Osmolality
PPCM	Peri-Partum Cardiomyopathy
PPM	Potentially Pathogenic Micro-organisms
PPV	Pulse Pressure Variation
$PslCO_2$	Predictive value of Sublingual PCO_2
P-V	Pressure-Volume Curve
PVT	Polymorphic Ventricular Tachycardia
PWA	Pulse Wave Analysis
QOL	Quality of Life
RAAS	Renin-Aldosterone-Angiotensin System
RAP	Right Atrial Pressure
RBC	Red Blood Cells
rFVIIa	Activated Recombinant Factor VII
RL	Ringer's Lactate
RNS	Reactive Nitrogen Species
ROS	Reactive Oxygen Species
ROSC	Return of Spontaneous Circulation
RRC	Residency Review Committee
RRT	Renal Replacement Therapy
RVEDV	Right Ventricular Enddiastolic Volume
RVP	Right Ventricular Pressure
SA	Spinal Anaesthesia
SCU	Slow Continuous Ultrafiltration
$ScvO_2$	Central Oxygen Venous Saturation
SDD	Selective Digestive Decontamination

SMR	Standard Mortality Ratio
SNS	Sympathetic Nervous System
SOFA	Sequential Organ Failure Assessment
SOP	Standard Operating Procedure
SPV	Systolic Pressure Variations
SV	Stroke Volume
SVR	Systemic Vascular Resistance
SVV	Stroke Volume Variation
t	Time
TBW	Total Body Water
TD	Thermodilution
TF	Tissue Factor
TGF-β	Latent Transforming Growth Factor
TIMPs	Tissue Inhibitors Of Metalloproteinases
TISS	Therapeutic Intervention Scoring System
TLRs	Toll-Like Receptors
TPN	Total Parenteral Nutrition
TRAF6	TNF Receptor-Associated Factor 6
TRRI-Surg	Trauma Readiness and Research Institute for Surgery
UConn	University of Connecticut
UIP	Upper Inflexion Point
US	Ultrasonography
V'-P	iso-volume relationships between flow and trans-pulmonary pressure
VAP	Ventilator Associated Pneumonia
VEGF	Vascular Endothelial Growth Factor
VF	Ventricular Fibrillation
VILI	Ventilator Induced Lung Injury
VT	Ventricular Tachycardia
WPW	Wolff-Parkinson-White syndrome
Zao	Aortic Impedance
ZEEP	Zero End-Expiratory Pressure

ETHICS

Chapter 1

Dying in the Intensive Care Unit

K. Hillman

"- and so drenched in sweat John fought his way to death through tortures indescribable."
Henry Handel Richardson: *The Fortunes of Richard Mahoney.*

In 2000 it was reported in *Time* magazine [1] that while 70% of Americans wanted to die at home, approximately 75% died in medical institutions and over 30% of those spent their last 10 days of life in an intensive care unit (ICU). Other studies have shown that approximately 50% of all deaths occur in the ICU [2]. Approximately 70% of Canadians now die in hospitals [2]. Not only is it not what people want, but as a result many of the families have faced financial hardship [3].

We spend about 50% of our health budget on patients who are in their last 6 months of life [4]. Given the choice, many of these patients would probably have cheerfully forgone the pain and suffering of major procedures if they had received more balanced information about their care.

How did this situation occur? Like many simple questions this one has complex answers. With increasing specialisation in medicine, there has also been fragmentation. The general practitioner (GP) would have delivered most health care before the Second World War; GPs now often serve as the first triage point for seriously ill patients on their journey into acute hospitals. There is pressure from families to do everything possible even if the family doctor suspects the patient is dying. Moreover, family physicians do not necessarily feel comfortable with dying patients; nor are they logistically able to provide time-consuming care to the dying patient at home. Because medical advances are reported on a daily basis, the GP does not necessarily know of the latest options available for medical care. It is easier to just call an ambulance. The dying patient is then triaged in the emergency department at the front door of the hospital. Emergency physicians or doctors of first contact usually see their role as resuscitating patients, not plucking them off the conveyor belt and letting them die. There may be potentially reversible aspects to their disease which require further tests and interventions.

Once in hospital, the patient often comes under the care of a single-organ specialist. While these doctors may have great skills in well-defined diseases, they often lack the skills and knowledge to understand the multi-system nature of serious illness. They feel out of their depth, and either they refer such patients electively to intensive care physicians or the patients are picked up by early warning systems for the seriously ill, such as the Medical Emergency Team (MET) concept [5, 6].

The conveyor belt then reaches its final destination, carrying the seriously ill, but often naturally dying, patient from home to the ICU.

The increasing tendency for the dying to be managed in the ICU has many drivers, including fear of litigation. Moreover, hospital specialists do not understand the limits of what the ICU can offer and so they often, out of ignorance, refer patients who are thought to be seriously ill to the ICU, whether or not there is any prospect of appropriate care. It is also easier for specialists to avoid difficult conversations with relatives and patients about dying and simply request admission to the ICU.

Whilst this is costing society enormous sums through increases in health bills, it is difficult for politicians and health administrators to restrict intensive care resources because it may result in potentially avoidable deaths and damaging publicity. It is easier to concentrate on easier targets, such as community and preventable health costs.

The problems are just beginning when dying patients are first admitted to the ICU. Not the least of them is the fact that the diagnosis of dying is difficult to make with certainty. Like death, dying is defined by a medical practitioner, and not by lawyers or ethics committees. There will always be uncertainty around dying, and intensive care physicians vary enormously in their practice. Withdrawing and withholding treatment after the diagnosis of dying is made usually results in death, and there is very wide variability in physicians' willingness to make these decisions, both between different countries and even between intensive medicine specialists within the same ICU.

Patients likely to benefit from care in the ICU include those with reversible or potentially reversible conditions; factors such as preceding chronic health status, preceding quality of life, physiological reserve, biological age, severity of the illness and anticipated disability must be taken into account. One of the problems with such concepts as frailty and futility is that these are difficult to measure and only become apparent as a result of a patient's failure to respond to maximum therapy.

One approach, therefore, in the face of uncertainty is to challenge the patient's physiology. We do this when the fluid status of the body is determined or by means of lung recruitment strategies. Often it is difficult to make a diagnosis of dying on admission to the ICU. One acceptable approach is to apply aggressive treatment for 24 h and then to rigorously assess the patient's response. If there is substantial improvement it may be appropriate to continue. If the patient is rapidly deteriorating in spite of maximum therapy and the other factors mentioned above are taken into account it may be reasonable to make a diagnosis of dying.

However, it can be frustrating to keep people alive for days or even weeks while they slowly fall apart despite maximum medical therapy. This can be difficult for healthcare workers directly involved in patient care as well as for relatives, to say nothing of the suffering endured by patients.

Every study shows that most people would not want to endure such an end to their life.

Intensive care has the potential to be able to deliver a death that can be regarded as "good", as defined by freedom from avoidable distress and suffering for patients,

families and carers, and that is also generally in accord with the patient's family's wishes and reasonably consistent with clinical, cultural and ethical standards [7].

While this sounds attractive it can be difficult to put into practice. The so-called four principles of medical ethics offer even less. They are autonomy, beneficence, nonmaleficence and distributive justice. Trying to apply these principles while making decisions about withdrawing and withholding treatment at an individual patient's bedside would, in theory, allow for almost any action or justification.

How do we make the diagnosis of dying and then make the decision to withhold and withdraw treatment? Dying is now the most common illness in ICUs, with over 20% of Americans dying in, or shortly after being in, an ICU [8]. Up to 90% of patients who now die in our ICUs die as a result of withdrawal of treatment [9]. And yet the doctors caring for patients in the ICU are systematically overoptimistic in their prognoses [10]. Nursing staff are often not formally included in the decision-making process [11, 12]. Under 5% of patients dying in the ICU have sufficient mental competence to make their own decisions [13].

Yet surrogates often fail to represent the patient's wishes. In fact, many of the families do not want to be involved in end-of-life decisions [14] and are left with high rates of anxiety and depression as a result of being burdened with making them [15].

Not surprisingly there is a wide range of end-of-life practices across countries and individuals [16], with little standardisation.

The approach in the United States of America puts an emphasis on the autonomy of the patient, with intensive care specialists posing the question "… What would you like us to do?" Posed with this question the answer is often inevitable: "We would like everything done", as relatives do not want to be seen to not care. In Australasia and Europe, in contrast, it is more common to put the inevitability of dying to relatives and highlight the cruelty and futility associated with further management, implying that this is a medical decision rather than one to burden relatives with. There is a difference between saying to relatives, "…The chances of recovery are slim" and telling them, "…There is a great risk that this person will remain neurologically devastated for the rest of their life" (S. Streat, personal communication).

At the same time, patients and their families state that their priorities include adequate pain and symptom control; avoiding inappropriate prolongation of dying; retaining a sense of control if possible; relieving the burden on the relatives of patients; and strengthening relationships with loved ones [17].

The principles of palliative care are well defined but apply mainly to patients dying of cancer. These patients are usually alert and co-operative and have months or even years to live. The principles to be applied in palliative care in the ICU are still being formulated. Patients in the ICU are usually unconscious, and the event precipitating their admission is often sudden and unexpected. We rely heavily on relatives for information about the patient's wishes, which may put an unfair burden on them. Moreover, community expectations about what modern medicine can offer are usually unrealistic. These can be reinforced by the impressive range of equipment in the ICU. Nevertheless, excellence in end-of-life care is as important

as excellence in maintaining tissue perfusion and should be the goal of every intensive care specialist [18].

Physicians working in intensive care need to be sensitive but honest. We need to seek consensus on withdrawing and withholding treatment when we think this appropriate, without necessarily asking for permission and putting the onus on relatives. They need to understand that we intend to withdraw active treatment without compromising care of the patient. We need to respect the sacredness of dying and the different attitudes and beliefs that various cultural groups in our community hold.

Some practical advice around the operational aspects of dying include turning the monitors off or turning them around so that the relatives focus on the patient and not on the physiological traces that they may have been looking at for weeks. We can ask the relatives to tell us a little about their loved one, explaining that we never had a chance to get to know them. We need to alleviate any guilt they feel and understand reactions such as anger as they gradually come to terms with the inevitability of the patient's death. Relatives should be advised to get adequate sleep and maintain their outside responsibilities; this is a way of relating to the relatives' own suffering and helping to deflect guilt feelings.

There are also practical issues after patients have died [19]. These include allowing the relatives to see the patient in the ICU after his or her death, and not in the morgue; removing all the lines, tubes and monitors; sitting the patient up slightly; washing and combing the hair; putting the patient's hands outside the sheets, especially if adornments such as a wedding ring can be displayed; drawing the curtains and allowing the relatives to spend as much time as they wish with the departed one. An envelope containing all the instructions and procedures that need to be followed after death should be prepared and handed to one of the close relatives. Finally, if possible, it is good to make contact with relatives at 6 months and 1 year after the patient's death, to ask how things are going and obtain feedback about the memories of the time they spent with their relatives in the ICU.

With an increasingly ageing population and pressures to overtreat every illness, curable or not, the specialty of intensive care is facing many challenges. Intensive care specialists need to lead discussions with our societies about realistic expectations of us and what we can and cannot deliver.

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LUNG

Chapter 2

Genetics and molecular biology in acute lung injury

R. Vaschetto, J.J. Haitsma, H. Zhang

Acute lung injury (ALI) is marked by compromised gas exchange following macrophage activation, surfactant dysfunction, and epithelial destruction. Activated macrophages release a myriad of cytokines, reactive oxygen and proteolytic enzymes, which in turn disrupt lung endothelium and epithelium. Together, these events lead to the key clinical manifestations, including immune cell infiltration, atelectasis, pulmonary oedema and, finally, respiratory failure.

The mortality rate varies between individuals who are initially classified with similar severity of their clinical symptoms; the ability to withstand the progression of lung injury might be explained in part by their genotypes. Gene–environment interactions are important in lung diseases, but numerous different environmental agents can induce common outcomes, so that common biological pathways may be controlling generalised responses to injury and repair. The relationships between individual exposure and individual risk are therefore very complex.

Genetic epidemiology

Common lung diseases are likely to be controlled by multiple genes with varying influences on the disease process [1]. This makes genetic analyses difficult; nonetheless, this task is becoming easier with the recent discovery of human genomic information, which has changed our concept of many diseases. For such complex diseases as ALI, gene–environment interactions are likely to be major factors in controlling individual susceptibility, and additional genomic information should be applicable to this condition.

The field of genetic epidemiology has much to offer us in our attempts to disentangle the effect of heritable variation and its contribution to susceptibility of sepsis and sepsis-associated ALI. Advances in the genetics of ALI—substantially aided by novel findings gleaned from well-designed genomic studies—have demonstrated striking differences in "high-risk" alleles in an ever-expanding list of candidate genes. The information gained from these studies will provide novel insights into the genetic basis for predisposition to the development of critical illness; findings derived from these and other efforts aimed at the identification of novel genetic modifiers of ALI, with a focus on vulnerable populations, will facilitate the development of new therapies to limit adverse effects of mechanical ventilation on the ALI and identify genetic markers that help direct other preven-

tative and therapeutic strategies in sepsis patients, and especially in those who are most at risk.

Pre–B-cell colony-enhancing factor (PBEF)

Recently, the novel ALI candidate gene *PBEF* was identified in animal (canine and murine) and human models of ALI, with validation by real-time PCR and immunohistochemistry. PBEF is also identified as a potential biomarker in ALI. Nonas et al. investigated whether common variants in the human *PBEF* gene might be associated with susceptibility to sepsis-associated ALI [2]. They recently reported direct DNA sequencing of the *PBEF* gene and identified 11 single nucleotide *PBEF* polymorphisms. Transversions of the promoter region of *PBEF* T-1001G and C-1543T showed the highest degree of representation in 12 subjects with ALI and were associated with an eight-fold risk of sepsis-associated ALI compared with that in healthy control subjects [3]. These results also suggest that genetically determined increased *PBEF* expression contributes to susceptibility to ALI [2].

NF-κB and Iκ-B

It is now recognised that the airway epithelium serves a number of essential functions within the respiratory tract, as part of the innate immune system. Many inflammatory cascades become activated within epithelial cells, and these intracellular signalling cascades generate inflammatory responses that aid in the elimination of infectious agents. However, they may also contribute to the development of respiratory disease. Of the many signalling cascades activated by airway epithelium in response to stimulation, NF-κB has been implicated as one of the most important for the regulation of inflammation. NF-κB becomes activated in response to cytokines, mitogens, physical and oxidative stress, infection and microbial products. Activity of NF-κB is tightly controlled by the inhibitory protein I-κB.

Selective expression of IκB kinases in airway epithelium results in NF-κB activation, inflammatory mediator production and neutrophilic lung inflammation [4]. Thus, airway epithelial NF-κB activation is sufficient to promote neutrophilic airway inflammation, implying that these cells are capable of inducing the expression of genes to initiate an inflammatory signalling cascade [4].

The airway epithelial cells play a prominent role in orchestrating the airway inflammatory response to LPS and suggest that NF-κB signalling in these cells is important for modulating innate immune responses to microbial products.

Everhart et al. compared the effects of a single dose of LPS stimulation and of a prolonged infusion of LPS stimulation on lung injury, using a selective inhibitor of I-κB kinase to block NF-κB activation [5]. Inhibition of the NF-κB pathway in vivo can attenuate LPS-induced lung injury.

Matrix metalloproteinases

It has been reported that matrix metalloproteinases (MMPs) increase during the course of ARDS; in particular, increased levels of MMP-2 and MMP-9 in the bronchoalveolar lavage fluid have been suggested to have a role in basement membrane disruption. MMP-2 is synthesised constitutively by mesenchymal cells, such as fibroblasts and endothelial and epithelial cells, whereas MMP-9 is produced mainly by inflammatory cells, such as monocytes/macrophages, neutrophils and eosinophils. MMPs are secreted in a latent form, which needs activation to exercise its catalytic activity. The activity of MMP is inhibited by specific inhibitors; the tissue inhibitors of metalloproteinases (TIMPs). MMP-2 is essentially inhibited by TIMP-2; and MMP-9 is inhibited by TIMP-1. Recently is has become apparent that the unbalanced MMP-9/TIMP-1 ratio will be involved in airway remodelling, leading to either short- or long-course ARDS, and that the MMP-9/TIMP-1 ratio could therefore be a predictive factor for the outcome of ARDS [6]. Interestingly, TIMP3 has been reported to inhibit TNF release. It has recently been demonstrated that the altered kinetics of ligand and receptor shedding enhances TNF signalling in *timp3*$^{-/-}$ mice. Physiologically, *timp3*$^{-/-}$ mice have an elevated susceptibility to LPS-induced mortality, indicating the important regulatory role of TIMPs in the innate immune system and suggesting a possible role in lung inflammation progression [7].

Migration inhibitory factor

Macrophage migration inhibitory factor (MIF) is a cytokine that is capable of activating T-cells and inducing pro-inflammatory cytokine in macrophages [8]. In patients with ARDS, MIF is present in the lungs and overrides the anti-inflammatory effects of glucocorticoids in a concentration-related fashion [9], suggesting that MIF may act as a mediator sustaining the pulmonary inflammatory response in ARDS and that an anti-MIF strategy might represent a novel therapeutic approach in ARDS [9]. These data suggest that overproduction of MIF in the lung during acute trauma could lead to neutrophilia that is refractory to suppression by both endogenous and therapeutic glucocorticoids. Clinical treatment with anti-MIF strategies may help reduce early neutrophil accumulation in ARDS and increase the effectiveness of glucocorticoid treatment.

Molecular mechanisms

Toll-like receptors

The first line of defence against microbial pathogens of the mammalian host is the recognition of molecular patterns by a set of germline-encoded receptors known as Toll-like receptors (TLRs) [10]. Since the discovery of TLR1 at least ten have been identified, and five have been linked to the recognition of specific pathogen-asso-

ciated ligands [11]. For example, TLR4 is crucial for lipopolysaccharide (LPS) recognition and transduces its signal across the cell membrane [12]. Based on their cytoplasmic domains, mammalian TLRs are also homologous to members of the interleukin-1 receptor (IL-1R) family. MyD88 is an adaptor protein that associates with the IL-1R protein by direct TLR–TLR domain interaction [13]. The death domain (DD) of MyD88, then, is recruited by a homotypic DD interaction, a family of IL-1R-associated protein kinases (IRAKs) [13, 14]. On IL-1 binding to the IL-1R, IRAK-1 is phosphorylated and dissociates from the receptor complex, associating with the signal transducer TNF receptor-associated factor 6 (TRAF6) [14]. TRAF6 then triggers downstream signalling pathways, which results in the activation of NF-κB and various stress kinases, such as c-Jun NH2-terminal kinase (JNK) and p38 mitogen-activated protein kinase (MAPK). This relatively simple cascade of MyD88→IRAK-1→TRAF6 functions in response to most, but not all, instances of TLR signalling [11].

P-Selectin in ALI

The accumulation of neutrophils in the lung is initially mediated through increased adhesion of neutrophils to endothelial cells of the inflamed pulmonary microvasculature, and this process requires the up-regulation of various adhesion molecules expressed on the surface of pulmonary endothelial cells, as well as circulating neutrophils. In 1994, Mulligan et al. have already reported that L-selectin plays a necessary part in tissue recruitment of neutrophils in neutrophil-dependent and oxygen radical-mediated lung injury [15]. In the case of neutrophil-independent lung injury, there appears to be no requirement for L-selectin [15]. Recently, Yiming et al. demonstrated that high tidal volume ventilation resulted in a modest increase in P-selectin expression in ex vivo blood-depleted lungs [16]. When whole blood was present the P-selectin expression was increased, suggesting that lung distension causes modest endothelial activation, followed by subsequent endothelial–inflammatory cell interactions, which augment P-selectin expression. Thus, interactions of circulating inflammatory cells with P-selectin are critical in determining proinflammatory endothelial activation during high-tidal-volume ventilation [16].

Coagulation in ALI

Alveolar fibrin deposition is an important feature of ALI/ARDS and pulmonary infection. The mechanisms that contribute to disturbed alveolar fibrin turnover are localised tissue factor-mediated thrombin generation and depression of bronchoalveolar urokinase plasminogen activator-mediated fibrinolysis, which is caused by the increase of plasminogen activator inhibitors [17]. These effects on pulmonary coagulation and fibrinolysis are regulated by various proinflammatory cytokines and are similar to those found in the intravascular spaces during severe systemic inflammation. Some studies also suggest that pulmonary coagulopathy is a feature of ventilator-induced lung injury (VILI) [17, 18].

Genetic predisposition could intensify the tendency to intravascular and intra-alveolar coagulation. Single nucleotide polymorphisms and single nucleotide polymorphism haplotypes of coagulation factor genes increase coagulation and impair anticoagulation and fibrinolysis, which could tip the balance in favour of coagulation. These polymorphisms could be associated with an increased risk of coagulation relative to anticoagulation/fibrinolysis in the vascular spaces and airspaces of the lung, thus increasing the risk of ALI in patients so affected [19].

PAR-1 in ALI

Thrombin can influence cell function through a group of cell surface receptors known as proteinase-activated receptors (PARs). There are four known PARs (PAR-1–4), and all are expressed by human lung epithelial cells [20]. As the main cellular mediators of potentially proinflammatory responses to coagulation proteases, PARs are well positioned to drive coagulation-induced inflammation.

Activation of latent transforming growth factor (TGF-β) by the vβ6 integrin is a critical step in the development of ALI. Recently Jenkins et al. showed that thrombin, and other agonists of PAR1, activates TGF-β in a vβ6 integrin-specific manner. This effect is PAR-1 specific, and intratracheal instillation of a PAR-1-specific peptide increased lung oedema during high tidal volume ventilation, while this effect is completely inhibited by a blocking antibody against the vb6 integrin. Furthermore, vβ6 integrin knock-out mice (*Itgb6*$^{-/-}$ mice) are also protected from ventilator-induced lung oedema [21]. These results suggest that PAR1-mediated enhancement of vβ6-dependent TGF-β activation could be one mechanism by which activation of the coagulation cascade contributes to the development of ALI [21].

TGF- ß in ALI

TGF-β is a multifunctional peptide capable of enhancing mesenchymal cell proliferation and extracellular matrix synthesis. TGF-β is the central mediator that initiates and terminates tissue repair and whose sustained production underlies the development of tissue fibrosis [22]. Expression levels of most of the known TGF-β-inducible genes are increased dramatically as early as 2 days after induction of bleomycin-induced lung injury [23]. TGF-β knockout mice differed from wild-type mice in higher survival rates and lower incidence rates for inflammation and pulmonary oedema in a model of ALI [24]. Pittet et al. demonstrated that mice lacking the integrin vβ6 (activating TGF-β) were completely protected from pulmonary oedema in a model of bleomycin-induced ALI [24]. Inhibition of TGF-β (pharmacologically) also protected wild-type mice from pulmonary oedema induced by bleomycin or *E. coli* endotoxin [24]. Thus, integrin-mediated local activation of TGF-β is critical to the development of pulmonary oedema in ALI, and blocking TGF-β or its activation could be a possible treatment for ALI.

ACE-2 in ALI

The renin–angiotensin system has an important role in the maintenance of both blood pressure homeostasis and fluid and salt balance. Angiotensin-converting enzyme (ACE)-2 is a homologue of ACE and functions as a negative regulator of the renin–angiotensin system by inactivating AngII; it is expressed in the lungs of humans and mice. Angiotensin II is up-regulated by ACE and drives severe lung failure through the angiotensin II type 1a (AT1a) receptor. On the other hand, ACE-2 and the AT2 receptor provide protection against lung injury. ACE-2 knockout mice demonstrate increased pulmonary vascular permeability, a hallmark of ALI/ARDS in humans [25]. Mice lacking this receptor (*Agtr1a*$^{-/-}$) have significantly attenuated vascular permeability, suggesting that loss of ACE-2 expression in ALI leads to leaky pulmonary blood vessels through AT1a receptor stimulation [25]. In patients with ARDS the ACE insertion/deletion (I/D) polymorphism is associated with ARDS susceptibility and adverse outcome [26], thus providing a mechanistic explanation for the pathogenesis of ALI. Administration of recombinant human ACE-2 attenuates ALI both in *Ace2* knockout and in wild-type mice. This combination of genetic, pharmacological and protein rescue experiments defines a new and critical role for the renin–angiotensin system in the pathogenesis of ALI [25].

Conclusions

With the unravelling of the human genome and increasing possibilities for linking diseases to this new information, we are now able to understand the mechanisms and pathways at molecular and cellular levels leading to ALI. A number of novel therapies to target a group of genes and coding proteins may one day help reduce the incidence of ALI and improve the prognosis of lung diseases.

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Chapter 3

Lung, respiratory mechanics, artificial ventilation

A. Koutsoukou, J. Milic-Emili

The lung's primary functions are to supply the blood with an adequate amount of oxygen and to remove carbon dioxide. These are achieved by the unique design of the lung, which ensures that air and blood are kept in intimate contact—though separate—to allow gas exchange, while maintaining its integrity in the face of the magnitude of insults that inevitably accompany a lifetime of exposure to ambient air and mechanical stress during cyclic breathing.

Despite the anatomical complexity of the lung, functionally it can be divided into the bronchial tree and the respiratory zone. The bronchial tree consists of the trachea, which bifurcates into the main bronchi, which in turn branch into lobar, segmental, and subsegmental bronchi and end in bronchioles, which lack cartilage and are about 1 mm in diameter. The function of the bronchial tree is to conduct air to the alveolar surface, where gas transfer takes place. The respiratory zone of the lung is composed of the respiratory bronchioles, alveolar ducts, alveolar sacs and the alveoli, whose primary function is the exchange of gases between air and blood. The intraparenchymal bronchi are invested with overlapping helical bands of smooth muscle. The amount of smooth muscle increases proportionally in the smaller bronchioles to occupy about 20% of the wall thickness. Elastic fibres are a well-developed component at every level of the lung. They stretch when the lung is expanded on inspiration, and their recoil helps the return of the lung to its end-expiration volume. Elastic fibres are a rich component of the connective tissue in the smaller bronchi and bronchioles. The smooth muscle stops at the portals of the respiratory zone, but elastic and collagen fibres contribute to the alveolar wall and form an irregular, wide-meshed net of delicate, interlacing fibres [1]. At the end of a deep breath, about 80% of the lung volume is taken up by air, 10% by blood, and only the remaining 10% by tissue. Because this small mass of tissue is spread over an enormous area, the tissue framework of the lung must be extraordinary delicate. Moreover, because the lung parenchyma is made up of interconnected alveolar walls, interstitial tissues, and fibres, any local distortion in a given region is opposed by the surrounding tissue. When distension of the surrounding alveoli fails to expand atelectatic areas, lung injury may develop as a result of extremely powerful forces that are generated at the interface [2]. Because the bronchi and blood vessels travel through and have attachments to the lung parenchyma, they too are affected by the surrounding tissue. As the lung expands, their calibre also increases, whereas at low lung volume airway closure may occur.

In humans, ventilation involves movement of the chest wall to produce a

pressure gradient that will permit flow and movement of gas. This can be accomplished by the respiratory muscles or by artificial ventilation during anaesthesia and/or acute respiratory failure. Mechanical ventilation can readily sustain adequate alveolar ventilation, improve arterial blood gases, and unload the patient's respiratory muscles. However, the mode and settings of a ventilator can significantly influence the course of a disease and the ultimate clinical outcome and may cause severe, life-threatening complications.

Monitoring and comprehending respiratory mechanics during artificial ventilation may give some guidance to understanding of the patient's pathophysiology or may promote techniques that counter the deterioration in gas exchange, but it can also help in minimising ventilator-induced complications. Over the last few decades, it has been shown that respiratory mechanics can be easily measured in intubated, mechanically ventilated patients with simple and widely available equipment [3–5]. The most popular method of measuring respiratory mechanics in relaxed, mechanically ventilated patients is rapid airway occlusion during constant flow inflation [6]. The end-inspiratory airway occlusion method is clinically used to measure the static compliance or its reciprocal, i.e. the elastance of the respiratory system [7]. Similarly, airway resistance can be measured with the rapid airway occlusion technique during constant flow inflation [6, 7]. Combined with measurement of tracheal and oesophageal pressure, the rapid airway occlusion method also allows partitioning of respiratory mechanics between the lungs and the chest wall [8, 9]. A pressure–volume curve for the respiratory system can be constructed in a paralysed patient by measuring the airway pressure as the lungs are progressively inflated with a 1.5- to 2-l syringe. The static recoil pressure of the respiratory system at end-expiration may be elevated in patients undergoing mechanical ventilation [7]. This positive recoil pressure or intrinsic positive end-expiratory pressure (static PEEPi), can be quantified in relaxed patients by using an end-expiratory hold manoeuvre on a mechanical ventilator immediately before the onset of the next breath.

Monitoring of respiratory mechanics in mechanically ventilated patients has seen several major advances in recent years. Detection of expiratory flow limitation during mechanical ventilation offers important information and assists in correct interpretation of respiratory mechanics and determination of the most appropriate therapeutic measures to be applied for their treatment. Furthermore, the last two decades have brought new insights into the mechanisms of lung injury. The recognition that airways and parenchyma can be injured by physical stress has redirected attention to lung mechanics and to the determinants of tissue damage.

Expiratory flow limitation

The term 'expiratory flow limitation' (EFL) should be used only to describe a condition in which expiratory flow cannot be augmented at a given lung volume. Thus, EFL reflects lack of dependence of flow on effort, or in other words the impossibility of increasing expiratory flow by further increasing pleural, and

therefore alveolar, pressure at that volume [10]. Two main mechanisms promote the occurrence of tidal EFL, namely reduction of expiratory flow reserve and increase in ventilatory requirements. The expiratory flow reserve is calculated as the difference between the maximal flows available and the actual flows that are developed during expiration. In normal individuals at rest the expiratory flow reserve is very high. The expiratory flow reserve can be reduced by (a) airway obstruction, a term that implies a reduction in maximal flow rate below the predicted normal range and (b) reduced functional residual capacity (FRC) caused by recumbency or disease (obesity, congestive heart failure). With advancing age maximal flows also decrease.

Until recently, the conventional method used to detect EFL during tidal breathing was one proposed in 1961 by Hyatt, which is based on the superimposition of tidal with maximal expiratory flow–volume curves [10]. This analysis requires the measurements to be done by body plethysmography, which seems a complicated technique in the ICU. Recently, a simple technique has been proposed for detecting expiratory flow limitation, the negative expiratory pressure (NEP) technique; this can be applied at the bedside in the ICU during both spontaneous and supported breathing [11]. A small negative expiratory pressure of about –5 cmH_2O is applied at the airway opening during tidal expiration, and the ensuing expiratory flow–volume curve is compared with the previous control curve. In the absence of expiratory flow limitation, expiratory flow increases with NEP, whereas in patients with flow limitation expiratory flows do not increase with NEP either throughout or for part of tidal expiration (Fig. 1). The NEP technique was first applied and validated

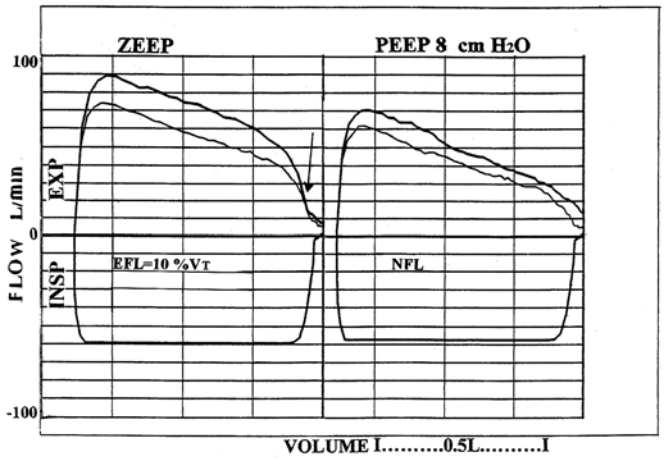

Fig. 1. Flow–volume (V'–V) loops of negative expiratory pressure (NEP) test breath and preceding reference curve of a morbidly obese subject on zero positive end-expiratory pressure (ZEEP) (*left*) and after application of 8 cmH_2O of positive end-expiratory pressure (PEEP) (*right*). On ZEEP expiratory flow limitation (EFL) amounted to 10% VT and was heralded by an inflection point (i.e. the expiratory V'–V curve was S shaped). With PEEP the inflection point disappeared and the entire V'–V curve became concave toward the volume axis, indicating absence of EFL. (From [16] with permission)

during mechanical ventilation in different body postures [12]. Based on this method, it has been shown that EFL is a rather common finding in mechanically ventilated patients. In fact, it has been shown that most mechanically ventilated patients with acute respiratory failure of pulmonary origin present tidal EFL [13], and also that most patients with acute respiratory distress syndrome exhibit EFL associated with a concomitant PEEPi [14, 15]. In all ARDS patients, the application of moderate levels of positive end-expiratory pressure (PEEP) abolished EFL and improved arterial oxygenation [15]. Tidal EFL and PEEPi are also common findings in supine, morbidly obese sedated-paralysed subjects after abdominal surgery [16]. In these patients, external PEEP of 4–16 cm H_2O was required to abolish EFL. The presence of EFL implies cyclic dynamic compression and re-expansion of the airways, with the attendant risk of "low-volume" injury (*see below*). Undetected expiratory flow limitation can result in suboptimal use of therapeutic resources such as bronchodilators or external PEEP to reduce its side effects. Therefore, the assessment of EFL in mechanically ventilated patients with the NEP technique is a potentially useful bedside approach that can yield information concerning respiratory mechanics and appropriate ventilatory settings. Although a prototype of a ventilator equipped with a NEP device has been built, providing easy and accurate assessment of EFL [14], it is unfortunately not commercially available.

Ventilator-induced lung injury

Mechanical ventilation is an important and often lifesaving tool in the management of patients with respiratory failure. However, soon after its inception, it became apparent that mechanical ventilation could lead to a number of serious complications [17]. Initially ventilator-induced lung injury (VILI) was synonymous with clinical barotrauma, meaning leakage of air owing to disruption of the airspace wall as a consequence of high airway pressures developed during positive pressure ventilation. This form of VILI can be very dramatic and has been recognised clinically for many decades. What is not entirely clear is which pressure (peak airway, mean airway, or PEEP) is of paramount importance and what values of these pressures are injurious. Although airway pressures are usually monitored clinically, transpulmonary pressures are clearly more relevant. The critical feature appears to be the degree of regional lung distension, rather than the absolute pressure reached. In addition to the obvious manifestations of overdistension, there are also more subtle types of injury that can be induced by mechanical ventilation. Wedd and Tierney [18] produced dramatic evidence that overdistension associated with high peak airway pressures could lead to the development of pulmonary oedema and death within 1 h in rats. Since this seminal finding, a large number of investigators have observed that high end-inspiratory lung stretch can lead to diffuse alveolar damage, pulmonary oedema, increased fluid filtration, epithelial permeability and microvascular permeability [19]. Dreyfuss et al. showed that lung volume, as opposed to pressure, was paramount in inducing an increase in the volume of lung water [20].

There are a number of possible mechanisms to explain the increase in alveolar-capillary permeability observed with high tidal volume ventilation. A number of studies by West et al. have highlighted the importance of stress failure as a mechanism of injury [21]. Moreover, recent studies suggest that microvascular permeability might be actively modulated by a cellular response to mechanical injury and that this response might be initiated by stretch-activated cation channels through increases in intracellular calcium concentrations [22].

In addition to the injury caused by ventilation at high lung volume, there is a large body of evidence indicating that ventilation at low lung volume may also contribute to injury. This injury is thought to be related to opening and closing of lung units. This concept of damage caused by repetitive opening-collapse of distal airways was first proposed by Robertson to explain the lung injury observed in infants with respiratory distress syndrome [23]. He suggested that in an atelectatic lung, the air–liquid interface may be found in a relatively proximal position in the terminal conducting airways rather than in the alveoli. Opening of these airways would require relatively high forces, and the shear stresses produced might cause epithelial disruption. Using an ex vivo-lavaged rat lung, Muscedere et al. showed that ventilation with physiological tidal volumes from zero PEEP (ZEEP) resulted in significantly higher histological injury scores in the respiratory and membranous bronchioles than did ventilation from PEEP above the lower inflection point at the static inflation volume–pressure curve of the lung [24].

Because lavaged lungs exhibit marked regional structural inhomogeneity, which would be expected to enhance the shear stresses and relative injury [2], D'Angelo et al. studied the effects of mechanical ventilation at low lung volume in the absence of pre-existing parenchymal lung injury. In normal open-chest rabbits they found that prolonged (3–4 h) mechanical ventilation with physiological tidal volumes at ZEEP induced histological evidence of peripheral airway injury characterised by denuded epithelium and sloughing, associated with a concomitant increase in airway resistance, which persisted after the restoration of physiological end-expiratory lung volume [25]. These findings have been attributed to shear stresses caused by cyclic opening and closing of peripheral airways with tidal ventilation at low lung volume, possibly combined with increased surface tension due to surfactant depletion or inactivation. Furthermore, they also observed that during the first 90 ms of inflation, the transpulmonary pressure increased five times as rapidly during ventilation at ZEEP than with PEEP, despite equal inflation flows under the two conditions, suggesting that the higher increase in transpulmonary pressure at the onset of inflation may contribute to lung injury with ZEEP. In fact, in a subsequent study the same group found that prolonged mechanical ventilation on ZEEP with cyclic opening–closing of peripheral airways caused alveolar–bronchiolar uncoupling and parenchymal inflammation with a concurrent persistent increase in airway resistance, which were all worsened by high inflation flow [26]. In these two studies, the static elastance of the respiratory system was found to be unchanged, but in a very recent study in closed-chest rabbits we found that prolonged mechanical ventilation with physiological tidal volumes at low lung volume resulted in a significant increase in airway resistance and static

elastance of respiratory system, probably due to interstitial oedema and surfactant depletion or inactivation [27].

The possibility that inflammatory cells and mediators such as proinflammatory cytokines contribute either directly or indirectly to VILI, or worsen it, has also been investigated [28, 29]. Parenchymal overdistension and abnormal shear forces could be the mechanical stimuli leading to release of mediators that prime polymorphonuclear leucocytes, which may represent the major effector cells in the generation of tissue injury and up-regulation of the inflammatory response [30]. Increased concentrations of proinflammatory cytokines, mainly tumour necrosis factor alpha and interleukin-6, have in fact been observed in bronchoalveolar lavage fluid of normal rat lungs after prolonged ventilation at ZEEP [31]. However, the functional damage found after prolonged mechanical ventilation at low lung volume in normal open- and –closed chest rabbits, mainly increased airways resistance and increased airways resistance plus elastance of the respiratory system, respectively, was not associated with increased concentrations of TNF alpha in the bronchoalveolar lavage fluid, indicating that the damage to small airways with ventilation at low lung volume is due to direct mechanical injury per se and not mediated by a proinflammatory process [27].

Clinical implications

General anaesthesia and supine position promote reduced functional residual capacity, atelectasis in the dependent lung zones and peripheral airway closure, even in normal lungs [32, 33]. These phenomena are more pronounced in old age and obesity [32]. Airway closure implies opening and closing of peripheral airways during tidal breathing and development of shear stresses that can damage peripheral airways [25, 26]. Moreover, in the presence of airway closure there is heterogeneous lung filling and emptying, which probably also contribute to lung injury [2, 15, 16]. On the other hand, the reduction of FRC with the concomitant reduction of expiratory flow reserve that is associated with anaesthesia-paralysis [34], abdominal surgery [35] or various diseases such as ARDS and obesity is expected to promote development of EFL during tidal breathing [13–16]. The presence of EFL implies cyclic dynamic compression and re-expansion of the airways with concurrent inhomogeneous filling of air spaces and risk of low lung volume injury [15, 16, 24]. In addition, recent model analyses suggest that heterogeneous peripheral airways constriction such as occurs during tidal EFL amplifies airflow-related shear stresses within the peripheral airways with risk of injury even in the absence of airway closure [36]. In this connection, it should be stressed that during mechanical ventilation there is a rapid initial increase in airway pressure which, by snapping open the closed or compressed airways and generating high shear stresses, enhances peripheral airway injury as shown in open-chest rabbits ventilated with different inflation flows [26]. Thus, in mechanically ventilated subjects who are elderly and obese and in patients with diseases that promote airway closure and EFL, such as ARDS [14, 15], chronic obstructive pulmonary disease [37] and chronic

heart failure [38], it may be prudent to avoid the risk of low volume injury. Accordingly, PEEP should be applied to increase the end-expiratory lung volume above both the closing volume and the expiratory flow limitation volume. However, it is essential that it be done with concurrent assessment of both EFL and PEEPi. In the absence of a NEP device, EFL can be assessed by inspection of the shape of the tidal flow–volume curves on the ventilator screen (Fig. 1). Furthermore, avoidance of a rapid increase in airway pressure at the onset of lung inflation by using lower constant flows or sinusoidal flows that are not decelerating seems important [26].

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Chapter 4

The pressure–volume curve

V.R. Cagido, W.A. Zin

Since it was first described, the pressure–volume (P–V) curve has been used as a physiological method to describe the mechanical properties of the respiratory system in health and disease [1]. In mechanically ventilated patients, the P–V curve is an interesting tool that can be used at the bedside to help in the diagnosis, follow-up and prognosis of lung disease, and also in the setting of ventilatory parameters to help in determination of the optimal positive end-expiratory pressure (PEEP) level and quantification of the alveolar recruitment [2]. However, after decades of research on P–V curves, there is still wide-ranging discussion on how to interpret it.

Physiological basis

The respiratory system is made up of the lungs, airways, respiratory muscles, chest wall and abdomen. To move air in and out of the lungs, the ventilatory pump needs to overcome the inertial, elastic and resistive properties of these structures. The elastic component of the respiratory system can be quantified by the relation between the driving pressure (ΔP) and the change in the volume (ΔV), which is called elastance ($\Delta P/\Delta V$) or compliance ($\Delta V/\Delta P$). Resistance represents the relation between the resistive pressure and airflow ($\Delta V'$), and is quantified by $\Delta P/\Delta V'$. Evaluation of the true elastic and resistive properties of the respiratory system requires inactivation of the respiratory muscles [3]. Without shear stress (resistance) the force–displacement relationship (pressure–volume) is constant. In the presence of shear stress the force used to overcome resistance adds to the elastic component. The inertial component is negligible.

The respiratory system can be divided into two compartments: lung and chest wall, and any abnormality in one of them may thus influence the P–V curve of the system. In healthy humans the shape of the respiratory system P–V curve from residual volume to total lung capacity is sigmoidal, presenting an upward concavity at low inflation pressures and a downward concavity at higher inflation pressures [2, 4]. This shape reflects the balance of forces between the chest wall and lung parenchyma. At lung volumes below functional residual capacity (FRC), the chest wall contributes more significantly to the curvature (fall in compliance) because of its progressively increasing rigidity (the anatomical structures do not allow a further decrease in volume) and large outward expansion force. Additionally, the

lung compliance falls at low lung volumes owing to alveolar instability and airway collapse [5]. At FRC, the inward retractile force of the lung counterbalances the outward expansion force of the chest wall, setting the elastic equilibrium volume of the respiratory system. At high lung volumes the lung contributes most to the curvature, presenting a large inward retractile force [2, 6]. The P–V curve is usually traced solely above FRC. Under this condition, the sigmoidal shape is not observed in normal subjects during tidal ventilation, since breathing takes place at the linear portion of the P–V curve.

An important phenomenon observed in P–V curves is hysteresis. To achieve the same lung volume, more pressure must be applied during inflation than deflation (Fig. 1) [2, 5]. Because the dependent regions of the lung have a natural tendency to collapse at low volumes, even the normal pressure–volume curve of the lung displays some degree of hysteresis [5]. This phenomenon depends on the tidal volume [7] and is determined by the air–liquid surface forces in alveoli [8], recruitment/derecruitment, stress relaxation and gas absorption during the measurement of P–V curves [2]. When the lung is filled with saline solution hysteresis vanishes and the pressure applied is used solely to overcome the tissue elastic component. However, when it is filled with gas the pressure required to overcome surface tension adds to the tissue elastic component. Surface tension rises without surfactant, and many alveoli close down (Fig. 1) [8].

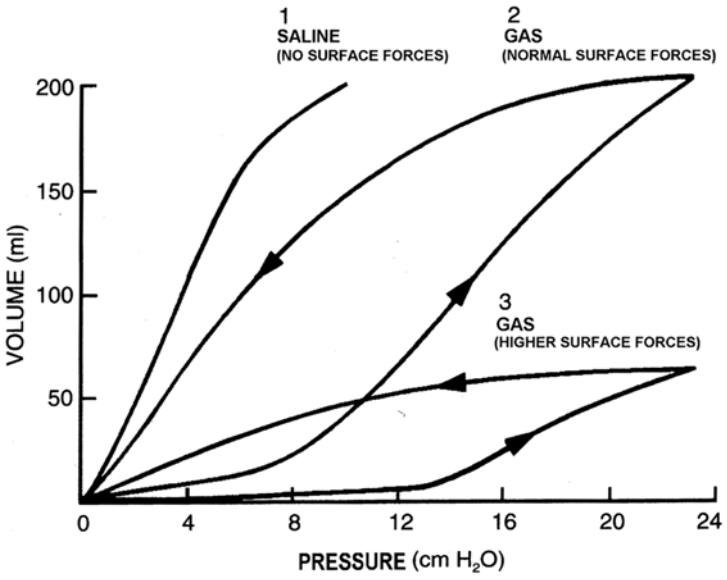

Fig. 1. Pressure–volume curves of an isolated lung. The curves were obtained from minimum volume to maximum inflation. If lungs with normal surface forces are inflated with air and, then, emptied, curve 2 results. When the surface forces are higher, e.g. absence of surfactant, with the same inflation pressure the volume is lower (curve 3). However, if the lungs are filled with liquid there are no surface forces, and the pressure necessary to inflate the lungs therefore falls and hysteresis almost disappears

Methods of constructing the pressure–volume curve

The P–V curve permits assessment of the mechanical properties of the respiratory system at different levels of lung volume. This can be accomplished by static [9, 10], quasi-static [11, 12] or dynamic methods [13, 14]. When dynamic methods are used, the resistive component must be taken into account in analysis of the P–V curve [15, 16]. Significant differences between dynamic and static P–V curves have been reported [17, 18].

Static methods

Super-syringe

This technique was the first method used to assess the elastic properties of the respiratory system in mechanically ventilated patients. It consists in slow inflation of the lungs with oxygen, from FRC up to a volume of 25 ml/kg or until an airway pressure of 40 cmH_2O is reached. Every 100–200 ml inflated is followed by a paused of 2–3 s, after which the airway pressure is computed [9, 19]. The expiratory curve can also be observed by applying the same manoeuvre during deflation. The disadvantages of this technique are the necessity for sedation, paralysis and disconnection from the ventilator, causing alveolar derecruitment, and a discrepancy between actually injected volume and the amount read on the syringe [20].

Inspiratory airway occlusions

The inspiratory occlusion technique is based on single-breath occlusions during mechanical ventilation, which allows measurement of plateau pressures at different tidal volumes [10]. Each occlusion lasts for 3 s or until a plateau appears in the airway pressure. The patient has to be sedated, paralysed and ventilated in a volume-controlled mode with constant inspiratory flow; the different tidal volumes are obtained by changing the respiratory rate. Since the patient remains connected to the ventilator there is no derecruitment and the injected volume is known. The result depends on many determinations of volume and pressure, and overall the measurement session lasts around 15 min [10, 19, 20].

Quasi-static inflation

Under constant inspiratory flow inflation the airway pressure change varies inversely with the compliance of the respiratory system [11, 12, 20]. When the constant flow is less than 10 l/min, the resistive component can be regarded as nil and the P–V obtained curve is quasi-superimposable on those obtained with static methods [16]. The patient must be sedated and paralysed, and the ventilator, set in a volume-controlled mode with constant inspiratory flow, a tidal volume of 500–1,500 ml, an inspiration/expiration ratio of 0.8 and a respiratory frequency of 5 breaths/min. A constant flow ranging between 3 and 9 l/min delivered results over

9.6 s. This technique provides useful data immediately, and the patient stays connected to the ventilator, avoiding derecruitment.

Dynamic methods

Pao × t curve

This method analyses the shape of the dynamic airway opening pressure over time during volume-controlled ventilation with constant inspiratory flow [13]. The basic assumption is that resistive and viscoelastic contributions to airway pressure remain constant throughout inspiration, promoting a linear relationship between airway pressure and time when compliance does not change with increasing lung volume. A downward concavity in the curve indicates that compliance increases during tidal inflation, suggesting the occurrence of recruitment, while an upward concavity indicates that compliance decreases during inflation, suggesting the occurrence of overdistension [13]. Since the patient is always connected to the ventilator, there is no alveolar derecruitment.

Inspiration with sinusoidal airflow

This is a low-flow inflation technique that allows recording of P–V curves during a single inflation following an adjustable expiration. Sedation and muscle paralysis are required. After a 6-s expiration under PEEP or ZEEP, a predefined tidal volume large enough to reach a pressure of 40 cmH_2O is administered during a 6-s-long inspiratory phase. The flow is modulated in a sinusoidal manner at 1 Hz during inspiration, allowing calculation of the inspiratory resistance of the respiratory system. However, the results can only be obtained after many calculations [14].

Chest wall and lung P–V curves

The methods described for construction of the P–V curve can be used to analyse the influence of each component of the respiratory system on the shape of the curve. For this purpose, the oesophageal pressure (Poes) must be measured: Poes swings (DPoes) reflect the changes in pleural pressure (DPpl) [21]. Oesophageal pressure can be measured by a catheter that incorporates a thin-walled balloon inflated with air or a water-filled catheter placed in the mid-oesophagus and connected to a pressure transducer. The patient is kept in the half-sitting position to minimise the effect of weight of the mediastinum in the supine position [19]. To check the correct positioning of the catheter, an "occlusion test" can be used [22]. If the ratio between changes in oesophageal pressure and occluded inspiratory pressure is close to 1 this confirms a correct position of the catheter and also indicates that oesophageal pressure closely estimates pleural pressure. Pleural pressures plotted against lung volumes generate the chest wall P–V curve, and the lung P–V curve is constructed by plotting transpulmonary pressures (difference between airway and oesophageal pressure) against lung volumes.

Traditional concepts about the P–V curve

The inspiratory limb of the P–V curve consists of three segments separated by two inflexion points. The lower inflexion point (LIP) separates the first segment with low compliance (starting compliance) from the intermediate linear segment with a larger compliance (inflation compliance). After its steep part the curve flattens again at the upper inflexion point (UIP) [4].

Analysis of the LIP could be used as a tool to assess the patency of the peripheral airways, since it is thought to reflect the pressure above which alveoli and collapsed airways reopen during inspiration. The UIP would indicate the point beyond which alveoli and small airways start to undergo hyperdistension [4, 14, 23, 24]. In clinical practice, the LIP is determined by a graphic technique. A tangent is drawn extending the slope of the starting compliance. Another tangent is drawn extending the slope of the inflation compliance down toward the horizontal axis. Where the two tangents intersect, a third tangent is drawn to the horizontal axis, and this point is considered the LIP. The same technique can be used to determine the UIP and the closing pressure on the deflation limb, which will be discussed below [25].

In the expiratory limb of the P–V curve a distinct closing volume can be identified as lung volume declines [5]. This behaviour is more pronounced in older persons and in those affected by some pulmonary diseases. In the first segment, the decrease in pressure represents the relaxation of overstretched units as volume decreases from total lung capacity. The second part of the deflation curve reflects the elastic-retraction properties of patent lung tissue. In the third segment the rate of closure progressively increases, meaning deflation of open units [26]. When the pressure falls below the highest alveolar closing pressures, the lung units start to collapse, resulting in steepening of the curve [24]. The "closing pressure" would therefore denote the point at which alveoli start to collapse. There is a fourth and final phase, in which extensive airway closure and air trapping occur, with the curve bending leftwards.

In patients with acute respiratory distress syndrome (ARDS) the inspiratory P–V curve traced above the FRC has a sigmoidal shape. There is also flattening of the entire curve owing to the reduction in the number of normally ventilated alveoli, thus decreasing the volume range available for tidal breathing [4]. Because of the sigmoidal static P–V curve of the respiratory system, it was traditionally accepted that mechanical ventilation should be performed along its steep portion between the lower and upper inflexion points [9, 27]. The slope of the P–V curve has also been used to determine the potential for recruitment and to set PEEP in mechanical ventilation [20, 28–30].

Factors altering the P–V curve

Duration of disease

The modifications of the P–V curve during the course of ARDS were described by Matamis et al., who used the super-syringe method [9]. They showed that in the early stage of ARDS, although the LIP could be detected the compliance calculated using the linear segment was normal. The late stage of the disease (approximately 2 weeks after its onset) was accompanied by the absence of LIP and a smaller compliance, probably due to the development of interstitial fibrosis [4, 9]. The LIP seen in the early stage of ARDS was believed to represent the reopening of collapsed airways and alveolar units during inspiration, while its absence in the late stage could reflect a stiffer lung.

Use of PEEP

During inspiration two phenomena may occur: recruitment and distension of the distal air spaces. When the alveoli open up compliance increases, and it persists throughout alveolar recruitment. However, after a certain point compliance falls.

The benefits of the use of PEEP come in part from the resulting increase in FRC. The shape of the P–V curve and the value of LIP may vary according to the end-expiratory lung volume that marks the beginning of inspiration [14]. Increasing PEEP values can eliminate the LIP and decrease the compliance at the linear portion of the curve. These phenomena may theoretically reflect recruitment of some parts of the lung and distension or overdistension of other regions. The effect of PEEP on LIP may indicate good lung recruitment [14, 31, 32].

Effect of the chest wall

The effects of the chest wall on the slope of the P–V curve have been investigated by many researchers [33–35]. In patients in whom ARDS was consequent on major abdominal surgery, a rightward shift of the thoracic and abdominal V–P curves was observed. The flattening of the P–V curve of the respiratory system and lung was attributed in part to the higher abdominal pressure, which increases chest wall stiffness and decreases its compliance, displacing the P–V curve to the right. A variety of clinical situations yielding higher abdominal pressure, such as positive fluid balance, abdominal distension, pleural effusion and oedema of soft tissue can induce the same findings [33].

The chest wall's mechanical properties can also affect the UIP and LIP [33, 34]. In the presence of chest wall mechanics altered by abdominal distension, the tidal volume at which compliance starts to decrease is an average of 28% greater in the lung P–V curve than in the respiratory system curve [33]. For the same reason, LIP determined on the lung P–V curve underestimates that determined in the respira-

tory system curve by 25–30% [33], since the chest wall adds between 0 and 5 cmH_2O to the LIP observed [34].

Effect of intrinsic PEEP

Intrinsic PEEP has been reported to produce a fallacious LIP [32, 36]. An uneven distribution of distal airway resistance in ARDS may result in the association of a "fast compartment" with a short time constant with a "slow compartment" characterised by a relatively long time constant [23]. This longer time constant limited to an alveolar zone is responsible for airflow limitation and the appearance of intrinsic positive end-expiratory pressure (PEEPi). It is suggested that the initial lung compliance of the P–V curve is progressively decreased by an increasing proportion of the slow compartment and LIP might represent the opening pressure of the slow compartment. Then, patients with PEEPi display LIP, while patients without PEEPi do not show LIP. When an extrinsic PEEP is applied the slow compartment opens, disappearance of PEEPi ensues and the inspiratory limb of the P–V curve becomes almost linear [23].

Effect of mechanical inhomogeneities

The P–V curve of an inhomogeneous lung having an infinite number of time constants and alveolar threshold opening pressures will not show a LIP. In this situation, the different alveolar compartments are opened one after another as the pressure increases, thus blurring the LIP on the P–V curve [37].

At the beginning of the disease, with a mild degree of inhomogeneity, there is a loss of gas volume because of oedema, but these alveoli are still recruitable, as indicated by the presence of a LIP. Later on fibroelastosis ensues and the possibility of recruitment diminishes [38].

A study comparing respiratory mechanics, computed tomography (CT) and radiological images of the lung in two groups of patients with and without LIP revealed that the former group had a much smaller volume of normally aerated lung and that their lungs were characterised by extensive diffuse radiological opacities, homogeneously distributed [39]. The latter group showed opacities predominating in the lower lobes, and the aeration of the upper lobes was relatively well preserved. PEEP induced overdistension only in those without a LIP, representing a risk of barotrauma.

With LIP there is no hyperdistension in already distended regions. In nonaerated areas the two types of P–V curve display similar results in the face of PEEP [39].

In ARDS patients with focal loss of aeration, interpretation of the P–V curve is even more complex. The shape of the curve results from the sum behaviour of the lung, which remains normally aerated at ZEEP with recruitment of the nonaerated lung regions (Fig. 2) [20, 40]. The lower and upper inflexion points can be absent or hardly prominent. The normal regions are inflated and distended before the recruitment of nonaerated lung regions commences. In the linear part of the curve,

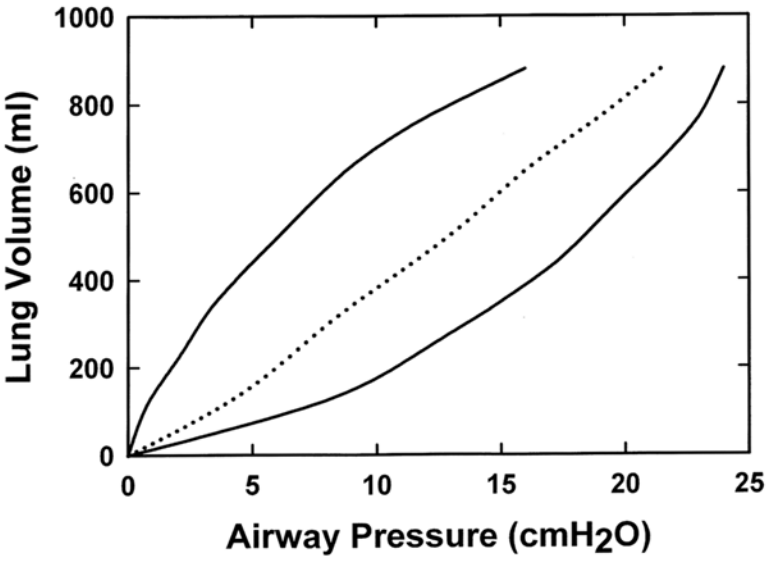

Fig. 2. Respiratory pressure–volume (*P–V*) curve obtained in the presence of zero end-expiratory pressure (*ZEEP*) in a patient with acute respiratory distress syndrome (*ARDS*) characterised by a focal loss of aeration. The *upper, solid curve* represents the P–V relationship of normal regions at ZEEP, and the *lower solid curve* reflects the behaviour of poorly aerated and nonaerated regions at ZEEP. The *broken curve* results from the sum of these two effects. (Modified from [20])

distension and recruitment occur simultaneously in different parts of the lung. At high pressures, overdistension of the normal lung may appear, while lung recruitment of nonaerated regions continues. Consequently, the slope of the P–V curve reflects not only the potential for recruitment but also the compliance of the aerated lung [20].

Effect of body posture

The effects of prone position on the respiratory system, chest wall and lung P–V curves of severely hyperinflated chronic obstructive pulmonary disease (COPD) patients were investigated by Mentzelopoulos et al. [41]. Pronation shifted the lung P–V curve to the left, yielded greater compliance, reduced the pressure at LIP and led to a higher UIP volume, when present. The chest wall P–V curve showed lower compliance and a higher pressure at LIP, while the respiratory system P–V curve did not exhibit posture-related differences on its variables.

Prone position facilitated inspiratory peripheral airway reopening and is consistent with the observed association between postural decreases in PEEPi and lung LIP pressure [41].

Present views

Initially, LIP, UIP and closing pressure were identified manually. The lack of standard procedures to determine these points led Venegas et al. [42] to create a method for evaluation of P–V curve parameters [43]. Their approach is applicable both to the inspiratory and expiratory limbs of the curve and depends on a mathematical fitting procedure to the P–V curve.

Mathematic modelling and experimental and clinical data indicate that alveolar recruitment takes place over the entire range of the P–V curve [31, 44, 45]. Alveolar recruitment is a complex phenomenon that cannot be signalled by the LIP alone. It represents the simultaneous opening of various alveoli, whereas its absence reflects different pressure thresholds for recruitment. Then, LIP seems to indicate a need for recruiting alveoli but may be of little help in determining optimal PEEP. On the other hand, the UIP may imply that recruitment is over and does not necessarily indicate only hyperdistension [14, 31, 32]. Moreover, the regional P–V curve of the thorax shows a higher LIP in the posterior region, indicating a differing recruitment behaviour according to the lung region [45, 46].

Studies suggest that the presence of LIP represents a qualitative marker for a recruitable lung, reflecting recruitment after a prolonged expiration, which probably differs from recruitment during tidal ventilation [14, 32].

The compliance of the linear segment of the P–V curve is also a good indicator of lung recruitability.

In lungs affected by acute lung injury (ALI), a progressive decrease in PEEP is associated with alveolar derecruitment across a wide range of pressures, which may be explained by the alveolar heterogeneity and high pleural pressure gradient caused by increased lung density in ALI [32].

Since ventilation occurs across the deflation limb of the pressure–volume curve, especially in recruited lungs [47], some authors have proposed that it might be more useful to set PEEP on the basis of the closing pressure derived from the deflation limb of the P–V curve, where a substantial fraction of alveoli remain in the open state. This limb of the curve displays a variable number of distinct subsections depending on the degree of lung injury and the maximum inspiratory pressure achieved in the respiratory system during the previous inspiration [26]. The use of the deflation limb to identify the distribution of closing pressures might better identify the optimal PEEP to prevent derecruitment of alveolar units [29, 31]. Although the use of the deflation limb to set PEEP in ALI patients was related to an increase in oxygenation, recruitment and alveolar stability, increase in hyperinflated lung tissue and signs of overstretching relative to a PEEP level above the LIP of the inflation limb of the P–V curve have also been reported [48]. When tidal volume was kept constant, the PEEP level set by the closing pressure had both benefits and drawbacks [48].

For many years, modifications of the P–V curve in ARDS were attributed to changes in lung compliance. More recently, the role of the chest wall in the slope of the curve has been stressed, showing that the chest wall properties should also be taken into account.

In patients with inhomogeneously distributed ARDS interpretation of the P–V curve is a rather difficult task. Its shape depends on the normally aerated lung in ZEEP and on recruitment of the nonaerated lung. In these patients, who are the majority, keeping the plateau pressure below the UIP does not assure an absolute protection against hyperdistension. The P–V curve might possibly represent the sum behaviour of all lung units, and given the heterogeneity of the lungs it may not allow the determination of ideal points of recruitment or overdistension [29].

Conclusions

The pressure–volume curve of the respiratory system has been widely used in attempts to increase our understanding of the mechanisms involved in alveolar recruitment/derecruitment, the lung impairment during acute respiratory lung disease/acute lung injury, and it has been advocated as a tool to develop lung protective ventilation strategies. However, its interpretation remains controversial, and its pathophysiological significance clearly deserves thorough re-evaluation.

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Chapter 5

Methods for assessing expiratory flow limitation during tidal breathing

N.G. Koulouris, S.-A. Gennimata, A. Koutsoukou

The term *expiratory flow limitation* (EFL) is used to indicate that maximal expiratory flow is achieved during tidal breathing at rest or during exercise and is characteristic of intrathoracic flow limitation [1] (Fig. 1, *right*). There are several methods of assessing EFL.

Oesophageal balloon technique

By definition, EFL implies that an increase in transpulmonary pressure will cause no increase in expiratory flow [2]. Therefore, direct assessment of expiratory flow limitation requires determination of iso-volume relationships between flow and transpulmonary pressure (V'-P). Fry et al. [3] were the first to develop such curves, in the 1950s and early 1960s. The explanation of an iso-volumic pressure flow curve lies in understanding its construction. Flow, volume and oesophageal pressure

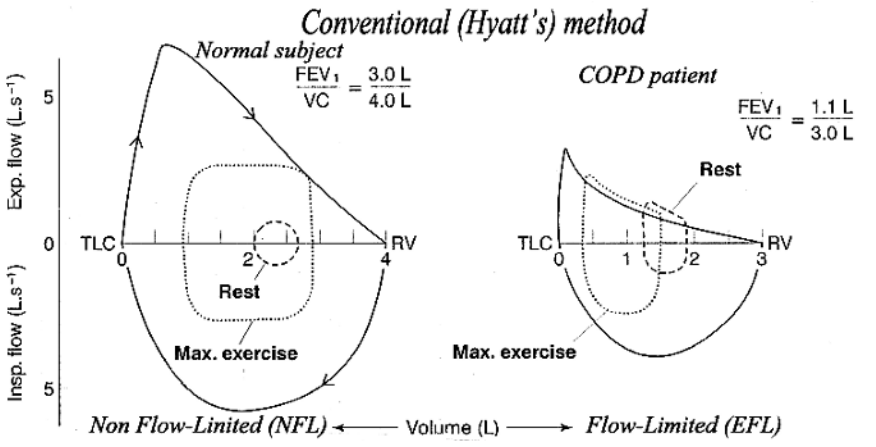

Fig. 1. Tidal breaths at rest and during maximal exercise compared to maximal expiratory (MEFV) and maximal inspiratory (MIFV) flow-volume curves in a normal subject (*left*) and a COPD patient (*right*). (Modified from [1])

(Poes) are measured simultaneously during the performance of repeated expiratory vital capacity efforts by a subject seated in a volume body plethysmograph, which corrects for gas compression. The subject is instructed to exhale with varying amounts of effort, which are reflected in changes of Poes. From a series of such efforts (~30) it is possible to plot flow against Poes at any given lung volume (Fig. 2) [2]. Figure 2 shows a case where flow reached a plateau at a low positive pleural pressure and once maximum flow for that volume was reached it remained constant despite increasing Poes achieved by means of expiratory efforts of increasing intensity. The Mead-Whittenberger method [4] relates alveolar pressure directly to flow. Mead-Whittenberger graphs can be obtained by plotting the flow measured at the airway opening against the resistive pressure drop during a single breath (Fig. 3, *upper panel*). In this way the phenomenon of flow limitation is documented. These methods used to be the gold standard in assessing expiratory flow-limitation, but they are technically complex and time consuming. Furthermore, these are invasive, requiring passage of an oesophageal balloon [2, 4].

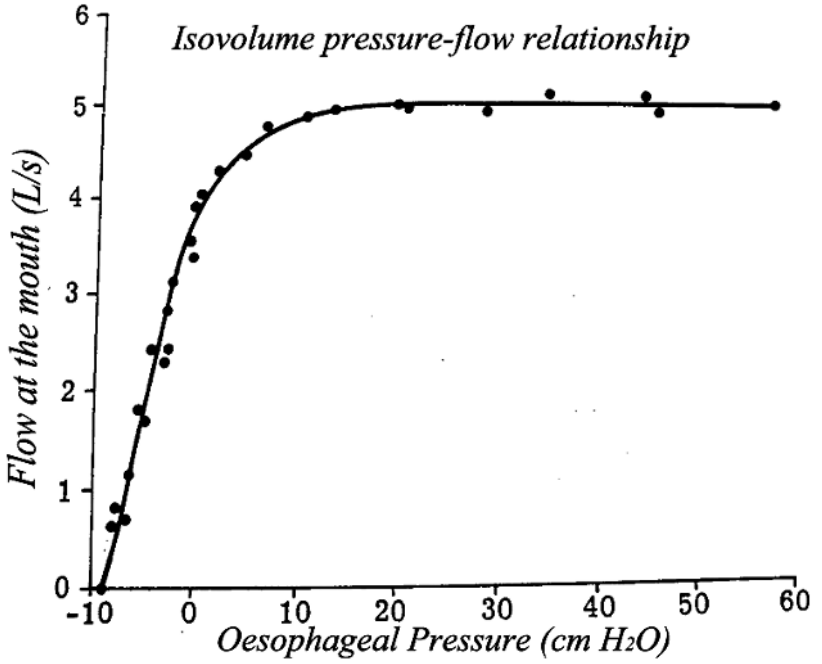

Fig. 2. Expiratory iso-volume flow-pressure curve at 60% vital capacity (VC) constructed after a series of measurements. Flow does not increase after a certain flow is reached by increasing pleural pressure (flow limitation). (Modified from [2])

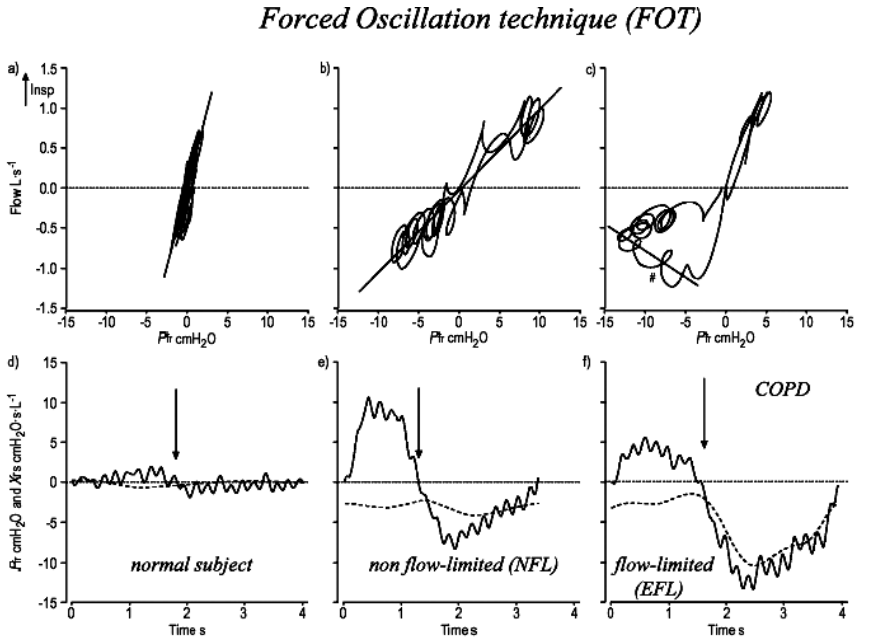

Fig. 3. Mead and Whittenberger graphs *(upper panels)* obtained by plotting the airway opening flow versus the resistive pressure drop (Pfr) during a single breath. *Left panels* show data from a healthy subject, *middle panels* data from a non-flow-limited and *right panels* data from a flow-limited COPD patient. The *regression lines* in the *left* and in the *middle graph* represent airway resistance at breathing frequency. In the right graph expiratory flow limitation is demonstrated by the presence of a region in which airway opening flow is decreasing while Pfr is increasing. Traces obtained during FOT application *(lower panels)* show the corresponding time courses of Pfr (*continuous line*) and Xrs (*dashed line*). The *arrows* indicate end-inspiration, i.e. time before this point is inspiration, afterwards is expiration. (Modified from [41])

Conventional (Hyatt's) method

Until recently, the conventional method used to detect EFL during tidal breathing was the one proposed by Hyatt [5] in 1961. It consists in correctly superimposing a flow-volume loop (F–V) of a tidal breath within a maximum flow–volume curve. This analysis and the "concept of EFL" are the key to any understanding of respiratory dynamics. Flow limitation is not present when the patient breathes below the maximal expiratory flow–volume (MEFV) curve (Fig. 1, *left*). According to this technique, normal subjects do not reach flow limitation even at maximum exercise [1, 6]. In contrast, flow limitation is present when a patient seeks to breathe tidally along or above the MEFV curve (Fig. 1, *right*). It has long been suggested that patients with severe chronic obstructive pulmonary disease (COPD) may exhibit

flow limitation even at rest, as reflected in the fact that they breathe tidally along or above their maximal flow–volume curve [1–6]. However, the conventional method of detecting flow limitation by comparing maximal and tidal expiratory flow–volume curves has several methodological deficiencies. These include:

a) Thoracic gas compression artefacts. To minimise such errors, volume should be measured with a body plethysmograph, instead of the common practice of using a pneumotachograph or a spirometer [7]. The corollary of this is that in practice flow limitation can be assessed only in seated subjects at rest.

b) Incorrect alignment of tidal and maximal expiratory F-V curves. Such alignment is usually made when the total lung capacity (TLC) is regarded as a fixed reference point. This assumption may not always be valid [8, 9].

c) Effect of previous volume and time history. Since the previous volume and time history of a spontaneous tidal breath is necessarily different from that of an FVC manoeuvre, it is axiomatic that comparison of tidal with maximal F–V curves is problematic. In fact, there is not a single maximal F–V curve but rather a family of different curves, which depend on the time-course of the inspiration preceding the FVC manoeuvre [10–12]. Therefore, comparison of tidal and maximal F–V curves is incorrect.

d) Respiratory mechanics and time constant inequalities are different during the tidal and maximal expiratory efforts, also making comparisons of the two F–V curves problematic [13–15].

e) Exercise may result in bronchodilatation or bronchoconstriction and other changes of lung mechanics, which may also affect correct comparisons of the two F–V curves [16].

f) Patient's cooperation. Another important limitation of the conventional method is that it requires the patient's cooperation. This is not always feasible [8, 9].

From the above considerations it appears that the detection of EFL on the basis of a comparison of tidal and maximal F–V curves is not valid even when a body box is used. In fact, this has been clearly demonstrated in several studies [17–20]. As a result, use of the conventional method is no longer recommended.

Negative Expiratory Pressure (NEP) technique

Recently, in order to overcome these technical and conceptual difficulties, the *negative expiratory pressure* or *NEP method* has been introduced [17–20]. The NEP technique has been applied and validated in mechanically ventilated ICU patients by concomitant determination of iso-volume flow–pressure relationships [18, 21]. This method does not require performance of FVC manoeuvres, cooperation on the part of the patient or use of a body plethysmograph, and it can be used during spontaneous breathing in subjects in any body position [22], during exercise [19, 23, 24] and in the ICU setting [25–29]. With this method the volume and time history of the control and test expiration are the same.

A flanged plastic mouthpiece is connected in series to a pneumotachograph and a T-tube. One side of the T-tube is open to the atmosphere, whilst the other side is

equipped with a one-way pneumatic valve, which allows for the subject to be rapidly switched to negative pressure generated by a vacuum cleaner or a Venturi device. The pneumatic valve consists of an inflatable balloon connected to a gas cylinder filled with helium and a manual pneumatic controller. The latter permits remote-control balloon deflation, which is accomplished quickly (30–60 ms) and quietly, allowing rapid exposure to negative pressure during expiration (NEP). Alternatively, a solenoid rapid valve can be used. The NEP (usually set at about –3 to –5 cmH_2O) can be adjusted with a potentiometer on the vacuum cleaner or by controlling the Venturi device. Airflow (F) is measured with the heated pneumotachograph, and pressure at the airway opening (Pao) is simultaneously measured through a side port on the mouthpiece. Volume (V) is obtained by digital integration of the flow signal [17–20].

While testing is in progress, the subjects should be watched closely for leaks at the mouthpiece. By monitoring the volume record over time on the chart recorder, the absence of leaks and electrical drift can be ensured by the fact that after the NEP tests the end-expiratory lung volume (EELV) returns to the pre-NEP level. Only tests in which there is no leak are valid [30].

The NEP method is based on the principle that in the absence of pre-existing flow limitation the increase in pressure gradient between the alveoli and the airway opening caused by NEP should result in increased expiratory flow. By contrast, in flow-limited subjects application of NEP should not change the expiratory flow. Our analysis essentially consists in comparing the expiratory F–V curve obtained during a control breath with that obtained during the subsequent expiration in which NEP is applied [17, 18].

Subjects in whom application of NEP does not elicit an increase of flow during part or all of the tidal expiration (Fig. 4; *middle* and *right*) are considered to be flow-limited (EFL). By contrast, subjects in whom flow increases with NEP throughout the control tidal volume range (Fig. 4; *left*) are considered non-flow-limited (NFL). If EFL is present when NEP is applied there is a transient increase in flow (spike), which mainly reflects a sudden reduction in volume of the compliant oral and neck structures. To a lesser extent a small artefact due to the common-mode rejection ratio of the system of measuring flow may also contribute to the flow transients [17, 19]. Such spikes are useful markers of EFL.

The degree of flow limitation can be assessed by means of three different EFL indices: (a) as a continuous variable expressed as %VT with the patient in both seated and supine positions (Fig. 4) [17]; (b) as a discrete variable in the form of the three-categories classification, i.e. NFL both seated and supine; EFL supine but not seated; EFL both seated and supine [17]; and (c) as a discrete variable in the form of the five-categories classification (5-point EFL score) [20].

Application of NEP is not associated with any unpleasant sensation, cough, or other side-effects [17–20]. However, there is a potential limitation of the NEP technique, which concerns normal snorers and patients with obstructive sleep apnoea syndromes (OSAS) [31–34]. With NEP expiratory flow shows a transient drop below control flow, reflecting a temporary increase in upper airway resistance. After this transient decrease in flow, expiratory flow with NEP usually exceeds

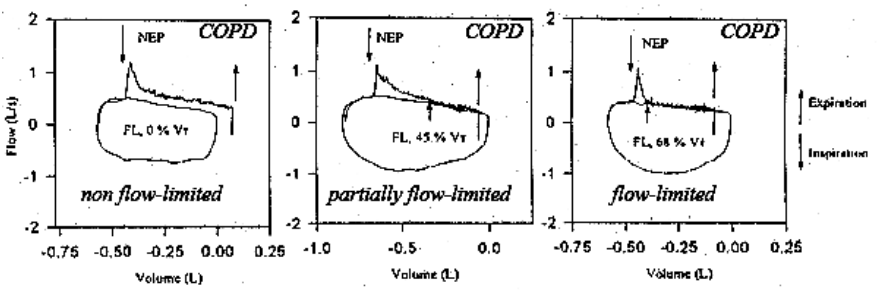

Fig. 4. Flow–volume loops of test breaths and preceding control breaths of three representative COPD patients with different degrees of flow limitation: not flow limited (NFL) (*left*), flow limited (EFL) over less than 50% VT (*middle*), and flow limited from peak expiratory flow (EFL) *(right)*. *Arrows* indicate points at which NEP was applied and removed. (Modified from [20])

control flow, showing there is no intrathoracic flow limitation. Occasionally, flow with NEP remains below control throughout expiration, reflecting prolonged increase in upper airway resistance. In this case, NEP test is not valid for assessing intrathoracic flow limitation. However, this phenomenon is uncommon in non-OSAHS subjects [34]. Furthermore, valid measurements may be obtained with repeated NEP tests using lower levels of NEP (e.g., –3 cmH_2O).

Turning this apparent drawback to advantage, Liistro et al. [32] and Verin et al. [33], in OSAHS patients with no evidence of intra-thoracic obstruction, found a significant correlation of the degree of flow limitation, expressed as %VT in the supine position, with desaturation index (DI) and apnoea/hypopnoea index (AHI).

It appears that the use of the NEP technique during tidal flow–volume analysis studies has led to realisation of the important role of EFL in exertional dyspnoea and ventilatory impairment for a surprisingly wide range of clinical circumstances [35–37]. Therefore, the NEP technique should be regarded as the new gold standard. It is a novel useful research, and clinical lung function tool.

In non-OSAHS and OSAHS patients [33, 34] in whom there is a consistent upper airway collapse in response to the application of NEP, EFL can be assessed by: (a) submaximal expiratory manoeuvres initiated immediately from end-tidal inspiration or (b) by squeezing the abdomen during expiration (see below).

Submaximal expiratory manoeuvres

Pellegrino and Brusasco [38] proposed an alternative technique for detection of EFL. Flow limitation during tidal breathing was inferred from the impingement of the tidal flow–volume loop on the flow recorded during submaximally forced expiratory manoeuvres initiated from end-tidal inspiration in a body box (Fig. 5). After regular breathing with no volume drift, the subject performs a forced expira-

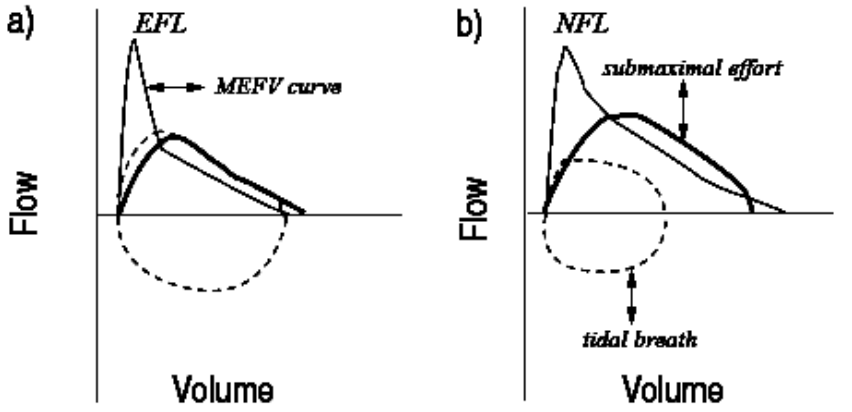

Fig. 5. Graphical representation of the method used to detect EFL by comparing tidal with submaximal effort flow–volume loops started from end-tidal inspiration: **a** a patient with EFL as tidal expiratory flow impinges on submaximal forced expiratory flow; **b** a non-flow-limited subject; tidal expiratory flow is much less than submaximal forced expiratory flow. (Modified from [38])

tion from end-tidal inspiration without breath-holding (partial expiratory manoeuvre). Care is taken to coach the subjects not to slow down the inspiration preceding the partial forced manoeuvre, thus minimising the dependence of forced flows on the time of the preceding inspiration. A deep inspiration to TLC recorded soon after the gentle forced manoeuvre allows the loops to be superimposed and compared at absolute lung volume. Flow limitation is defined as the condition of tidal expiratory flow impinging on the maximal flow generated during the gentle forced expiratory manoeuvre. This method also requires a body box, rendering measurements difficult in various postures, in the ICU and during exercise testing.

Squeezing the abdomen during expiration

Workers in Brussels have shown that manual compression of the abdomen coinciding with the onset of expiration can be used as a simple way of detecting flow limitation at rest [39] and during exercise [40]. With one hand placed on the lower back of the patient and other applied with the palm at the level of the umbilicus perpendicular to the axis between the xiphoid process and the pubis the operator first detects a respiratory rhythm by gentle palpation and then after warning the subject applies a forceful pressure at the onset of expiration. As in the NEP technique, the resulting expiratory flow–volume loop recorded at the mouth is superimposed on the preceding tidal breath (Fig. 6). If expiratory flow fails to increase this indicates flow limitation. This technique produces clear differences between normal subjects and patients with COPD. In one study, the presence of

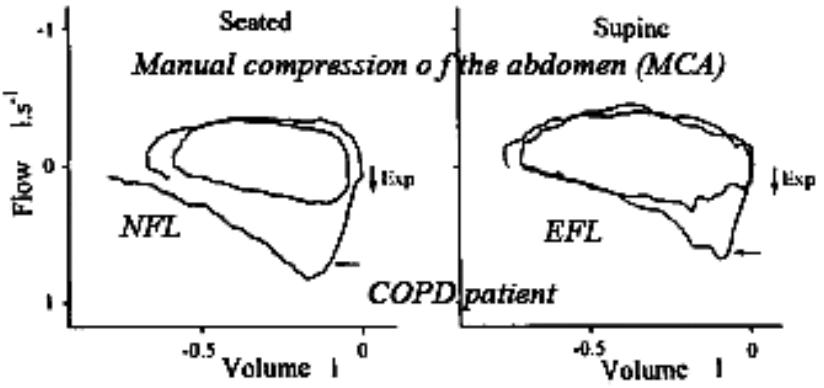

Fig. 6. Flow–volume loops of test breaths and preceding control breaths of a representative COPD patient with different degrees of flow-limitation in seated and supine posture: non flow limited (NFL; *left*) and flow-limited (EFL; *right*), respectively. *Arrows* indicate points at which manual compression of the abdomen (MCA) was applied. (Modified from [39]).

flow limitation detected during exercise in COPD patients was associated with increases in the end-expiratory lung volume (EELV) [39]. Interestingly, not all subjects with COPD exhibited flow limitation when lung volume changed, a finding that requires confirmation in other series. The method is appealingly simple, overcomes problems with the preceding volume history of the test breath and is not influenced by the upper airway compliance. Despite initial concerns about the possibility that gas compression in the alveoli would produce false-positive results, this does not seem to be a practical problem. However, it can be extremely difficult to determine whether flow limitation is occurring for the whole or only part of the preceding breath unless the timing of the technique is very precise. Breath-to-breath variation in EELV can produce contradictory results, as the method assumes that EELV is always constant. Thus far this technique has not been widely applied despite its relative simplicity.

Forced oscillation technique

The most recent approach to detecting expiratory flow limitation during tidal breathing has been to use the forced oscillation technique (FOT) previously applied to look at the frequency dependence of resistance in a range of lung diseases and now available commercially in a modified form using impulse oscillometry [41, 42]. To date, only a few studies with this method have been reported. The principle here is that flow limitation will only be present in patients with obstructive pulmonary disease during expiration. Normally, oscillatory pressures generated by a loudspeaker system at the mouth are transmitted throughout the respiratory system, and

studying the resulting pressures that are in and out of phase with the signal makes it possible to compute both the respiratory system resistance and reactance (a measure of the elastic properties of the system). When flow limitation occurs, wave speed theory predicts that a choke point will develop within the airway subtended by that 'unit' of the lung. In these circumstances the oscillatory pressure applied at the mouth will no longer reach the alveoli and the reactance will reflect the mechanical properties of the airway wall rather than those of the whole respiratory system. As a result, reactance becomes much more negative and there is a clear within-breath difference between inspiration and expiration (see Fig. 3). Dellaca et al. [42] used this property to investigate the distribution of changes in within-breath reactance in normal subjects and in COPD patients who had balloon catheters in place. This allowed a comparison of flow limitation using this new method with that obtained by means of the classic Mead-Whittenberger method [4] directly relating alveolar pressure to flow (Fig. 3). Although this latter technique also proved to have limitations, and specifically could not exclude the presence of flow limitation at low lung volumes, the authors were able to obtain a clear separation between flow-limited and non-flow-limited breaths, using a number of indices of within-breath reactance. In contrast, within-breath resistance showed little fluctuation and did not permit the identification of flow-limited breathing. Some subjects showed consistency in the presence of flow limitation on every breath tested while others had a more variable pattern, presumably reflecting spontaneous fluctuation in EELV. Although within-breath reactance changes are likely to be detecting EFL, a role for airway closure during tidal breathing cannot be completely excluded. This is a problem for all the current tests designed to identify EFL. In a recent study Dellaca et al. [43] found good agreement between NEP and FOT even though the FOT method may detect regional as well as overall EFL. NEP detects the condition in which all possible pathways between airway opening and the alveoli are choked. When this occurs, the total expiratory flow is independent of the expiratory pressure, a condition of 'global' EFL. By contrast, FOT assesses the proportion of the lung that is choked during expiration only. This measures "regional" flow-limitation, and a threshold value indicates when the regional flow limitation reaches the condition of global flow limitation. Therefore, when global EFL is reached, the two techniques should produce the same response [43].

Like the other methods, this technique is independent of the previous volume history of the breath tested, but unlike them it can give breath-by-breath data continuously and provide an aggregate estimate of the probability that flow resistance will be present in an individual. It can be used during exercise and can be automated, which may offer widespread application for the detection of expiratory flow resistance in the ICU and in the routine physiology laboratory.

Technegas method

Technegas is an aerosol of ^{99m}Tc-labeled carbon molecules with small diameter (<0.01 μm) [44], which are capable of becoming deposited in even the most

peripheral regions of the lung. Pellegrino et al. [44] used the inhalation of Technegas to reveal sites of EFL after induced bronchoconstriction in asthmatic patients. They claim that this technique is useful to detect regional EFL well before the NEP and submaximal expiratory manoeuvre techniques can reveal it.

Extensive comparisons between these different methods are needed before the best method or methods for correct assessment of EFL can be recommended. Each of them represents a substantial advance on traditional approaches. By freeing both the doctor and the patient from the confines of the body plethysmograph they have opened up a new era in our understanding of the important principles of flow limitation in a wide variety of settings [35, 37].

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Chapter 6

How to ventilate brain-injured patients in respiratory failure

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It is common knowledge that in brain-injured patients the principal morbidity and mortality are most frequently caused by the primary disease, i.e. cerebral nervous system injury and its neurological consequences [1]. Nevertheless, extracerebral organ dysfunctions are frequent in brain-injured patients, increasing morbidity and mortality [2, 3]. Among them, the most frequent complication is respiratory dysfunction including pulmonary oedema and pneumonia. It is now clear that there is an entire spectrum of pulmonary abnormalities caused either directly or indirectly by acute brain injury. Although respiratory problems seem to play a relevant role in the clinical management of brain-injured patients, very few studies have investigated respiratory function abnormalities in this category of patients [4].

Causes of brain injury are trauma, spontaneous haemorrhage (subarachnoid or parenchymal or both) and surgery (after trauma, haemorrhage, malignancies, etc). It is possible, however, that lung-related problems and consequent prevention and treatment may differ in different categories of brain-injured patients. The aim of this review is to discuss: (a) functional abnormalities; (b) clinical treatment; and (c) possible prevention of respiratory function abnormalities in brain-injured patients.

The role of extracerebral organ dysfunctions in brain-injured patients

Recently, it has been emphasised that the outcome in brain-injured patients is more frequently the result of a progressive dysfunction of organ systems remote from the site of the primary disease process, i.e. multiple organ dysfunction process. Table 1 summarises the average prevalence of extracerebral complications (partitioned into overall and severe) in brain-injured patients, as reported in the most recent literature. Several reports indicate that medical complications after brain injury may significantly contribute to the overall mortality rate [5]. They indicate that pulmonary alterations account for up to 50% of the deaths after brain injury. The mortality in these studies was significantly higher in patients in whom brain injury was associated with at least one organ failure than in those with brain injury alone (65% vs 17%, respectively). The occurrence of pulmonary failure was also associated with longer ICU and hospital stay [6].

Table 1. Prevalence of extracerebral organ dysfunctions in brain injured patients

		Total	*Severe*
Pulmonary	Pneumonia	40%	25%
	Embolism	<1%	100%
Gut		40%	5%
Cardiac	Arrhythmia	30%	5%
	Cardiac failure	5%	1%
Metabolic	Electrolyte disorders	30%	2%
	Diabetes insipidus	7%	7%
Hepatic		25%	4%
Haematological		20%	6%
Renal		10%	15%

In summary, extracerebral organ dysfunctions, and in particular pulmonary failure, are important causes of morbidity and mortality in brain-injured patients.

Why do pulmonary complications occur in brain-injured patients?

We can identify three major causes of pulmonary complications in brain-injured patients: (1) neurogenic pulmonary oedema (NPO); (2) abnormalities in ventilation–perfusion mismatch; (3) structural parenchymal abnormalities.

Neurogenic pulmonary oedema

The most dramatic pulmonary complication in brain-injured patients has been reported to be NPO. In the 1960s, Simmons et al. [7] reported that 85% of their series of combat casualties from Vietnam who died with a severe isolated head injury demonstrated a significant pulmonary pathology, so-called NPO, which included alveolar oedema, haemorrhage and congestion and was not the result of direct lung injury such as might be caused by chest trauma. However, NPO is very rare in civilians with brain injury, except in young patients with massive and usually rapidly fatal brain damage.

Ventilation–perfusion mismatch

Several authors have observed that the majority of brain-injured patients with moderate to severe hypoxaemia do not have evident radiographic abnormalities. Thus, it was postulated that respiratory failure could occur without the presence of interstitial or alveolar oedema, but only because of a ventilation–perfusion mismatch [8].

Three main mechanisms leading to ventilation–perfusion mismatch in brain-

injured patients are: (1) redistribution in regional perfusion which has been found partially mediated by hypothalamus; (2) pulmonary microembolisms which could lead to increased dead space ventilation; and (3) lung surfactant depletion attributable to excessive sympathetic stimulation and hyperventilation.

Structural parenchymal abnormalities

The main reasons explaining respiratory insufficiency in brain-injured patients are structural parenchymal abnormalities.

We can identify five main causes of structural parenchymal alterations: (1) an abnormal breathing pattern; (2) release of inflammatory mediators; (3) release of catecholamines ("sympathetic storm"); (4) infectious processes; and (5) "direct" consequences of trauma, such as the presence of lung contusion, pneumothorax and pain-induced hypoventilation from rib fractures.

Abnormal breathing pattern

Abnormal breathing patterns are commonly seen after brain injury. In particular, both hyperventilation and hypoventilation have been described. Hyperventilation is usually associated with periods of hypoventilation, which together with a reduction in cough reflexes and impaired airway patency from inspissated secretions, can induce alveolar atelectasis and consolidations [9].

Release of inflammatory mediators

Brain injury causes a marked release in the brain and in the systemic circulation of pro- and con- inflammatory agents, which can lead to peripheral organ dysfunction, predominantly of the lung, and to moderate to severe immunosuppression [10, 11].

Thus, the release of these inflammatory mediators can lead to multiple organ failure, where the lung parenchyma appears to be a preferential and more susceptible target. However, possible further mechanisms for brain injury-related symptoms of systemic inflammation include the high incidence of aspiration pneumonia in patients with a poor condition, which can provide a nidus for systemic inflammation. Impaired pulmonary gas exchange could further contribute to systemic inflammation, as invasive strategies of mechanical ventilation can cause volutrauma and barotrauma, which in turn can trigger pulmonary cytokine release.

Interestingly, in a recent study [12] it has been shown that massive brain injury enhances lung damage in an isolated lung model of ventilator- induced lung injury. This was probably due to the release of inflammatory mediators from the injured brain. On the other hand, other investigators have found that respiratory failure per se induced changes in the hippocampus with an increase in SP100, a marker of neuronal damage [13]. Overall, these findings suggest a tight cross-link between pulmonary and brain function, which has to be taken into account when brain-injured patients without or with respiratory failure need mechanical ventilation.

Release of catecholamines

Brain injury is followed by prolonged sympathetic hyperactivity, which may lead to hypertension and/or tachycardia. This circulatory hyperactivity induces an increase in cerebral blood volume and/or cerebral blood flow and hence in intracranial pressure. Moreover, the outcome after brain injury appears to be related to the intensity of the plasma catecholamines [13]. Catecholamines, and mainly norepinephrine, have been shown to produce two prevalent effects on the lung: (1) an increase in the alveolar capillary barrier permeability; (2) an increase in the pulmonary lymph flow.

Infectious processes

Brain-injured patients are characterised by an elevated risk of developing ventilator-associated pneumonia (VAP) [14, 15]. Its incidence is estimated to range between 30% and 50% among brain-injured patients, being extremely severe in only 20–25% of the cases. Table 2 shows the independent risk factors for VAP in brain-injured patients. It is evident that altered consciousness has been found to be an important independent risk factor for VAP in most of the studies that included such patients in the research. VAP can be arbitrarily divided into "early" (occurring within the first 4 days after admission to the ICU) and "late" pneumonia (occurring later). Early pneumonia accounts for about 50% of the overall VAP during ICU stays. Microorganisms can be classified into potentially pathogenic and nonpathogenic microorganisms. The most frequent aetiological agents for early VAP include *Staphylococcus aureus* and, less frequently, *Streptococcus pneumoniae* and *Haemophilus influenzae*. In contrast, the most frequent aetiological agents for late VAP are Enterobacteriaceae, *Acinetobacter* spp. and *Pseudomonas aeruginosa*.

Table 2. The independent risk factors for ventilator-associated pneumonia (*VAP*) in brain-injured patients

Type of risk factor	Specific factor	***Risk***
Related to brain injury	Altered consciousness	6.6
Associated with treatment of brain injury	Aspiration	7.0
	Emergency intubation	6.4
	Mechanical ventilation >3 days	2.3
Associated with treatment of a general population of critically ill patients	Reintubation	5.4
	Age 60 years	5.3
	Supine position	4.8
	Previous disease	3.6
	Prior antibiotics	2.9

Although the predominant pathogens of early-onset pneumonia in patients with brain injury have been well established in several epidemiological studies, the precise relation of prior upper airway, tracheobronchial and gastric colonisation patterns with the development of pneumonia and microbial patterns has not been well investigated. In conclusion, patients with brain injury are characterised by a high incidence of VAP. Patterns of colonisation and pneumonia suggest that these patients can suffer from an alteration of airway immune defence very early in their illness. The upper airways are the most significant reservoir of subsequent tracheobronchial colonisation with early-onset pathogens, which in turn are associated with early-onset pneumonia (within 4 days). Both the upper airways and the stomach may be independent reservoirs for tracheobronchial colonisation with late-onset pathogens and late-onset pneumonia. Preventive measures to reduce the incidence of early-onset pneumonia in this population of patients will probably aim at eradication of both upper and lower airway colonisers.

Lung morphological pattern in brain-injured patients

The morphological pattern of the lung parenchyma in brain-injured patients who develop respiratory insufficiency has not been fully investigated. The lung CT scans in patients with VAP are characterised by marked lung densities in the dependent regions. In contrast, the nondependent regions appear relatively healthy and well aerated, without any presence of "ground-glass" radiological alteration. These dependent densities are poorly responsive to the application of recruitment manoeuvre or high PEEP levels, but are partially recruited when the patients are positioned prone. This probably means that the main structural lung alteration during VAP in these patients is not the alveolar consolidation, but rather alterations or the peripheral airways with consequent alveolar collapse [16]. These findings can have important implications for the prevention and treatment of VAP in these patients.

Prevention of respiratory function abnormalities in brain-injured patients

Since respiratory dysfunction plays a relevant part in the outcome of brain-injured patients, its prevention is extremely important. Unfortunately, very few studies have investigated the efficacy of specific protocols in preventing respiratory dysfunction in such patients, and most of them were not randomised.

We believe that the main goals should be: (1) to prevent ventilator-induced lung injury; (2) to prevent lung collapse and/or consolidation; (3) to prevent lung infections; and (4) to accelerate weaning from mechanical ventilation as soon as possible.

Low tidal volume

It is now widely accepted that mechanical ventilation itself can initiate or propagate a type of lung injury that is histologically indistinguishable from diffuse alveolar damage arising from other causes [17]. Three mechanisms of ventilation-induced lung injury (VILI) are volutrauma (overdistension injury); atelectrauma (opening–closing injury); and oxygen toxicity. The importance of VILI has increased recently as its adverse systemic effects, or biotrauma, have been documented [18].

Because of the heterogeneity in terms of disease distribution within the lung of an ALI (acute lung injury)/ARDS (acute respiratory distress syndrome) patient, a situation is created whereby overdistension, or volutrauma, is likely to occur. When a given tidal volume is delivered it will go predominantly to the relatively small areas of the lung where there is less disease, since these are generally more compliant. These areas, therefore, may receive volumes significantly in excess of what has been found to be a safe level if tidal volumes that are suited for an entire lung are used. Through mechanical transduction of alveolar wall stretch or stress failure of the lung ultrastructure, this overdistension may then be translated into an inflammatory cascade that can have systemic consequences.

The heterogeneity of lung injury also leads to alveolar instability and localised lung unit collapse. The unstable alveoli may then undergo tidal opening and collapse with each respiratory cycle. Owing to local overdistension resulting from alveolar interdependence, or because of shearing forces, this atelectrauma can contribute to VILI. According to the major mechanisms of VILI outlined above, lung-protective ventilation or minimisation of VILI should avoid lung overdistension to minimise volutrauma; provide adequate end-expiratory lung volume to avoid cyclical end-expiratory lung unit collapse and subsequent atelectrauma; and avoid high inspired oxygen concentrations. The clinical importance of lung protection has been demonstrated through a reduction in mortality in a number of randomised controlled trials. In the largest of these studies 861 patients were enrolled, and the results documented a 9% absolute risk reduction in mortality for the group randomised to receive a targeted tidal volume of 6 ml/kg predicted body weight versus those who received tidal volumes of 12 ml/kg [19]. In neurosurgical patients the direct generalisability of these studies is not clear, as in all the studies available patients with head injuries and those in whom hypercapnia might be contraindicated were excluded. Clearly brain-injured patients who develop ALI/ARDS are not immune to VILI, but the question is how best to balance the potentially competing therapeutic strategies of lung-protective ventilation and brain-protective concepts.

Hyperventilation therapy for acute brain injury

Hyperventilation has been widely used in the treatment and prevention of raised intracranial pressure (ICP) following head injury, with many centres aiming at a target $PaCO_2$ of less than 25 mmHg [20]. Technically, induced hypocapnia is the more precise terminology that should be used, but for the sake of clarity we will

continue to use the more common term, hyperventilation. Hyperventilation lowers ICP by lowering the $PaCO_2$, thereby inducing cerebral vasoconstriction and a subsequent decrease in cerebral blood volume. Considerable controversy exists, however, about the appropriateness of hyperventilation in this context [21]. Studies examining the potential for the induction of cerebral ischaemia with hyperventilation have yielded mixed results: two studies published in 2002 supported the theory that hyperventilation produces cerebral ischaemia [22, 23], whereas two separate papers concluded that hyperventilation in patients with TBI does not lead to ischaemia [24, 25]. While intermittent hyperventilation may be helpful for transient raised ICP and acute neurological deterioration, current recommendations are against the use of chronic prophylactic hyperventilation [26]. Indeed, a recent Cochrane review on this subject [27] concluded that there are inadequate data to allow an assessment of potential benefit or harm that might accrue from treatment with hyperventilation in severe head injury. Establishing that normocapnia, rather than hyperventilation and hypocapnia, is the routine target in brain-injured patients certainly makes the goals of brain protection and lung protection easier to reconcile. In some cases, however, it can be challenging to maintain a normal $PaCO_2$ while avoiding overdistension injury. In Fig. 1, our general approach to mechanical ventilation in brain-injured patients is shown. The first step we recommend in these cases (regardless of whether or not the patient is brain injured) is a careful evaluation of the patient to look for factors that could improve CO_2 clearance—

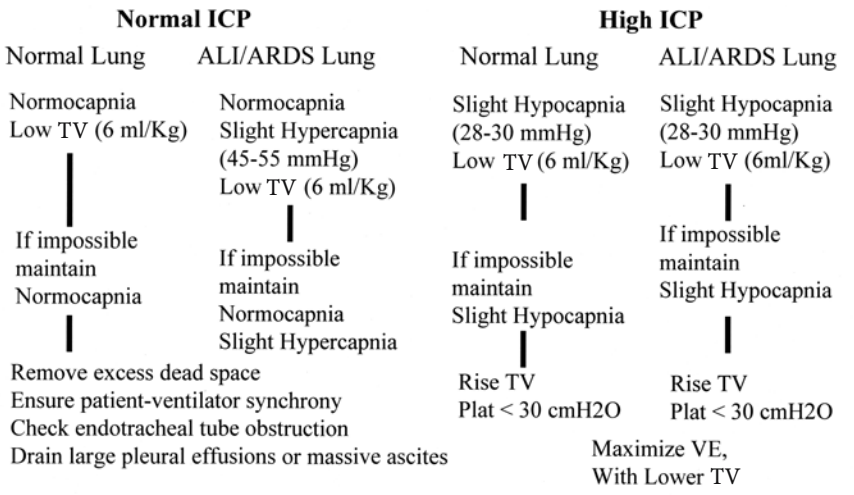

Fig. 1. Ventilatory management in brain-injured patients (*ALI* acute lung injury, *ARDS* acute respiratory distress syndrome, *ICP* intracranial pressure, FiO_2 inspiratory oxygen fraction, *Plat* inspiratory plateau pressure of the respiratory system, $SatO_2$ oxygen saturation, *TV* tidal volume, *VE* minute volume)

these include removing any excess deadspace from the ventilator circuit, ensuring adequate patient–ventilator synchrony, checking the endotracheal tube for partial obstruction and considering manoeuvres to improve respiratory system compliance, such as draining large pleural effusions or massive ascites. If a high $PaCO_2$ remains a problem after these steps then the risks and benefits of targeting eucapnia and of a limited tidal volume must be carefully weighed against each other. As stated above, there is no direct clinical evidence to guide these decisions. Our practice is first to clarify whether brain-injured patients truly have ALI/ARDS or whether they have been receiving lower tidal volumes in a prophylactic fashion. If the latter is the case, we typically let tidal volumes rise to ensure a normal $PaCO_2$. If they truly have ALI/ARDS we next consider whether the patient has a raised ICP, using by clinical examination and by direct measurement. If ICP is not high and the patient does have ALI we would usually continue to target a low tidal volume, allowing the $PaCO_2$ to rise slightly. We continue to monitor the ICP and clinical status of the patient closely, but if these are stable we might allow the $PaCO_2$ to stay in the range of 45–55 mmHg. From this point the $PaCO_2$ could still be acutely corrected back down to normal by means of hyperventilation if a clinical neurological deterioration were to develop. Finally, in patients with ALI/ARDS who have raised ICP or are in need of active management, such as administration of mannitol to control their ICP, we avoid hypercapnia, even if this means allowing tidal volumes to rise. We are still cognisant of VILI, however, and attempt to maximise alveolar ventilation using the lowest tidal volumes possible.

Hyperoxia therapy

Currently, no neuroprotective therapy has been shown to reduce the secondary neuronal damage occurring after TBI. Recent studies have addressed the potential of hyperoxia to ameliorate brain ischaemia after TBI [28, 29]. Increasing the inspired fraction of oxygen results in a decreased cerebral lactate concentration measured in the extracellular space using microdialysis, but not surprisingly (given its dependence on haemoglobin transport), does not substantially improve oxygen delivery to the brain [28]. The ratio between lactate and pyruvate (a better indicator of the cellular redox state than lactate alone), however, is not changed by hyperoxia [29]. In addition, it has been postulated that lactate might be an alternative fuel for neurons during the acute postinjury phase. Both because of a lack of demonstrated efficacy and because of concern about potential pulmonary oxygen toxicity, our practice is to target reasonable oxygen saturations of 91–94% in our brain-injured patients.

Prevention of lung collapse and/or consolidation

Positive end-expiratory pressure

The use of PEEP has long been controversial in the management of the head-injured patient because of concerns about decreased cerebral perfusion—resulting both

from decreased cerebral venous outflow and increased ICP—and also an effect on venous return and subsequent reduced mean arterial pressure. There are also reasons for considering the use of significant levels of PEEP, however, including improving oxygenation and avoiding atelectrauma. Overall, it appears that when PEEP is set at levels that are lower than ICP this does not have a subsequent significant effect on ICP [30]. More recent studies are also consistent with the concept that in a euvolaemic patient, an increase in mean airway pressure is not detrimental. Huynh et al. [31] looked retrospectively at the effects of increasing PEEP (0–5, 6–10, 11–15 cmH_2O) on ICP; they found that as PEEP increased ICP decreased, without any effect on systemic oxygen delivery or consumption. Another recent study [32] investigated the relationship between PEEP and ICP in patients with subarachnoid haemorrhage, who were divided into groups based on their respiratory system compliance. ICP did not change in either group as PEEP was increased from 0 to 12 cmH_2O. Not unexpectedly, haemodynamic effects of PEEP including a reduced mean arterial pressure were observed only in patients with normal respiratory compliance [32]; those with a reduced compliance (as commonly seen in ALI/ARDS) were protected. The interaction between the pulmonary and cerebral systems has also recently been emphasised by Mascia et al. [33], who demonstrated that patients in whom significant alveolar recruitment was achieved with increases in PEEP (one of the goals being lung-protective ventilation) had no observed increases in ICP. Those whose lung volumes did not increase with PEEP had a rise in $PaCO_2$ and a subsequent increase in cerebral blood flow and ICP [33]. Overall, it appears that the use of at least moderate levels of PEEP in brain-injured patients should be safe [34] and is likely to have fewer adverse consequences in ALI/ARDS patients, because of their decreased lung compliance. Indeed, in some patients with heterogeneity in local cerebral perfusion pressures, applied PEEP above levels of ICP may be helpful in improving perfusion to injured areas by reducing venous steal. The systemic haemodynamic effects of PEEP with subsequent reductions in mean arterial pressure and cerebral perfusion pressure may be an issue, but these can usually be overcome with the administration of intravenous fluids or vasoactive drugs. We use at least 5 cmH_2O PEEP in all our patients, and use significantly higher levels in many with oxygenation difficulties. Of course, this therapy must be individualised, with responses to PEEP in terms of haemodynamics, ICP, and neurological status being observed carefully and adjusted when appropriate.

Prone position

In addition to PEEP, preventive use of the prone position could be extremely useful in reducing the occurrence of lung worsening [35, 36] or improving respiratory function when severe respiratory failure is established [37].

Furthermore, the prone position has proved effective in improving brain tissue oxygenation of the brain in severely hypoxaemic patients, with minimal negative effects on ICP and CBF (cerebral blood flow) [38]. However, it should be borne in mind that both during recruitment manoeuvres and when the patient is in the prone

position accurate monitoring of the physiologic cerebral function is warranted to minimise possible negative effects of the manoeuvre itself on the brain [39, 40].

Fluid balance

Careful fluid balance is probably important to reduce progressive accumulation of fluids in the interstitial pressure, which would favour development of respiratory failure. Recent studies indicate that ICP- rather than cerebral perfusion-targeted protocols can lead to a reduction in the fluid requirement and consequently to a reduction in the number of episodes of respiratory insufficiency, all of which is associated with a better neurological outcome [41, 42].

Drugs

Specific drugs, such as low-dose corticosteroids, with strict control of glucose serum levels could be useful to reduce the local and systemic inflammatory response, especially in the presence of VAP, but studies in humans are lacking [43]. Furthermore, the use of antisympathetic drugs (clonidine) and selective β_1-antagonists to reduce the negative systemic effects of the sympathetic storm on the lung has been found to be associated with better pulmonary and neurological outcome [44].

Prevention of lung infection

Several treatments have been proposed to prevent lung infection.

Antibiotic prophylaxis with a second-generation cephalosporin (cefuroxime or cefoxitin) can be useful to prevent early pneumonia. However, some studies indicated an increased rate in late pneumonia when antibiotic prophylaxis was used for more than 24 h [45].

Selective digestive decontamination (SDD) has been proposed to reduce the microbiological load in the oro-pharynx and in the stomach, and few studies showed any beneficial effects in trauma patients in terms of reducing the incidence of ventilator-associated pneumonia. However, its effects on mortality and morbidity are controversial [46, 47].

An upright position also can be useful in reducing VAP and length of ICU stay in a general population of critically ill patients. The upright position is in any case usually adopted in brain-injured patients, so as to reduce ICP, when necessary [48].

Continuous oro-pharyngeal aspiration has been found to reduce upper airway contamination and the occurrence of VAP [49].

Correct use of antiacid drugs is warranted because of the elevated risk of gastric haemorrhage in these patients [50].

Nutrition improves outcome in brain-injured patients, but it is not clear what the respective roles of enteral and parenteral nutrition will be [51, 52].

Staff hygiene protocols are warranted: in particular, a careful hand-washing policy seems to reduce the incidence of infections and improve patients' outcome [53].

Accelerate weaning from the ICU

Early tracheostomy may play a relevant part in weaning and in improving clinical management of these patients [54, 55]. Tracheostomy is better tolerated than translaryngeal intubation, allows a better cleaning of the oro-pharynx and reduces the incidence of sinusitis and work of breathing. With the development of percutaneous techniques, the manoeuvre now appears to be easier and safer [56]. Daily evaluation of the presence of spontaneous or minimally assisted breathing during the weaning phase is mandatory in brain-injured patients, in order to avoid delay in intensive care unit discharge and to reduce costs. The common weaning parameters do not apply in brain-injured patients, while neurological clinical evaluation plays the main part [57, 58].

Aggressive chest physiotherapy, positioning and fibreoptic fibroscopy can remove deep secretions, reducing the risk of developing VAP, although clinical data are sparse.

Finally, daily interruption of continuous sedation shortens the time the patients spend on the ventilator in a general population of critically ill patients [59]. However, in brain-injured patients the optimal level of sedation is controversial, since while sedation is necessary to limit intracranial hypertension crisis, on the other hand it can delay the start of weaning and prolong the duration of mechanical ventilation.

Conclusions

In conclusion, brain-injured patients are at elevated risk of extracerebral organ dysfunctions, and in particular of ventilator-associated pneumonia, which can lead to a worse neurological outcome. In these patients, ventilator-associated pneumonia is characterised mainly by atelectasis or consolidation of the lower lobes. Thus, strategies should be implemented to prevent lung collapse and/or consolidation and lung infections, and to accelerate weaning from mechanical ventilation [60]. We believe that an integrated approach could be extremely useful, not only because respiratory failure might be prevented or treated more rapidly, but also because neurological outcome might be improved and stay in intensive care, shortened.

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Chapter 7

Helping surgical patients to give up smoking

D.O. Warner

Perioperative physicians encounter the consequences of long-term tobacco use daily. Patients may require surgery specifically as a consequence of tobacco (e.g., in the case of lung cancer), or smoking-related diseases (e.g., coronary artery disease) may require specific management during surgery for other indications. However, perioperative physicians seldom intervene to help their patients give up smoking. This is most unfortunate, because effective interventions can have two types of benefit. First, there is growing evidence that even short-term abstinence from smoking can improve immediate perioperative outcomes, such as the rate of wound infection [1]. Second, the perioperative period represents a "teachable moment" for smoking cessation [2], and if patients use this opportunity to give up smoking permanently this will have tremendous benefit for their long-term health. For example, in most healthcare facilities, smokers must maintain abstinence while in the facility. This period of forced abstinence may be an excellent opportunity to initiate an attempt at giving up. Also, patients may be much more aware of their health status at such times, and thus more amenable to changes in behaviour that will promote health.

We recently surveyed anaesthesiologists and surgeons in the United States to document current practices and attitudes of these physicians to interventions relating to tobacco [3]. Over 90% of both groups almost always ask their patients about tobacco use, and almost all respondents felt that surgical patients should maintain abstinence after surgery. Most felt that it was their responsibility to advise their patients to stop smoking, but only 30% of anaesthesiologists and 58% of surgeons routinely do so, and very few in either group actually provided any assistance to the patients to help them give up smoking. Further questions revealed several barriers to intervention. The remainder of this paper will discuss these barriers, many of which are simple misconceptions, and how they might be overcome. More comprehensive reviews of these topics are also available [1, 4, 5].

Does giving up smoking improve perioperative outcomes?

Some physician question whether giving up smoking, especially if it occurs only a short time before surgery, will improve outcomes. Although many questions remain, there is good reason to believe that even a brief abstinence may improve cardiac and wound-related outcomes.

Recent smoking may contribute to acute vascular events by increasing myocardial work, decreasing oxygen delivery secondary to carbon monoxide, causing coronary vasoconstriction and releasing catecholamines [6]. As a result, smoking acutely decreases exercise capacity, and relatively brief abstinence improves it [7]. In smokers, expired CO concentration, an indicator of recent smoking, is correlated with the frequency of significant ST depression during general anaesthesia [8]. Thus, although the period of abstinence needed to reduce perioperative risk is not known, even relatively brief preoperative abstinence may be beneficial. The healing of surgical wounds is impaired in smokers [9]. Preoperative abstinence can dramatically decrease the frequency of wound-related complications [10]; the duration of abstinence necessary for this benefit is not known, but it appears to be less than 4 weeks [11]. Thus, there is good reason to think that even relatively brief periods of abstinence may be beneficial.

Is it harmful for smokers to give up immediately before surgery?

In our survey, some physicians expressed concern that brief preoperative abstinence might actually be harmful [3]. Two factors contribute to this concern. First, the results of some prior studies have been interpreted as showing that pulmonary complications are actually increased in patients who give up smoking within the last few days or weeks before surgery [12, 13]. However, more recent studies have shown that abstinence starting within a few weeks of surgery does not significantly increase the rate of complications [13–16]. It is true that several weeks of abstinence may be necessary before pulmonary outcomes improve, but this should not stop physicians from recommending preoperative abstinence, even if this can be achieved only a few days before surgery. Second, many smokers view cigarettes as a stress management tool and may therefore be reluctant to abstain at a time when they face the considerable stresses associated with surgery. Furthermore, nicotine is highly addictive, and nicotine withdrawal can become manifest in the form of several unpleasant symptoms, including irritability, restlessness, sleep disturbances, and depression, all of which could potentially complicate postoperative recovery. However, our recent work shows that smokers report no greater increases in psychological stress over the perioperative period than do nonsmokers, and nor do they consistently develop symptoms of nicotine withdrawal [17, 18]. Thus, patients (and their physicians) can be reassured that craving for tobacco will not routinely hamper their recovery if they remain abstinent. In addition, nicotine replacement therapy can be used to help manage any withdrawal symptoms that do occur.

Since it is so hard to give up smoking, are the methods to help patients give up effective?

Many people have the impression that treatments for tobacco dependence are not particularly effective, which discourages physicians from even attempting to intervene. It is true that nicotine is highly addictive, and that it is very difficult to give up—rates of "spontaneous" giving up in the general population are relatively low (~4% of smokers per year), although approximately 50% of smokers make an attempt to give up each year in the United States. However, the good news is that the majority of smokers do want to stop smoking and that millions of smokers do succeed, usually after multiple attempts [19]. There are now more ex-smokers than active smokers in the United States. It is helpful to think of tobacco dependence as a chronic disease and to approach its management as such—requiring persistent, repeated efforts to control. And effective interventions are available; most interventions will at least double the success rates of attempts to give up, a treatment effect that would be regarded as highly significant in the context of other diseases, such as cancer. These interventions can be categorised as using counselling (i.e., information exchange with patients) or using pharmacotherapy. The evidence base for interventions has recently been updated (2000 #34).

Even just advising patients to stop smoking increases the quit rates, and smokers should be advised to give up by every physician they encounter. Even brief counselling (less than 3 min) on the subject of giving up smoking from clinicians will increase the rate of abstinence further. More intensive interventions are even more effective, and there is a dose–response relationship between total time spent in counselling and efficacy. Pharmacotherapy is another important element of strategies to help smokers give up [20] and can approximately double the success rate. There are several means of replacing nicotine, including gum, inhalers, nasal spray, patches and lozenges, all of which are equally effective. Nicotine gum, patches, and lozenges are available without a prescription in the USA. Other medications also are useful in promoting cessation. Sustained-release bupropion, which is also used as an antidepressant, also approximately doubles success rates. Recently, varenicline, a partial nicotinic agonist administered orally, has been approved for the treatment of tobacco dependence.

Is it safe to use nicotine replacement therapy in surgical patients?

Some physicians have expressed concern that nicotine replacement therapy (NRT), the most commonly-used pharmacotherapy used to treat tobacco dependence, might not be safe in surgical patients. Concerns included the effects of nicotine on cardiovascular function and its effects on wound and bone healing.

It is now well established that NRT is safe in cigarette smokers with coronary artery disease, even if they continue smoking [6]. NRT may even lower cardiovascular risk if cigarette consumption is reduced but not eliminated [21]. As far as wound-related complications are concerned, several studies have shown that nico-

tine itself can impair wound healing in experimental animals [22]. However, in most animal studies the nicotine doses used are far in excess of that provided by NRT in humans. An important recent study showed that giving up smoking dramatically decreased the incidence of surgical wound infection in humans; this benefit was observed whether or not the subjects used NRT to help them in giving up [11]. Thus, as in the case of cardiovascular function, the avoidance of the other constituents of cigarette smoke is likely to be beneficial even when nicotine is continued. Studies specific to the surgical setting remain to be performed, but the evidence available does not support a detrimental effect of NRT in surgical patients. It is almost certain that abstinence achieved even with NRT is far preferable to continued smoking, and we have shown that in the absence of intervention most smokers will almost immediately resume smoking after discharge from a surgical facility.

I don't have time to help my patients give up smoking, and I don't know how to help

Even though most respondents to our survey expressed a willingness to help their patients stop, many also felt as though they did not have time to do so, and very few have had any training in intervening. These are very real challenges. All physicians face time pressures, and perioperative physicians may have relatively limited contact with their patients, especially before surgery, when opportunities to intervene may be greatest. However, with even a small investment of time, perioperative physicians can make a difference. For primary care physicians, components of clinical interventions have been codified as the "5 A's": *A*sk about tobacco use, *A*dvise to stop, *A*ssess willingness to make an attempt to stop, *A*ssist in this attempt, and *A*rrange follow-up [19]. Even with limited preoperative patient contact, perioperative physicians can perform these first three intervention elements at any time in the perioperative period, ideally beginning as early in the preoperative period as possible.

Ask—With every new patient encounter, all perioperative physicians should ask their patients about their tobacco use. Some feel that this is a personal decision on the part of the patient and thus should not be addressed, but this is simply not true—nicotine dependence is a medical condition that should be addressed by every medical professional with every patient.

Advise—At every opportunity, every smoker should be strongly urged to stop, and in a clear and unambiguous fashion. This message can easily be tailored to take advantage of the unique circumstances of surgery. All patients can be told that continued smoking may have direct consequences for their recovery from surgery, so that they should try to refrain from smoking for as long as possible after their operation. If seen at least 1 day before surgery, patients should be advised to "fast" from cigarettes beginning the evening before surgery, using nicotine gum or lozenges if desired on the morning of surgery. The physicians should then take advantage of the imminent surgery as a teachable moment, telling patients that this

is an excellent time to consider giving up permanently and that the forced abstinence associated with their visit to a healthcare facility will be an opportune time to initiate and extend an attempt to stop. All this information can be easily conveyed within a 2- to 3-min counselling session and does not require specialised training.

Refer—Recognising that busy physicians often do not have the time or training necessary to provide more extensive interventions, including the follow-up visits that are important in the process, public health authorities are recommending that physicians take advantage of referrals to nicotine dependence resources, much as referrals are made for the provision of other specialised medical services. In the United States, and in many other countries, there are now numerous resources to which patients can be referred if they want help in giving up smoking. Many healthcare systems have specialised nicotine dependence treatment centres that provide a wide range of services. Telephone counselling services, referred to in the USA as "quitlines", have also enjoyed recent popularity [23]. These are very convenient for the patients, offering the potential for multiple counselling sessions and, in many cases, access to free NRT. Each perioperative physician should take some time to determine what referral resources are available in his or her practice setting. Once identified, referral information can be incorporated into a card that can be distributed to patients [5].

Conclusions

There is now considerable evidence that even brief perioperative abstinence from tobacco may be beneficial in smokers undergoing surgery. For this reason, perioperative physicians should strongly recommend abstinence and should help their patients to achieve this goal. This may not only improve immediate perioperative outcomes; it could also be embraced as an excellent opportunity for smokers to achieve permanent abstinence. In this way, our relatively brief patient encounter can have a lasting beneficial effect on the long-term health of our patients who smoke.

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Chapter 8

Respiratory issues and ventilatory strategies for morbidly obese patients

J. Sprung

In the United States, the increasing incidence of morbid obesity (MO) is a national health care crisis that has resulted in a corresponding increase in the number of bariatric surgeries performed annually. MO and associated respiratory comorbid conditions, such as obstructive sleep apnoea or pulmonary hypertension, may create considerable challenges for the anaesthetic management of patients and involve possible complications. Sugerman [1, 2] showed that markers of respiratory insufficiency (e.g. low arterial oxygenation, carbon dioxide retention, frequent apnoeic episodes, reduced lung volume, and presence of polycythaemia) greatly improved after bariatric surgery and weight loss. Therefore, respiratory comorbid conditions should prompt an aggressive surgical approach for weight reduction.

Tracheal intubation issues and potential for respiratory depression

Whether tracheal intubation is more difficult in obese patients is debatable. Juvin et al. [3] reported that intubation was difficult in 15.5% of obese patients and in 2.2% of lean patients. No predictor of difficult intubation in the lean population was relevant in the obese population. Brodsky et al. [4] found that neither obesity nor high body mass index predicted problems with tracheal intubation. However, a high Mallampati score and a large neck circumference may potentially increase the degree of difficulty experienced in intubation or laryngoscopy. A conservative approach includes fibreoptic intubation of all questionable patients and patients for whom mask ventilation might be difficult. It might also be easier to decide on the method of tracheal intubation if an array of alternative intubating devices (e.g., intubating laryngeal mask airway, Bullard scope, or Wu scope) is available for use by an anaesthesiologist proficient in these less common techniques.

Approximately 10% of MO patients have hypoventilation syndrome [1], and more than 50% have moderate to severe sleep apnoea [5]. Intraoperative use of opioids in these patients may be associated with excessive postoperative respiratory depression. Use of shorter-acting anaesthetics, opioids or regional anaesthesia is desirable. A recent prospective randomised study showed that adult MO patients who underwent major abdominal surgery regained consciousness considerably faster and had higher oxyhaemoglobin saturation upon entering the postanaesthesia recovery room after desflurane anaesthesia than after sevoflurane anaesthesia [6].

However, additional studies are necessary to confirm whether anaesthetic agents with shorter pharmacokinetic properties improve postoperative outcomes in MO patients.

Alternatives to opioids, such as α_2-adrenergic receptor agonists, have been used to sedate patients during fibreoptic intubation. Because these drugs are free of effects on respiratory function, they may be used during the course of anaesthesia in MO patients, especially those who have obstructive sleep apnoea. Dexmedetomidine hydrochloride, an α_2-adrenergic receptor agonist approved by the US Food and Drug Administration for use as a sedative in the intensive care unit, has hypnotic, anaesthetic-sparing, analgesic, and sympatholytic properties. However, its role in intraoperative anaesthesia practice has not yet been established, although a recent case report describing its potential usefulness has been published [7].

Intraoperative arterial oxygenation

Another challenge of anaesthetising MO patients may be intraoperative maintenance of partial oxygen pressure in arterial blood (PaO_2). During anaesthesia, MO patients have large alveolar–arterial oxygen gradients that require high inspiratory oxygen concentrations to maintain PaO_2 levels comparable to that of normal-weight patients. MO patients also have larger reductions in lung volume than do normal-weight patients, and these reductions parallel greater impairment of gas exchange [8, 9]. After atelectasis develops, treatment with positive end-expiratory pressure (PEEP) may be insufficient. In the past few decades, different strategies were used to re-expand collapsed lungs during anaesthesia and to optimise oxygenation levels.

Strategy 1: large tidal volume

Theoretically, large tidal volume ventilation improves PaO_2 by intermittently increasing mean lung volume above the closing volume [10]. However, tidal volumes between 15 and 20 ml/kg of ideal body weight had little or no beneficial effect on oxygenation levels in MO patients [11]. In another study, large tidal volume and doubled respiratory rate did not improve arterial oxygenation (Fig. 1) [9]. It is possible that the collapsed alveolar units did not reopen, despite the high tidal volume, because of intermittent lung inflation.

Strategy 2: use of PEEP

Isolated effects of PEEP during mechanical ventilation either are of no benefit [12] or only slightly improve PaO_2 levels [8] for MO or normal-weight patients (Fig. 2). Alveolar recruitment with PEEP was higher in obese patients than in normal-weight patients [8]. Greater alveolar recruitment was associated with an increase in PaO_2 [8]. For example, a PEEP of 10 cmH2O increased PaO_2 from 110±30 mmHg

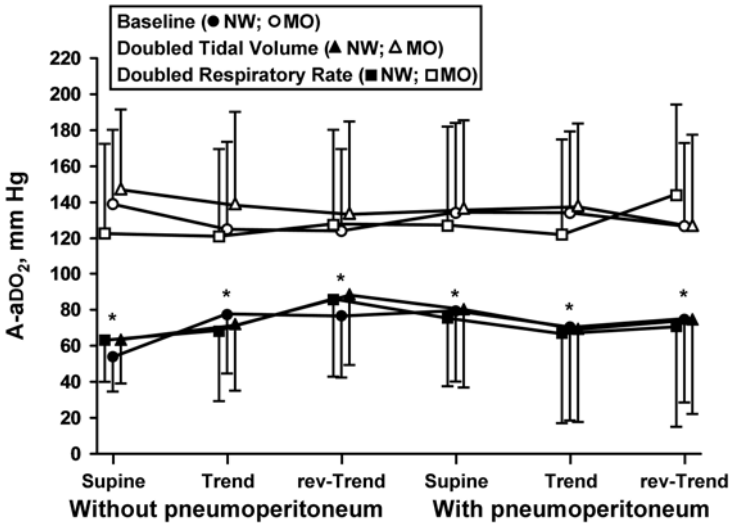

Fig. 1. Effects of obesity, body position, pneumoperitoneum, and mode of ventilation on alveolar-arterial oxygen difference ($A–aDO_2$). The *asterisk* indicates statistically significant differences of $A–aDO_2$ between MO patients (any mode of ventilation) and normal-weight patients (any mode of ventilation). *MO* morbidly obese, *NW* normal weight, *rev-Trend* reversed Trendelenburg position, *Trend* Trendelenburg position. (From [9]. Used with permission)

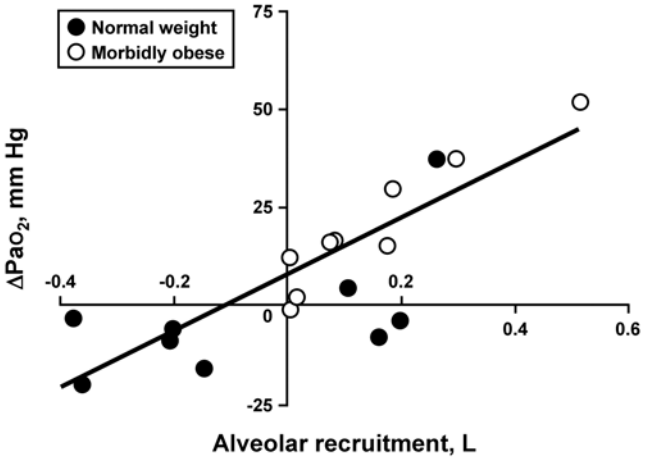

Fig. 2. Relationship between alveolar recruitment with positive end-expiratory pressure and changes in arterial oxygen tension in normal weight and morbidly obese patients. (From [8]. Used with permission)

to 130±28 mmHg in MO patients. Routine use of PEEP is not recommended because its benefits are minor, but its application early in the induction of general anaesthesia may prevent atelectasis and improve oxygenation for MO patients [13].

Strategy 3: alveolar recruitment manoeuvre

Physiologically, high air pressure is needed to open collapsed alveoli during anaesthesia [14]; an opening pressure of at least 40 cmH_2O is required for full reversal of anaesthesia-induced collapse of healthy lungs in normal-weight patients [15–18]. For atelectatic lungs to be re-expanded, three conditions must be met [14]. First, insufflation pressure must exceed alveolar opening pressure. Second, insufflation pressure must be sustained, because alveoli may not respond to intermittent pressure. Third, open recruitment must be followed by higher PEEP to maintain alveolar units. Thus, high tidal volume or PEEP alone is insufficient to reduce the incidence of atelectasis [14, 15]. Although PEEP will not consistently reduce atelectasis, it may delay its redevelopment after recruitment [14, 19].

The recruitment manoeuvre has been studied in patients undergoing laparoscopic bariatric Roux-en-Y surgery [20]. Whalen et al. [20] used a modified recruitment method from Tusman et al. [19] to treat MO patients, who typically have low respiratory system compliance [9, 21]. Higher recruitment pressures were achieved by incrementally increasing PEEP ($\leq$20 cmH_2O) and simultaneously limiting maximum peak inspiratory pressure ($\leq$50 cmH_2O) (Fig. 3). After high PaO_2 levels were achieved, lungs were ventilated with tidal volumes of 8 ml/kg of ideal body weight and 12 cmH_2O of PEEP. A repeat recruitment manoeuvre was performed whenever PaO_2 levels declined by more than 25 mmHg below the maximum level achieved during the initial recruitment manoeuvres. Whalen et al.

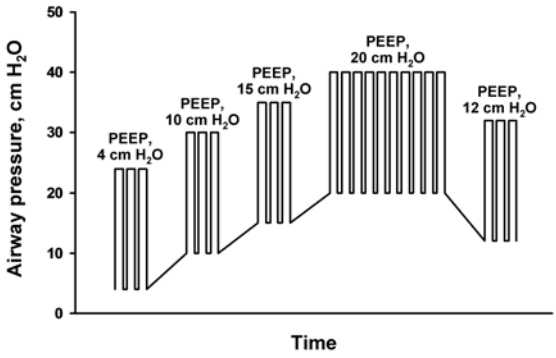

Fig. 3 Recruitment manoeuvre described by Whalen et al. [20]. Three breaths are taken at PEEPs of 4, 10, 15, and 12 cmH2O, and 10 breaths are taken at a PEEP of 20 cmH2O. *PEEP* positive end-expiratory pressure. (From [20]. Used with permission)

[20] showed that a recruitment manoeuvre and subsequent PEEP of 12 cmH_2O effectively increased intraoperative oxygenation in MO patients undergoing laparoscopic abdominal surgery. For most patients, the improvement in oxygenation was sustained only while endotracheal intubation and high PEEP were maintained; the effects dissipated within 30 min of postoperative tracheal extubation.

In anaesthetised patients undergoing laparoscopic surgery, body weight is a primary determinant of the intraoperative ratio of partial oxygen pressure to fraction of inspired oxygen (PaO_2/FiO_2). We have previously shown that oxygenation is not affected by pneumoperitoneum, body position, or large tidal volume ventilation [9, 21]. Besides being ineffective, large tidal volume ventilation in MO patients results in high end-inspiratory (plateau) pressures [9] that may increase the risk of ventilator-induced lung injury [22, 23]. Similarly, PEEP does not consistently improve PaO_2 levels in MO patients (Fig. 3) [8, 9, 11, 12].

Although Whalen et al. [20] did not measure recruited lung volume directly, the significant increases in PaO_2 after performance of the recruitment manoeuvre were presumably caused by decreased lung atelectasis. This increase in mean lung volume would be consistent with the observed increase in dynamic respiratory system compliance (Fig. 4). High PEEP did maintain higher PaO_2 in the recruitment group, but it could not prevent partial lung derecruitment. Dynamic respiratory system compliance decreased as surgery progressed, despite a PEEP of 12 cmH_2O (Fig. 4). By 30 min after recruitment, dynamic respiratory system compliance was

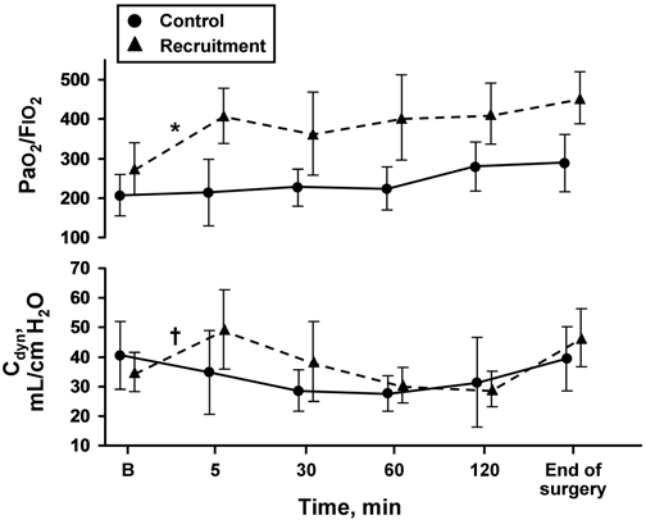

Fig. 4. Ratio of arterial oxygen partial pressure to inspiratory oxygen concentration (PaO_2/FiO_2) and dynamic respiratory system compliance (Cdyn) in control and alveolar recruitment groups. PaO_2/FiO_2 improved after recruitment and remained higher throughout surgery after adjustment for baseline values, age, sex, and body mass index. The *asterisk* and *dagger* indicate statistically significant differences in PaO_2/FiO_2 and Cdyn between the beginning of surgery and 5 min after recruitment. (From [20]. Used with permission)

not substantially different from prerecruitment baseline values. Dependent lung segments may become progressively atelectatic from sustained intraabdominal pressure; maintenance of oxygenation can occur through simultaneous redistribution of pulmonary blood flow to expanded nondependent areas. However, a simple relationship between compliance and oxygenation does not appear to exist, which suggests that the beneficial effects of the recruitment manoeuvre on oxygenation may not be directly associated with resolution of atelectasis.

A recruitment manoeuvre using high peak pressure followed by higher PEEP did not have clinically significant haemodynamic consequences in MO patients (Fig. 5) [20]. No changes in mean blood pressure or heart rate were observed over time, nor were differences between groups. The cardiac index was somewhat lower in the alveolar recruitment group after adjustment for baseline values, age, sex and body mass index, but the differences were not clinically significant. The lower respiratory system compliance and higher respiratory system resistance of MO patients [9, 21, 24] decreased the transpulmonary pressure achieved for a given airway opening pressure. Lower pressure may decrease the effectiveness of the recruitment manoeuvre, but it can also decrease the likelihood of clinically significant haemodynamic effects.

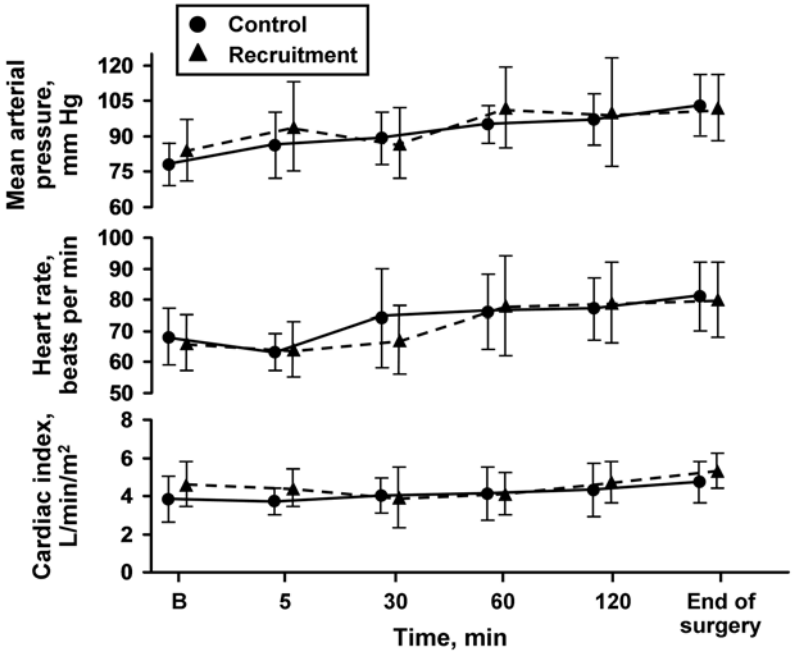

Fig. 5. Mean arterial blood pressure, heart rate, and cardiac index in control and alveolar recruitment groups. (From [20]. Used with permission)

Postintubation issues

Tracheal extubation after anaesthesia must be performed with the patient fully awake, cooperative, and satisfying criteria for extubation. Regardless of when a nondepolarising muscle relaxant was administered or what type was used, a full dose of reversal agent must always be provided. To prevent atelectasis while the patient is supine, we may consider performing tracheal extubation after the patient is transferred to a hospital bed and is in a semi-sitting position. Oxygen administration must be uninterrupted to prevent immediate postextubation hypoxaemia. Because most of these patients require oxygenation while asleep (especially after anaesthesia), the use of continuous positive airway pressure (CPAP) or bilevel positive airway pressure (BiPAP) devices should be considered soon after tracheal extubation.

Future studies should explore the effects of CPAP or BiPAP applied immediately after tracheal extubation on the maintenance of alveolar expansion. In a recent study of patients with hypoxia that developed while they were in the recovery room, the administration of CPAP had a dramatic positive impact on postoperative outcomes [25]. During monitored anaesthesia care with sedation, CPAP or BiPAP may be alternatives to a nasal cannula. Furthermore, patients should be monitored continuously with pulse oximetry during transfer to the recovery room. On the basis of preoperative conditions and immediate postextubation assessment of respiratory risk, some patients may require an overnight stay in the telemetry unit for observation.

Other pulmonary outcomes

Duggan et al. [26] used an animal model to show that intraoperative atelectasis may increase pulmonary vascular permeability and that recruitment manoeuvres successfully prevent lung injuries associated with hypoxaemia that could be caused by protracted atelectasis. Newer lung recruitment strategies for intraoperative respiratory management of MO patients efficiently improve intraoperative oxygenation, but whether they improve outcomes and reduce postoperative pulmonary complications is unknown. Also, more studies are needed to show whether shorter-acting anaesthetics, opioids or neuraxial blockade reduce the postoperative respiratory risks in MO patients.

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FLUID AND ELECTROLYTE EMERGENCY

Chapter 9

Fluid and electrolyte emergency

J. Boldt

Fluid deficits and electrolyte imbalances are common among surgical, traumatised and intensive care unit (ICU) patients. Fluid deficits can occur in the absence of obvious fluid loss secondary to vasodilation or generalised alterations of the endothelial barrier resulting in diffuse capillary leak. Thus, especially in the inflammatory patient, large fluid deficits become obvious. This situation is characterised by panendothelial injury with subsequent development of increased endothelial permeability, leading to a loss of proteins and a fluid shift from the intravascular to the interstitial compartment and resulting in interstitial oedema. Fluid deficits (or overload) are often associated with compromised acid–base status and electrolyte imbalance (Fig. 1).

Causes of Acid-Base Imbalances

- ***Metabolic Acidosis***
  - – Diabetic Ketoacidosis, lactic acidosis
  - – Salicylate poisoning (children)
  - – Methanol, ethylene glycol poisoning
  - – Renal failure
  - – Diarrhoea
- ***Metabolic Alkalosis***
  - – Prolonged votiming
  - – Diuretic therapy
  - – Hyperadrenocortical disease
  - – Exogenous base (antacids, bicarbonate IV, citrate toxicity after massive blood transfusions

Fig. 1. Some causes of derangement in acid–base balance

Principles of fluid/volume replacement and maintenance of electrolyte balance

Managing patients with fluid deficits and/or disturbed electrolyte balance demands some basic consideration of the mechanisms, reasons and regulation (Figs. 2–4): fluid administered may stay in the intravascular compartment or equilibrate with the interstitial/intracellular fluid compartments. The antinatriuretic system (ANH), the renin–aldosterone–angiotensin system (RAAS) and the sympathetic nervous system (SNS) and other hormone systems are involved in the control of volume and the composition of each body compartment. The principal action of these neurohumoural systems is to retain water in order to restore water or intravascular volume deficits, to retain sodium in order to restore the intravascular volume, and to increase the hydrostatic perfusion pressure through vasoconstriction. Enhanced activity of ANH, RAAS and SNS is known to occur in stress situations, e.g., during surgery. Although the normal response to surgery and starvation results in increased metabolic activity, a pre-existing deficit of water or intravascular volume can be expected to increase this activity further. If water or intravascular volume deficits and the stress-related stimulus of ANH, RAA and SNS are additive, fluid management could inhibit this process through counterregulatory mechanisms. There have been several attempts to inhibit or attenuate the activity of ANH and RAAS by administering different volumes of isotonic crystalloid solutions. It is known that ANH production is dependent on the maintenance of the extracellular volume and, in particular, the intravascular compartment ("preload"). Administration of a restricted amount of crystalloid could possibly replace a previous

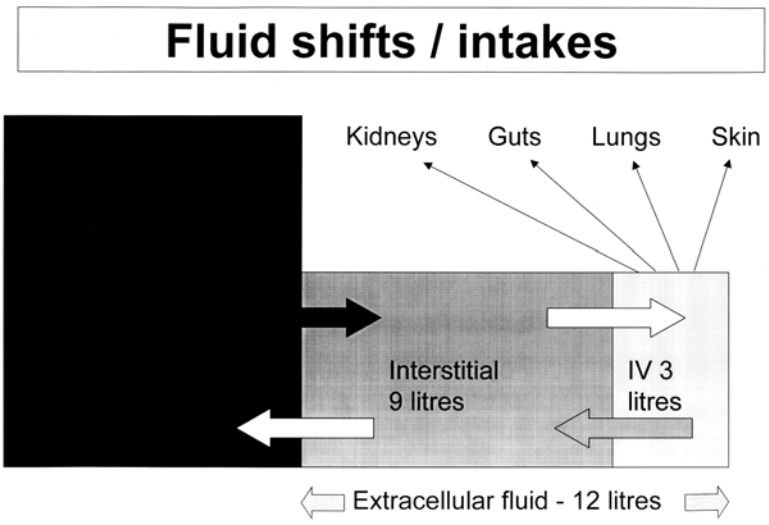

Fig. 2. Composition and fluid shifts of the different compartments

Fluid balance

- Adequate water is present and is distributed among the various compartments according to the body's needs
- Many things are freely exchanged between fluid compartments (e.g. water)
- Fluid movements by:
  - bulk flow (blood and lymph circulation)
  - diffusion and osmosis

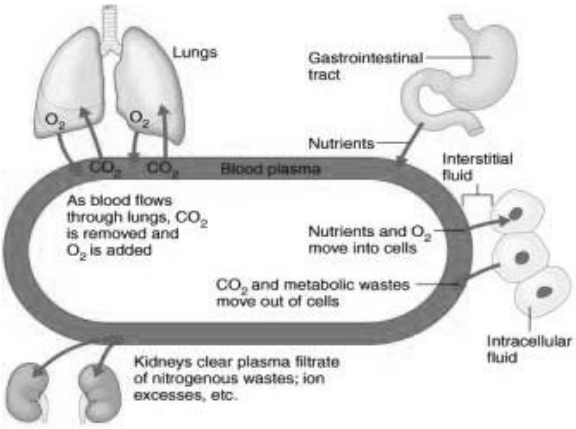

Fig. 3. Organs that are involved in guaranteeing adequate fluid balance

Electrolyte Balance

- Aldosterone ↑ $[Na^+]$ $[Cl^-]$ $[H^2O]$ ↓ $[K^+]$
- Atrial Natriuretic Peptide (opposite effect)
- Antidiuretic Hormone ↑ $[H^2O]$ (↓ [solutes])
- Parathyroid Hormone ↑ [Ca++] ↓ $[HPO_4^-]$ (opposite effect)
- Calcitonin
- Female sex hormones ↑ $[H_2O]$

Fig. 4. Some mechanisms that are involved in guaranteeing electrolyte balance

deficit of water, but the replacement of an intravascular volume deficit would require a much greater volume to inhibit the secretory stimulus of all the hormone systems committed to maintaining it. Thus, it can be expected that the replacement of water alone will not inhibit the normal response of ANH and RAAS, whereas administration of a combination of crystalloid and colloid solutions (replacement of water deficit simultaneously with improvement in the effective intravascular volume) may achieve this goal.

The primary goal of volume administration is to guarantee stable haemodynamics by rapid restoration of circulating plasma volume. Excessive fluid accumulation, particularly in the interstitial tissue, should be avoided. Starling's hypothesis describes and analyses the exchange of fluid across biological membranes. Colloid oncotic pressure (COP) is an important factor in the determination of fluid flux across the capillary membrane between the intravascular and interstitial spaces. Thus, manipulation of COP appears to be useful for guaranteeing adequate circulating intravascular volume. The magnitude and duration of this volume effect will depend on the specific water-binding capacity of the plasma substitute and on how much of the infused solution stays in the intravascular space. Because of varying physicochemical properties, the solutions commonly used for volume replacement differ widely in COP, initial volume effects, and duration of intravascular persistence.

Special conditions: fluids, electrolytes and the renal system in the elderly

Renal function declines with age, and diseases affecting the kidney become more prevalent. Body composition changes with age: there is a relative decrease in total body water and a relative increase in body fat. In 80-year-olds, there is a 10–15% loss of total body water, mostly limited to the intracellular compartment; plasma volume and extracellular volumes are maintained. This results in altered proportions of extracellular and intracellular fluids: there is decreased intracellular fluid in proportion to total body water but a relative increase in extracellular fluid [1].

Approximately 0.5–1% of nephrons are lost with each year of life, mostly from the cortex [2]. Serum creatinine, however, remains generally unchanged, since skeletal muscle mass decreases at a similar rate to glomerular filtration rate (GFR). The elderly mainly lose cortical nephrons; the remaining medullary nephrons have less concentrating ability and thus excrete more free water, after which the homeostatic mechanisms of sodium and water balance are impaired: renal tubular response to aldosterone is reduced, and thus the ability to conserve sodium. There is a slow response to a sodium load owing to reduced GFR and impaired tubular function, and the ability to excrete a free water load and mobilise third-space fluid is decreased. The elderly have increased osmoreceptor sensitivity—they release more antidiuretic hormone (ADH) in response to hypertonicity. End-organ response to ADH, however, is altered so that less water is retained than in the young [1, 3]. Thirst perception is altered, and associated disease states may reduce the amount of fluid ingested.

In the setting of abnormal cardiovascular compensatory mechanisms, conservation and delayed excretion of sodium and free water could potentially result in hypervolaemia or hypovolaemia [4]. The elderly are vulnerable to electrolyte disturbances owing to abnormal physiology, pathology and iatrogenic causes. Most serum electrolytes do not alter in the healthy elderly, but serum potassium may increase with age, even though total body potassium is reduced. There is a significant risk of hyponatraemia after surgery, owing to ADH secretion provoked by surgical stress, chronic disease and such medications as thiazide diuretics. This may be compounded by the use of hypotonic maintenance fluids after surgery. Finally, the elderly are at risk of hyper- and hypokalaemia, which can be due to concurrent medication, disease or inadequate potassium supplementation in intravenous maintenance fluids.

Possible strategies of fluid/volume replacement

Crystalloids

Hypotonic (e.g., dextrose in water), isotonic (e.g., normal saline solution; Ringer's solution [RL]) and hypertonic crystalloids (e.g., 7.5% saline solution) have to be distinguished when using crystalloids for volume replacement. Crystalloids are freely permeable to the vascular membrane and are therefore distributed mainly in the interstitial and/or intercellular compartment. Only 25% of the infused crystalloid solution remains in the intravascular space, whereas 75% extravasates into the interstitium [5]. Dilution of plasma protein concentration may also be accompanied by a reduction in plasma colloid oncotic pressure (COP) subsequently leading to tissue oedema. It has been shown in animal experiments that even massive crystalloid resuscitation is less likely to achieve adequate restoration of microcirculatory blood flow than is a colloidal-based volume replacement strategy [6]. In a study in patients who underwent major abdominal surgery and in whom crystalloids (RL) or colloids were used for volume replacement, Prien et al. [7] demonstrated significantly more voluminous intestinal oedema with the use of RL than with colloids. In an experimental trauma–haemorrhage model either colloids (dextran) or crystalloids (Ringer's acetate) were used to replace blood loss after surgical trauma [8]. The crystalloid group showed significantly larger amounts of tissue water in muscle and jejunum than the colloid-treated group of animals.

Crystalloids are frequently preferred because they are inexpensive and appear to be almost free of significant negative side-effects, and especially of any linked with coagulation. Interest has recently been focused on the influence of crystalloids on haemostasis. There is convincing evidence that use of crystalloids has a substantial influence on coagulation. Ruttmann et al. [9, 10] and Ng et al. [11] showed that in vivo dilution with crystalloids resulted in significant enhancement of coagulation. The reason for the hypercoagulable state appears to be an imbalance between naturally occurring anticoagulants and activated procoagulants, a reduction in

antithrombin III probably being the most important [9]. Other authors have also documented hypercoagulability with the use of crystalloids [12]. This increase in coagulation seems to be independent of the type of crystalloid that has been used [12]. An early study reported that the increase in coagulation in patient in whom crystalloids were given during surgery was associated with an increased incidence of deep vein thrombosis [13]. Thus, taking new data into account, crystalloids can no longer be generally considered as the "good guys" with regard to the coagulation process.

What's new in fluid/volume replacement strategies and treatment of electrolyte imbalances?

It is now generally accepted that significant alterations in acid–base balance develop in patients to whom considerable amounts of 0.9% saline solution are infused. This has been described as "hyperchloraemic acidosis" [14, 15]. Thus use of large amounts the "physiological", normal (0.9%) saline (NS) solution should be urgently avoided, because of the risk of producing (hyperchloraemic) acidosis (Fig. 4). One study in patients undergoing major spine surgery showed that this phenomenon occurred only when considerable amounts of normal saline solution were infused; use of RL was not associated with hyperchloraemic acidosis [16].

Unfortunately, most of the available colloids are not "balanced", but include unphysiologically high concentrations of sodium and chloride, so that they do not fit into the concept of a balanced fluid/volume replacement strategy. Use of large amounts of such colloids may also be associated with metabolic acidosis: acute normovolaemic haemodilution (ANH) using either 5% albumin or 6% HES 200/0.5 (aim: haematocrit 22%) in patients undergoing gynaecological surgery resulted in metabolic acidosis in both groups [17]. Dilution of extracellular bicarbonate or changes in strong iron differences and albumin concentration may be explanations of this type of acidosis. Others found decreases in base excess (BE) only after the use of standard HMW-HES and not after albumin [18].

Little information is available on the clinical value of this type of acidosis. Negative consequences of hyperchloraemic acidosis on organ function have been elucidated by some studies: in patients undergoing abdominal aortic aneurysm repair, either RL (total dose: 6,800 ml) or NS (total dose: 7,000 ml) was used for volume replacement in a double-blind fashion [19]. Only the NS-treated patients developed hyperchloraemic acidosis. They needed significantly more blood products than the RL-treated patients. There is also some evidence that hyperchloraemic acidosis may impair end-organ perfusion and organ function (e.g. splanchnic perfusion [19]) or interfere with the cellular exchange mechanism [20]. In animal experiments, hyperchloraemic acidosis was associated with a reduction in renal blood flow (which was most probably due to vasoconstriction) and a negative effect on glomerular filtration rate [20]. In noncardiac surgical patients, Bennett-Guerrero et al. [21] demonstrated that administration of unbalanced salt solutions resulted in reduced urine output and increased serum creatinine levels postopera-

tively. In elderly patients undergoing elective surgical procedures, either conventional HMW-HES (hetastarch) or a hetastarch in a balanced electrolyte and glucose formulation (Hextend®) was used [19]. Only patients treated with the conventional hetastarch developed hyperchloraemic acidosis (postoperative BE: –0.2 versus –3.8 mmol/l). Gastric tonometry indicated better gastric mucosal perfusion in the group treated with the balanced hetastarch solution (Hextend®) than in the group treated with a hetastarch dissolved in saline.

The search for more physiologically balanced i.v. fluids that fulfil the principle of a balanced volume and fluid replacement strategy is fundamentally important. In a prospective, randomised, controlled, and double-blind study conducted in patients undergoing major abdominal surgery, a total balanced volume replacement strategy including a new balanced hydroxyethyl starch solution (HES) and a balanced crystalloid solution was compared with a conventional, nonbalanced fluid regimen [22]. The new balanced 6% HES 130/0.42 contained Na^+ 140 mmol/l, Cl^- 118 mmol/l, K^+ 4 mmol/l, Ca^{2+} 2.5 mmol/l, Mg^{2+} 1 mmol, acetate 24 mmol/l, malate 5 mmol/l (B Braun, Melsungen, Germany). The complete balanced volume replacement strategy, including a new balanced HES preparation, resulted in significantly fewer derangements in acid–base status than did a nonbalanced volume replacement regimen.

How to avoid under-/overloading the patient?

Although the principles of fluid/volume therapy are widely accepted (Fig. 5), estimating the necessary fluid/volume still remains a challenge. The question of how volume/fluid therapy should be guided has not yet been decided. In spite of some negative data, pulmonary artery (PA) catheters are still used in several centres, and data obtained by means of this monitoring instrument can be helpful in guiding volume therapy. It has to be emphasised that cardiac filling pressures (central venous pressure [CVP], pulmonary capillary wedge pressure [PCWP]) are often misleading as an index for assessing optimal LV loading. Cardiac filling pressure may be influenced by several factors other than blood volume, including those influencing cardiac performance, vascular compliance and intrathoracic pressure. Particularly in patients with altered ventricular compliance, commonly monitored parameters such CVP, right atrial pressure (RAP) or right ventricular pressure (RVP) have not always proved sufficiently valid to be used in judgement of loading conditions. Measurement of right ventricular end-systolic and end-diastolic volumes (RVESV, RVEDV) by the thermodilution (TD) technique is another easily performed bedside monitoring technique with no accumulation of toxic indicators, and loading can probably be achieved more accurately by this means. It is unaffected by arbitrary and poorly reproducible zero points for pressure transducers and can be carried out at the bedside. Echocardiography appears to be the most reliable monitoring instrument; owing to its cost, however, it is not available for every cardiac surgery patient in the perioperative period. Measurement of intrathoracic blood volume (ITBV) by the PICCO system is another technique by which

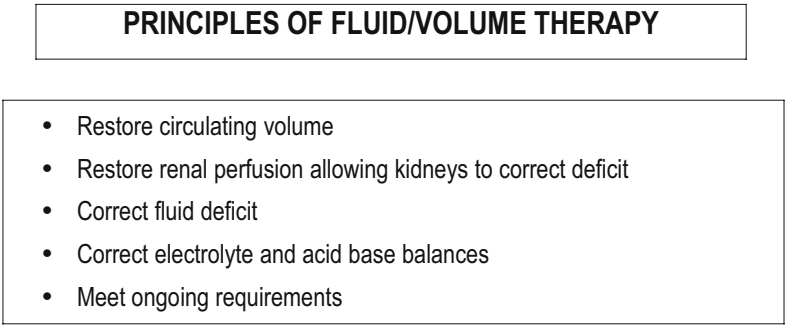

Fig. 5. Main principles of fluid/volume replacement strategies

volume therapy can be guided. There is no documentation to confirm superiority of any one of these monitoring systems.

The importance of occult hypovolaemia in the development of organ perfusion deficits has been supported by several studies. There is no reliable, optimal routine clinical monitoring system to detect perfusion failure. Cardiovascular instability appears to put patients at risk of experiencing significant splanchnic hypoperfusion, with the subsequent development of translocation, and eventually multiple organ failure (MOF) [23, 24]. Gastric intramucosal pH (pHi) measurement may be an option for diagnosis and monitoring of splanchnic hypoperfusion. In patients undergoing major noncardiac surgery maintaining haemodynamic stability was no guarantee of an adequate splanchnic perfusion and did not definitely protect against significant postoperative complications [23]. Monitoring of pHi had a higher importance for predicting postoperative complications (sensitivity 93.3%, specificity 50%). Although this monitoring instrument has produced some promising results, it is far from being the new "gold standard" for guiding volume/fluid administration [25].

At present, combining as much information as possible appears to be the best way to detect hypovolaemia and subsequently guide volume replacement. This includes systemic haemodynamic data (e.g. blood pressure and heart rate), filling pressures (e.g. CVP, PCWP), flow variables (e.g. cardiac output), data from blood gas analysis (e.g., acidosis, lactate) and urine output.

Conclusions

Considerable progress has been made in our understanding of the importance of adequate fluid/volume therapy in various situations. A well-balanced fluid/volume therapy avoiding electrolyte and acid–base imbalances appears to be essential in management of the critically ill. The "ideal" therapeutic approach und the "ideal" monitoring device for guiding fluid/volume replacement, however, remain matters of dispute.

Fluid requirements will depend on the patient's age, any co-morbidities and certain other circumstances (e.g. length and complexity of a surgical procedure). The primary goal of fluid/volume replacement therapy is to augment intravascular volume and maintain stable haemodynamics. Pros and cons of each solution that might be used for fluid/volume replacement have to be considered. The choice of solution for maintenance of circulating volume in the individual patient should be based on the pharmacokinetics and pharmacodynamics of the solution used and also on the pathophysiology of the patient's underlying disease. In spite of the absence of any definitive evidence suggesting that any might be superior to the others, consensus guidelines on the use of the different solutions have been published. Although crystalloids appear to be less likely ro prove appropriate for resuscitation of the intravascular space (IVS), as they are distributed mainly to the interstitial space (ISS), they have been recommended as the initial fluid of choice in patients being resuscitated from hemorrhagic shock [26]. It remains completely unclear, however, what kind of "crystalloid" is recommended in this situation. When colloids are used because of their better volume-replacing properties, there is convincing evidence to suggest that balanced solutions have considerable advantages compared to nonbalanced fluid/volume replacement strategies. An extensive search is currently in progress to improve our fluid/volume replacement regimens—to optimise therapeutic strategies for use in our patients remember the saying: *Don't be afraid to try a new procedure, be prepared.*

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Chapter 10

Electrolyte emergencies, anion gap, osmolality

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In the critically ill we often observe some dysregulation of the fluid–electrolyte balance; far from being an innocent bystander, the intensive medicine specialist could sometime be responsible for this, by way of overzealous correction, drug interference, or a "cosmetic" approach to the problem. In this short review, we will try to recall some basic principles that could help to improve therapeutic strategies.

Applied physiology background

From a mitochondrial point of view, the first priority to be always satisfied is the O_2 delivery (DO_2) to the cells, which is heavily dependent on adequate fullness of the intravascular space with adequate fluids (IVF): as the physicochemical properties of fluids influence the cellular well-being, it seems logical to take osmolality as our starting point.

Osmolality

Because of the requirement for osmotic equilibrium between the cells and the extracellular fluid, any alteration in extracellular osmolality is accompanied by a corresponding change in intracellular osmolality, with a concomitant change in cell volume and possibly in cell function [1]. To put it another way, extra- and intracellular fluids have different compositions, but almost equal solute concentrations: because water diffuses from the compartment with lower concentrations to the other, what makes the water move across the membranes is a "temporary" difference between solute concentrations, i.e. an osmotic gradient (think of extracellular glucose in diabetic emergencies).

It is useful to start with some simple physiological statements applying to regulation of the transmembrane watery fluxes in human subjects.

Total body water (TBW) is calculated as 60% of body weight in normal adult subjects, but can vary from 45% in older groups to 75% in the newborn [2].

Intracellular fluids (ICF) are responsible for two thirds of TBW, whilst extracellular fluids (ECF) account for one third. Intravascular fluids make up one quarter of ECF, i.e. only one twelfth of TBW.

Normally, the major osmotic solutes in the ECF are potassium, magnesium,

phosphates and protein, while those in the ECF are sodium and its chloride and bicarbonate anions.

Plasma osmolality (Posm) is normally between 280 and 295 mosmol/kg water, while urine osmolality (Uosmol) can vary from 300 to 1200 mosmol/kg [3].

Hyperosmolality is present when Posm exceeds 295 mosmol/kg, which is followed by a water shift from ICF to ECF, thirst stimulation and antidiuretic hormone (ADH) release.

The solutes must be divided, from a physiological point of view, into osmotically active ones, which are mostly confined in the extracellular or intracellular spaces, and osmotically inactive ones (urea, ethanol), which are free to cross the cellular membranes [4].

Therefore, it is useful to conceptualise the osmolality clinically as the tonicity (i.e. the accumulation of osmotically active solutes in ECF is hypertonicity, which is invariably a hyperosmolar syndrome; while when urea accumulates in the blood as a result of renal insufficiency, osmolality may build up but tonicity could still be normal, or even be reduced) [5].

This distinction underlines the fact that hypertonicity usually implies ICF volume depletion and neurological impairment, while hyperosmolality sometimes does not. The distinction between osmolality and tonicity is also useful in tailoring of the intravenous fluid therapy: an iso-osmotic solution can be "nonisotonic" (5% dextrose in water is iso-osmotic but hypotonic: as glucose is metabolised, what remains is electrolyte-free water). This explains why the serum sodium concentration, once pseudohyponatraemia is excluded, is a more valid measure of body fluid tonicity than is the plasma osmolality [6].

Therefore, the cornerstones of effective osmolality (tonicity) regulation are strictly linked to the control of extracellular sodium concentration, which is mainly determined by:

- Salt and water intake
- ADH secretion
- Aldosterone release
- Atrial natriuretic peptide
- Intrarenal haemodynamics

The main receptors involved are first the osmotically sensitive and later, if circulating volume depletion is superimposed, the volume receptors [7].

The intimate relationship between osmotic sensors and water balance is clearly underlined by the following mathematical equation:

$$\Delta \text{ Uosmol} = 95 \, \Delta \text{ Posmol}$$

This relationship indicates a remarkable role in the osmoregulatory mechanism for vasopressin, since a change of 1 mosmol/kg in plasma osmolality is able to produce a 95-mosmol/kg change in urine osmolality if the renal function is not impaired.

However, once the urine is maximally concentrated, further increases in vasopressin secretion are incapable of limiting urinary water losses any further, so that the last defence is only the thirst. It should not to be forgotten that stretch receptors

in the left atrium and baroreceptors in the great vessels are the "haemodynamic" modulators of similar responses.

Fullness

The sense of "fullness" is one of the most finely tuned in the body, so that sophisticated sensors can activate integrated neurohormonal responses aimed at keeping the intravascular fluids (IVF) within acceptable limits. Moment by moment there is a tentatively perfect interplay between venous capacitance and IVF (e.g. the compulsive diuretic response attributable to atrial natriuretic factor secretion in paroxysmal tachycardia with atrial overdilatation); on the other hand, vasoconstriction, tachycardia, thirst and oliguria are almost always linked to a hypovolaemic hypoperfusive state.

Since 1972, one of the most challenging tasks for intensive care specialists has been IVF monitoring, and there has been a desperate search for reliable numbers to optimise vascular filling and the DO_2 to vital organs [8–11].

Pulse rate, arterial blood pressure, peripheral perfusion and urine output are weak indicators of the intravascular fluid status, as all of them could be influenced by age, underlying diseases, drugs etc.

A huge body of experience has therefore been derived from the invasive assessment of intravascular pressure, i.e. central venous pressure (CVP) and measurement by Swan-Ganz catheter of pulmonary occluded wedge pressure).

Both can be useful or misleading at the same time, owing to their relatively simple insertion technique but relatively complex understanding of the resulting numbers. There is a general agreement, on the other hand, that both these techniques yield useful information if the respective trends are evaluated rather than the corresponding absolute numbers.

Recently, a growing bulk of scientific reports has highlighted the pivotal role of a dynamic ultrasound evaluation of the heart and great vessels in prediction of the fluid responsiveness of critical patients [12, 13].

Urine news

A first clue in approaching dysosmolar states is given by a "spot" urinary sample matched with the clinical or instrumental evaluation of the IVF:

1. In hypotonic states (i.e. hyponatraemia) associated with IVF reduction, the expected renal response is a maximal Na reabsorption, with Nau <30 mEq/l; if this response is not observed, a renal (salt wasting, diuretics) or endocrine (Addison's disease) problem should be suspected.
2. In hypotonic states associated with TBW expansion, heart failure, cirrhosis and nephrosis will claim for low Na excretion fraction (<1%) or [Na]u mEq/l; while in advanced chronic renal failure it is common to find [Na]u>30 mEq/l.
3. Near-normal or slightly expanded TBW with [Na]u>30 mEq/l and hypona-

traemia should be regarded as a potential syndrome of inappropriate antidiuretic hormone secretion (SIADH), hypothyroidism or glucocorticoid deficiency [14, 15].
4. In hyperosmolar syndromes (HS), the measurement of the urine osmolality and, where indicated, its response to ADH administration is helpful: indeed urine osmolality should be very high (>800 mosmol/l = urinary gravity >1,022) in HS if ADH release and renal response are intact.
5. In diabetes insipidus (central or nephrogenic) urine osmolality is inappropriately low (<300 mosmol/l), owing to ADH deficit or blunted renal response [16].

The osmolal gap (OG)

In normal circumstances the measured osmolality (Posm mean) is fairly in excess of the calculated osmolality (Posm calc) due to some usually not measured substances, hence:

Posm meas–Posm calc=Osmolal Gap (OG)=5–7 mosmol/l, and
Posm calc=Na (mEq/l)×2+Gluc (mg/dl)/5

It could be useful to recall that if any intoxicant of low molecular weight were added to serum, we would find an increase in measured osmolality, while the calculated osmolality would be almost unchanged, with OG increased: in the setting of any unexplained metabolic acidosis this should raise the strong suspicion of a low-molecular-weight intoxicant.

Treatment of dysosmolality

Apart from its possible impact on "fullness", the target organ in any dysosmolal state is the brain. As a general rule, the faster the onset of the disorder, the poorer the prognosis, owing to lack of time to compensate for the disorder at the metabolic/structural neuronal level. From the evolutionary studies on different species, it seems easily understandable that even extreme osmolar disturbances can be tolerated, given that there is enough time to cope with the "water stress" [17, 18]. Current opinion, largely based on autopsy studies in humans [19, 20], is tentatively centred on implementation of the so-called two steps strategy for approaching extreme hyper- or hypo-osmolar states: a first emergency treatment aimed to correct the serum Na at 1 mEq $l^{-1} h^{-1}$ for the first 12–24 h, slowing down to <0.5 mEq $l^{-1} h^{-1}$, depending on the neurological response [21]. In hyponatraemic states, some authors recommend that a loop diuretic should be given with the hypertonic saline infusion, to enhance free water clearance, but caution must be exercised as this may cause a too-rapid rise in sodium concentration.

Electrolyte emergencies (magnesium, potassium)

Berlyne once defined magnesium as the "Cinderella" of the divalent ions. Nevertheless, an increasing amount of interest is being devoted to Mg-related problems in the ICU. Magnesium and potassium share many physiological actions and interplay with each other in neuromuscular and cardiovascular functions, which are very likely to be deranged in the critically ill. Theoretical knowledge of and practical attention to both of them is required of the intensive care specialist.

Magnesium

Normal values for serum magnesium concentration are 1.3–2 mEq/l or 1.8–2.5 mg/dl. It has been suggested that hypomagnesaemia is probably "the most underdiagnosed electrolyte deficiency in current medical practice" [22]. In addition, as symptomatic magnesium depletion is often associated with multiple biochemical abnormalities, such as hypokalaemia, alkalosis and hypocalcaemia, it may be difficult to define manifestations as due specifically to hypomagnesaemia [23]. The main causes of hypomagnesaemia can be related to (a) redistribution, (b) gastrointestinal losses and (c) renal losses.

a) Redistribution: as in the case of calcium, the physiologically active part of magnesium is the ion, while the protein-bound and chelated fractions can be considered inactive; as outlined in Table 1, the relative distribution among the three is closely related to the blood pH. The biologically active fraction of magnesium is reduced by alkalaemic states or iatrogenic alkalinisation of a patient [24].

Table 1. Relationship between Mg^{2+} and pH

		Normal pH	↑ pH
Mg^{2+}	Ionised	50%	30%
	Protein bound	35%	50%
	Chelated	15%	20%

Other causes of redistribution are refeeding after starvation and chelation complicating acute pancreatitis or massive citrate transfusions.

b) Gastrointestinal losses: steatorrhoea, bowel resection, biliary fistulas and, more frequently, prolonged nasogastric suction (NSG) can all reduce the absorption of magnesium and, particularly in NSG, induce renal losses due to enhanced renal tubular exchange (↑ Aldo).

c) Renal losses: renal magnesium wasting, as defined by continued urinary magnesium excretion in the face of hypomagnesaemia, can have renal or extrarenal causes (loop diuretics, aminoglycosides, cyclosporin, Bartter's syndrome, alcohol ingestion, DKA). It is noteworthy that magnesium losses in diabetic ketoacidosis are multifactorial, depending on magnesium coupling

with ketoaciduria, osmotic diuresis and extra-/intracellular shifting after insulin.

It is also useful to remember that renal handling of Mg is finely regulated in normal subjects, urinary elimination being usually less than 15 mEq/day, so that in magnesium-depleted patients no more than 1–2 mEq/day should be found; otherwise a renal cause should be suspected.

Consequences of magnesium depletion

Some of the major effects of low $[Mg]_p$ are related to a multiple ion channel modulation, mainly affecting the calcium channel current and the outward potassium current (see below). Nevertheless, serum magnesium levels of 1 mEq/l or less warrant immediate therapy to prevent important clinical consequences. Increased neuromuscular excitability to the point of tetany, anxiety, delirium, psychosis and hallucinations can all be seen as some of the neurotoxic effects. The most important clinical disturbance is the frequent association of hypomagnesaemia with ventricular arrhythmias, particularly during myocardial ischaemia [25].

Moreover, magnesium deficiency, like potassium deficiency, sensitises patients to digitalis toxicity. Magnesium administration prolongs the effective refractory period, depresses conduction, increases the membrane potential (makes it more negative) and can control ventricular tachyarrhythmias: in the ICU setting this could be very useful when conventional antiarrhythmic drugs do not succeed. In those patients it could be better to aim for a serum magnesium concentration of 2.8–3.5 mEq/l, by infusing magnesium salts as suggested in Table 2.

Table 2. Emergency administration of magnesium

Magnesium, parenteral supplements	$MgCl_2$ 1 g=9 mEq
	$MgSO_4$ 1 g=8 mEq

Give 10 ml $MgSO_4$ 10% (=1 g) in 20 min every 6 h i.v., or 2-g bolus (=16 mEq) in 100 ml of 5% dextrose in 10 min in emergencies

There are also several reports on the improved efficacy of digoxin combined with magnesium, owing to their synergistic action on the AV node [26, 27].

Whenever magnesium salts are given by the i.v. route frequent checks on the blood pressure are mandatory (hypotension), as are ECG monitoring (various degrees of heart block) and close observation of the patient's ventilatory pattern (respiratory depression; see below). Sometimes it could be useful to add potassium chloride (2 mEq in 100 ml normal saline in 1–2 h), which may help in suppressing some ventricular arrhythmias, or calcium chloride or gluconate (10–30 ml of 10% solution in 20 min) when alkalaemia or ionised hypocalcaemia is associated (tetany, delayed heart repolarisation).

Hypermagnesaemia

Addison's disease, renal insufficiency and some phases of DKA (contracted diuresis, dehydration, acidaemia before the start of therapy) are the main causes of hypermagnesaemia in the ICU. Sometimes it might be iatrogenic, as a result of overenthusiastic therapy of pre-eclampsia/eclampsia.

Consequences of hypermagnesaemia

Any plasmatic magnesium concentration in excess of 3 mEq/l could be complicated by hypokinetic arrhythmias (from sinusoid bradycardia to AV blocks), depending on whether there is pre-existing heart disease and/or associated antiarrhythmic therapy with Ia, Ic, II, III, IV class drugs.

Moreover, the main clinical manifestations of hypermagnesaemia can be quite closely related to the speed at which the blood level is rising and, obviously, to the absolute value of the serum concentration (Table 3).

Table 3. Clinical effects of hypermagnesaemia

	Serum Mg (mEq/l)
Normal	1.3–2
Long P–R, bradycardia	35
Hypotension	4–6
Respiratory insufficiency	7–9
Heart block	7–9
Respiratory paralysis	>10

Treatment

The first step in the treatment of symptomatic hypermagnesaemia is the i.v. administration of 5–10 mEq of calcium in 5 min for rapid improvement of respiratory function and/or bradycardia.

Hyperkalaemia

Since urinary potassium excretion is basically a secretory function of the distal nephron and is minimally dependent on glomerular filtration, it follows that, as long as urine output is maintained, renal potassium excretion is essentially adequate to handle dietary load. Obviously, in acute oliguric states serum potassium levels may increase rapidly in the absence of significant extrarenal potassium loads; by contrast, in chronic stable renal failure hyperkalaemia may occur when the intake is decreased; when mineral corticoid hormones are decreased (even in normal renal function); or following the use of potassium-sparing drugs. Clinical

organic acidosis (more frequently DKA) is commonly associated to hyperkalaemia, and digitalis intoxication can induce severe hyperkalaemia by the extracellular shift of potassium as digitalis inhibits the Na–K pump. When the blood creatinine level is normal and the blood level of potassium is high, this must always raise the suspicion of aldosterone deficiency.

Consequences of hyperkalaemia

Owing to reduction of the resting potential (less negative) and the increased rate of repolarisation, there are two main clinical problems that can be induced by hyperkalaemia. The neuromuscular manifestations include paraesthesias and weakness in the arms and legs; these may be followed by flaccid paralysis of the extremities, later involving the respiratory muscles to the point of ventilatory insufficiency. Very often the cardiac toxicity is the major source of morbidity and mortality in hyperkalaemia patients.

As a consequence of the reduction of the resting potential (Em), the threshold potential (Er) is reached more easily than normal and the repolarisation is shortened (increased gK): this results in a decrease in conduction velocity, with various degrees of AV and intraventricular blocks, producing widening of the QRS complexes and tall T-waves. If appropriate therapy is not begun, ventricular fibrillation or asystole will follow.

Everyone is well aware of the different approaches available to antagonise the clinical effects of hyperkalaemia, but it could be useful to remember the different onset, mechanism and duration of effect of the various therapies (Table 4) [28].

Table 4. Management of hyperkalaemia

Therapy	Mechanism	Onset	Duration
Calcium chloride or calcium gluconate (6–12 mEq)	Membrane antagonism	1–3 min	30–60 min
Sodium bicarbonate 1 M (50–100mEq)	Redistribution	3–5 min	120 min
Insulin plus glucose	Redistribution	30 min	4–6 h
Dopexamine (2.5–5 $\mu g\ kg^{-1}\ min^{-1}$)	Redistribution	30 min	1–6 h
Kayexalate(25–50 g p.o.)	Excretion	1–2 h	4–6 h
Dialysis	Excretion	Minutes	Until completed

It is important to note the specific electrophysiological antagonising effect of calcium salts in hyperkalaemia. As depicted in Fig. 1, calcium is unique in raising the threshold potential, almost immediately improving AV and intraventricular conduction and myocardial contractility; so it must be used as a first-line drug in such emergencies [29].

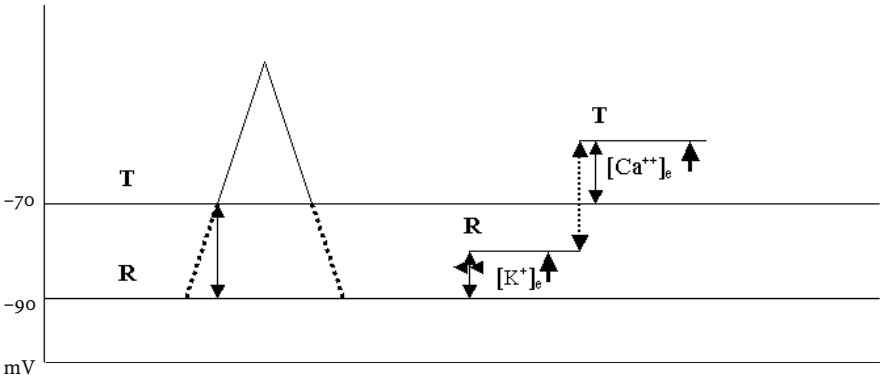

Fig. 1. Calcium correction of reduced resting potential due to hyperkalaemia

Electrical gaps (anionic, cationic, apparent, effective, simplified…)

The "classic", widely accepted, classification of metabolic acidosis (MA), which differentiates between MA with high anion gap (AG, lactic, diabetic, uraemic, toxic) and MA with near-normal AG, i.e. hyperchloraemic (renal tubular or following enteral HCO_3 losses), is still useful in promoting understanding of almost every acid–base disturbance. Such an approach, if integrated by the evaluation of the ratio between the bicarbonate difference (normal minus actual) and the AG difference (actual minus normal), is even helpful to obtain clear disclosure of the dominance of any specific disorder among the mixed ones [30].

Moreover, some interesting recent studies have allowed further pathophysiological insights, having also considered some other, previously unmeasured, anions (e.g. pyruvate, beta-hydroxybutyrate, aceto-acetate, pyroglutamate, phosphate…) [31].

To summarise this extension of the AG-based approach, the key point seems to be: "In metabolic acidosis always look for any H^+ donor other than lactate" [32–34]. Nevertheless, some 30 years ago other authors, following Stewart's principles of physical chemistry (electroneutrality, mass conservation, dissociation of weak acids, albumin relevance …), introduced a third "road map" directed at a more complete understanding of the biochemical derangements—produced by diseases and/or doctors—in the acid–base disturbances [35, 36]. The essentials of the Stewart approach start from the concept of an "expanded" anion gap, which takes account not only of the usual electrolytes, but also of Mg^{2+}, Ca^{2+}, lactate, albumin and phosphate. Starting from this fully comprehensive concept, three equations need to be solved for the relative specific responsibility of each term as a cause of the suspected metabolic acidosis to be understood.

The method first involves calculating the apparent strong ion difference (SIDa) in mEq/l:

$$SIDa=[Na^+]+[K^+]+[Mg^{2+}]+[Ca^{2+}]-[Cl^-]-[lactate]$$

This SIDa is referred to as "apparent" because it does not take account of the roles of HCO_3, albumin and phosphate in the electrical balance in plasma water; the next step therefore is to calculate the "effective" strong ion difference (SIDe); the formula is astonishingly cumbersome:

$$SIDe=1000\times2.46\times10^{-11}\times PCO2/10^{-pH}+[Alb]\times(0.12\times pH-0.631)+[phos]\times(0.309\times pH-0.469)$$

This SIDe formula quantitatively accounts for the contribution of weak acids and, more interestingly, in this way the SIDa to SIDe difference should be equal to zero, unless there are unmeasured charges to explain this "ion gap", expressed as the "strong ion gap" (SIG):

$$SIG=SIDa-SIDe$$

A positive value for SIG must represent unmeasured anions (sulphate, keto-acids, citrate, pyruvate, acetate, gluconate…), which must be included to account for the measured pH. This could explain some light metabolic alkalosis attributable to hypoalbuminaemia and is tightly linked to the otherwise puzzling understanding of the acidifying effect of large infusions of saline. Indeed, the crystalloid effect from the Stewart perspective can help to disclose the "mystery" of dilutional acidosis. Many reports have in fact pointed out that overzealous saline infusions can cause a metabolic acidosis [37, 38]; this has been best documented during repletion of extracellular fluids deficit, acute normovolaemic haemodilution, and cardiopulmonary bypass. The mechanism is obviously not bicarbonate dilution. (Otherwise why would the proton donors not be diluted at the same time?) The key to the explanation is that the SID of saline is zero, because the strong cation concentration $[Na^+]$ is exactly the same as the strong anion concentration $[Cl^-]$, but what is different is the "percentage" impact of the infusion on the respective starting concentrations, which are different. The net result, if more than 2,000 ml of saline has been infused in less then 24 h, is an infusion-related metabolic acidosis; interestingly, hypertonicity makes solutions more acidifying, as more water is drained from the intracellular space, which ultimately contributes to the final equilibrium. What can be accepted about such a cumbersome approach as that proposed by Stewart, then, is the emphasis on the relevance of hypoalbuminaemia on the one hand and of the acidifying effect of massive saline infusions on the other.

Interestingly, another lesser known aspect of the AG utility is the occasional finding of a low anion gap, which could suggest to make more detailed investigations to exclude myeloma, gammopathies or hyperviscosity syndromes [39]. Indeed, usually proteins behave as anions, contributing about 14 mEq/l to the unmeasured anion pool. As myeloma proteins have isoelectric points >7.4 they become positively charged in the serum and behave as cations. In this way they may lead to a reduced AG by creating an excess of positively charged ions. That has to be counterbalanced by an increase in anions, mainly chloride. This explains why in about 30% of myeloma or gammopathies the AG could be <3 mEq/l.

Conclusions

Fluid balance, electrolytic pattern and acid–base derangements share common pathophysiological processes. Moreover, in the critically ill a full understanding of the ongoing interplay among all these is needed for a correct approach to a therapeutic strategy.

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Chapter 11

Acute renal failure

M. Palazzo

Although clinicians recognise when a patient develops acute renal dysfunction, there is still no universally accepted definition; nor is there consensus on endpoints, which represent management success for clinical trials. It is therefore not surprising that it has been difficult to agree on guidelines for best renal management.

What is the role of the kidney?

The main role of the kidney is to compensate for haemodynamic perturbations in order to maintain appropriate tissue perfusion. Perfusion is dependent on adequate circulating volume and arterial pressure. Other, minor, roles include removal of metabolic waste, maintenance of acid–base balance, osmolarity control and erythropoietin secretion.

Signalling from great vessel and atrial volume and pressure sensors results in a fully integrated renal sympathetic and hormonal response (renin–angiotensin, aldosterone, adenosine, endogenous catecholamines, bradykinin, prostaglandins, ADH, and ANP) designed to maintain normal circulating volume and pressure through sodium and water retention. However, a persistent need for compensation progressively results in renal cortical, medullary and glomerular vasoconstriction, reduced glomerular filtration and oliguria. In extremis, maximal renal compensatory results in poor kidney perfusion, a seemingly self-destructive mechanism. The ease with which this occurs is predicated by the premorbid state of the kidney and the presence of specific nephrotoxins, which on closer inspection have adverse microcirculatory effects.

The emphasis the kidney places on volume control relative to its other activities is readily seen when two or more disturbances simultaneously stress the body. For example, if patients in hyperosmolar nonketotic coma are simultaneously stressed by hypovolaemia and hyperosmolarity, renal compensation is directed overwhelmingly at retaining sodium so as to restore circulating volume in spite of significant hypernatraemia. Similarly, patients with pyloric stenosis and severe vomiting develop volume and acid–base disturbances, namely metabolic alkalosis, through acid loss. These patients compensate with proximal tubular sodium and bicarbonate retention, with bicarbonate retained (this is because chloride is being lost through vomiting) in order to preserve volume. Both these examples demonstrate that

volume preservation is given priority over either osmolarity or acid–base balance. Incidentally, the compensation also leads to reduced urine production and loss of excretory function, and these are clearly necessary compromises. Paradoxically, this strong renal compensatory mechanism, which is directed at preserving life but results in oliguria and acute renal failure, might be considered a "success" [1].

The realisation that renal shutdown is a compensatory mechanism for haemodynamic embarrassment, which is exaggerated by nephrotoxins, should cause management to be directed at immediate volume and pressure resuscitation sufficient to eliminate the reason for compensation. The success with which this is achieved in addition to eliminating the toxins depends on resuscitation response time and on the achievement of appropriate haemodynamic targets for the individual concerned [2].

What is acute renal dysfunction and how is it measured?

Clinical acute renal dysfunction is recognised when the compensatory mechanisms result in ineffective urine output, which leads in turn to a progressive inability to excrete nonvolatile acids, potassium, nitrogenous waste and fluids. These changes become associated with a rise in serum urea and creatinine. Although acute renal dysfunction is usually associated with a sustained fall in urine output, it can also be associated with normal or large volumes of poorly concentrated urine.

Plasma creatinine concentration is universally accepted as an approximate indicator of renal function. Creatinine is produced by hepatic dehydration of creatine. Creatine is constantly released from muscle phosphocreatine. Phosphocreatine is a high-energy compound that transfers energy to ADP to increase available ATP, releasing creatine in the process. Any excess ATP produced combines with creatine to re-form phosphocreatine. Muscle mass is a determinant of creatine availability. Consequently, at steady state the creatinine derived from creatine dehydration is related to muscle mass.

Creatinine is completely filtered by the glomerulus and not reabsorbed by the tubules. However, as renal function deteriorates creatinine is progressively secreted by the tubules. Therefore, although useful as marker for glomerular filtration rate (GFR) tubular secretion can lead to overestimation of GFR as function worsens.

Creatinine plasma concentration can also be altered by factors unrelated to renal function; these include abnormalities in liver function and large changes in muscle mass and volume of distribution. High-protein diets can result in higher body creatine content and a slight rise in creatinine, but such changes occur over several months. Conversely, a low-protein diet can reduce creatinine by as much as 15%.

In a steady state the total creatinine produced is constant and is equal to the creatinine excreted. The latter depends on GFR and the plasma creatinine concentration. Consequently, for a given creatinine excretion, plasma creatinine varies inversely with GFR. This means that when there is a sustained 50% fall in GFR doubling of plasma creatinine will result. Figure 1 represents an idealised relationship between GFR and plasma creatinine.

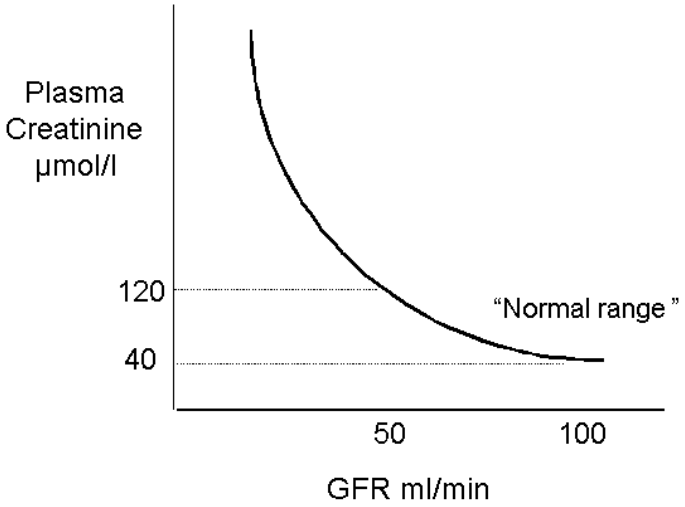

Fig 1. The curve for the relationship between plasma creatinine and glomerular filtration rate (*GFR*) shows that large changes in GFR within the normal range have modest effects on plasma creatinine, while modest falls in GFR to values outside the normal range result in large creatinine changes. In the steady state plasma creatinine is inversely related to GFR

When a population's normal range is superimposed on this graph it can be seen that creatinine can remain within the "normal" range despite a significant fall in GFR. The concept of a normal range based on creatinine rather than on GFR can be misleading; in particular, clinicians may underestimate the extent to which the kidney is stressed in patient with low muscle mass. Table 1 illustrates that a single normal range is inappropriate when renal function for individuals is to be quantified. The relationship between GFR and serum creatinine is further complicated by the fact that as GFR falls the remaining functioning nephrons undertake compensatory hyperfiltration and tubular creatinine secretion, thereby limiting rises in plasma creatinine [3, 4]

Table 1. Estimated expected baseline creatinine (µmol/l) calculated (modified from [9]) for patients with glomerular filtration rate (GFR) assumed to be at the lower end of the normal range (75 ml/min per 1.73 m^2)

Age (years)	Black men	White men	Black women	White women
20–24	133	115	106	88
25–29	133	106	97	88
30–39	124	106	97	80
40–54	115	97	88	80
55–65	115	97	88	71
>65	106	88	80	71

Although GFR can be determined by formal urine collection over 24 h, it can be more conveniently estimated from single serum creatinine concentrations with formulae such as that proposed by Cockcroft and Gault [5]:

GFR ml/min = (140–age) × weight (kg) (1.2 for males) / serum creatinine μmol/l

This nomogram works well for patients with stable reduced renal function, but will overestimate GFR when renal function is normal.

The lack of agreed definitions for acute renal failure and dysfunction has adversely influenced research progress in renal management. Some experts have suggested definitions that might help in the systematic approach to future research (www.ADQI.net) [9, 10]. They have included serum creatinine and measurement of change from baseline creatinine and urine output as the basis of the definitions. They consider acute and chronic renal failure as separate entities. The RIFLE system proposed is outlined in Table 2.

Table 2. The Acute Dialysis Quality Initiative (ADQI) Group proposal for categorisation of patients with acute renal dysfunction. The RIFLE categorisation. (www.ADQI.net).

Category	GFR criteria	Urine output criteria
Patient at **risk** of ARF	Increased creatinine to 1.5× baseline	< 0.5 ml kg^{-1} h^{-1} for 6 h
Patient has suffered acute renal **injury**	Increased creatinine to 2× baseline	< 0.5 ml kg^{-1} h^{-1} for 12 h
Patient in acute renal **failure**	Increased creatinine to 3× baseline	< 0.3 ml kg^{-1} h^{-1} for 24 h or anuria for 12 h
Patient with **loss** of renal function	Persistent ARF is complete loss of kidney function for >4 weeks	
Patient with **end-stage** renal disease	Complete loss of kidney function for >3 months	

Earlier baseline creatinine might be unknown, and it has therefore been suggested that it be estimated by applying the "modification of diet in renal disease" formula (MDRD). This formula is normally used to determine GFR normalised to surface area and is based on serum creatinine, age, sex and race [6–8]. To determine baseline creatinine the formula has to be used in reverse, and it is assumed that the patient started with a normal GFR. The normal GFR has a range 95±20 ml/min for women and 120±25 ml/min for men. For the purposes of the calculation of baseline creatine it is assumed that the patient had the lowest value for GFR that still falls in the normal range, i.e. 95 ml/min (120–25) for a man and 75 ml/min for a woman. These values can be inserted in the MDRD formula to determine the unknown baseline creatinine.

Table 1 shows the estimated baseline creatinine that would be expected when the GFR is at the lower end of the GFR range for different types of patients.

Patients with acute on chronic renal dysfunction are at the highly sensitive end of the creatinine GFR curve, meaning that small changes in GFR cause dispropor-

tionately large increases in creatinine (see Fig. 1). Consequently these patients are difficult to equate with those starting from normal GRF baselines.

Some clinical considerations—renal chemistry data

The relationship between serum creatinine and renal function can lead to clinical misjudgements. Three observations are worth highlighting. First, that within the "normal" range for serum creatinine concentrations can conceal a 50% fall in GFR. Second, that laboratory ranges are often not itemised separately for males and females or ethnic origin. There is a significant difference between the acceptable upper limit for an elderly white women and for a well-built young black man (see Table 1). Third, that clinical practice which relies on urine volumes 0.5 ml $kg^{-1} h^{-1}$ as evidence of adequate renal function ignores the importance of urine quality. The author proposes that it might be more appropriate to take effective urine output volume (EUO) as the desired target; this means the minimum hourly urine volume required to prevent a rise in plasma creatinine over 24 h. The value of EUO will vary from 0.5 to 4 ml $kg^{-1} h^{-1}$, depending on the concentrating ability of the kidney and the age and size of the patient. A continuing daily rise in creatinine implies that urine output is inadequate regardless of its absolute value. For such an individual the target EUO is higher and requires interventions that provide a larger circulating volume or higher blood pressure to increase urine output.

What causes renal dysfunction?

Acute renal dysfunction usually follows an event, whether sudden or insidious, that results in reduced cardiac output. When such events occur in patients with "preconditioned" kidneys oliguria readily follows and, if sustained, results in kidney failure. Preconditioned kidneys are those with chronic or intrinsic renal disease, such as glomerular nephritis, or those exposed to diabetes, hypertension or specific toxins. Toxins identified by epidemiological studies include ACE inhibitors, non-steroidal anti-inflammatory agents (NSAI), aminoglycosides and contrast media [9–16].

These conditions and toxins cause progressive renal microcirculatory changes mediated through nitric oxide, endothelin, prostacyclin, angiotensin II and adenosine. The presence of widespread small vessel endothelial plaques in diabetics, for example, causes an imbalance between endothelial NO and endothelin production, which in turn promotes vasoconstriction.

ACE inhibitors reduce angiotensin II-mediated glomerular efferent arterial tone and decrease glomerular filtration, particularly in patients with renal arterial stenosis.

Aminoglycosides inhibit phospholipase A2, which limits the production of PGI_2 and PGE_2 precursors. The latter is a renal vasodilator whose production is also inhibited by NSAI.

Pigment breakdown products, whether derived from haemoglobin or myoglobin, increase tubular NO uptake, which in turn leads to glomerular vasoconstriction.

Contrast media stimulate both renal vasodilator and vasoconstrictors, but in circumstances where there is pre-existing renal insufficiency the vasodilator response is impaired [17].

Cyclosporin A injures glomerular endothelial and renal tubular cells. Damage to the former results in vasoconstriction through decreased NO activity, leaving the vasoconstrictor effect of endothelin 1 (isoform of endothelin) unbalanced.

It is not surprising that patients exposed to these toxins have a preconditioned reduced microcirculatory state which, if compromised by further renal vasoconstriction in response to a fall in cardiac output, will result in limited glomerular filtration and urine output.

History of renal replacement therapy

The first dialysis experiments were published in 1861 by Thomas Graham (famous for his laws on the diffusion of gases). Later, in 1913, Benjamin Turner described the use of dialysis to remove blood-borne substances. Dialysis technology made a major step forward in 1937, when Thalheimer used cellophane as a membrane and heparin as the anticoagulant. However, it was Willem Kolff who constructed the first artificial kidney and used it to treat a patient in 1943. By 1956 Kolff and Watschinger were ready to describe the use of a twin coil kidney to treat uraemia in two patients, and this dialyser/ultrafiltration construction became the basis for a commercially available and disposable artificial kidney.

In 1960, access to the circulation was facilitated by the introduction of an indwelling Teflon Silastic arteriovenous shunt by Quinton, Dillard and Scribner. This seemingly minor technological advance provided a major practical step for repeated haemodialysis.

Peritoneal dialysis techniques were developed in parallel. The idea of using a natural membrane, the peritoneum, was investigated by Friederich Wegner in 1877, and later by Hartog Hamburger in 1895. The first description of the experimental use of peritoneal dialysis in uraemia was published in 1923 by Ganter. It was subsequently used by many for control of uraemia, including Fine, Frank and Seligman, who together reported on its application in the treatment of acute renal failure in 1946. In 1947 peritoneal irrigation, as it was then known, was also described for the management of incompatible blood transfusion and poisoning. It was 1962 before John Merrill invented a plastic conduit for placement inside the peritoneum for repeated peritoneal lavage. Merrill had earlier been credited with conducting the first human kidney transplant in 1956.

Continuous dialysis techniques were first introduced by Kramer in 1977 [18]. In 1980 he described his experience of managing acute renal failure in 14 patients with a continuous arteriovenous haemofiltration (CAVH) technique. Continuous venovenous haemofiltration (CVVH) was described in 1979 and allowed more control

of filtration rates. In 1984 Geronemus and Schneider described continuous arteriovenous haemodiafiltration (CAVHD), which enabled a more efficient removal of low-molecular-weight products, such as urea and creatinine. In 1988 Tan applied an arteriovenous haemodiafiltration system to a venovenous system (CVVHD), and this has become the method of choice for continuous dialysis of the critically ill patient.

Principles of renal replacement therapy

The aim of renal replacement therapy (RRT) is to remove excess body fluids and solutes while replenishing buffer base without causing haemodynamic disturbance. Continuous RRT systems pump blood past a semipermeable membrane, which allows movement from the blood across the membrane of plasma water rich in solutes to produce an ultrafiltrate.

Plasma water follows the pressure gradient across the membrane. The solute in plasma water is convected across the membrane. If the other side of the membrane is bathed by a physiological solution, solute will also move from blood across the membrane to the physiological solution (dialysate) by a process of diffusion. Small quantities of solute are also removed by adsorption onto the filter membrane.

Convection

The rate at which plasma water from blood moves across a semipermeable membrane is directly related to the hydrostatic transmembrane pressure gradient. Convection of plasma water, also known as ultrafiltration, drags dissolved solutes with it. The rate at which solutes move across the membrane is related to the convection rate and depends on the molecular size of the solute relative to membrane pore size. The ease with which a solute passes the membrane is represented in the membrane rejection coefficient, σ. For substances failing to pass it at all, such as albumin, the rejection coefficient is 1, whilst for urea, which passes freely it, is 0. Other factors also impair the passage of solutes, such as interactions between the membrane and solute. A more convenient method of describing ability to pass through a membrane is the sieving coefficient S. This is defined as $1-\sigma$; according to this, urea has a sieving coefficient of 1 while the corresponding value for albumin is 0.

For all practical purposes, the sieving coefficient can be estimated from the ratio of solute concentrations between blood and ultrafiltrate. It follows that substances with sieving coefficients of 1 will have plasma clearance values equal to the ultrafiltration rate. Consequently, for such substances plasma clearance can only realistically be increased by higher ultrafiltration rates. A filter has a defined life-span, and over time it becomes progressively fouled by proteins; the sieving coefficients fall and clearance rates are reduced. In most cases, a change of filter(s) should be considered when the urea clearance or the sieving coefficient falls by 50%, which is usually after 48 h.

Diffusion

For a given solute-semipermeable membrane combination, factors that influence diffusive movement are membrane thickness, surface area and the solute concentration gradient between solute-rich blood and low-solute dialysate fluid.

The concentration gradient is maintained across the filter membrane by continuous countercurrent dialysate and blood flows. Increasing the blood flow rate can increase urea clearance in a diffusive system. In continuous dialysis machines blood flow rate is limited to about 180 ml/min, and therefore for a given solute, membrane and blood flow rate the greatest influence on solute clearance is exerted by the dialysate flow rate. Dialysate flow rates in standard machines can be increased to 2,500 ml/h, during which there is a near linear rise in urea clearance. Note that as flow rates increase the time for equilibration decreases and potentially reduces clearance efficacy. In a purely diffusive system there is no ultrafiltration.

For a given concentration gradient between blood and low-solute dialysate, diffusion favours the movement of smaller molecules. Solutes with molecular weights below 500 Da readily move across the membrane. Indeed for these molecules there is very little difference in the efficiency of a RRT system using diffusion alone or convection alone. Molecules such as urea, creatinine, amino acids and most antibiotics have molecular weights below 500 Da.

Molecules such as vancomycin and teicoplanin (mol. wt. 3,300 and approximately 1,880, respectively), cytokines, complement, β2-microglobulin and albumin are much larger and are poorly removed by diffusion. Convection-based systems have greater efficiency for clearance of these larger molecules.

It is important to note that while solutes diffuse from blood there is also simultaneous movement of molecules in the dialysate fluid into blood. By design, dialysate fluids containing lactate or bicarbonate are used to replenish buffer base to reduce acidosis. In systems based on convection the plasma water lost through ultrafiltration is replaced with physiological solutions containing lactate or bicarbonate.

Adsorption

Adsorption, the binding of solutes onto solid material, tends to be independent of solute concentration and related to chemical attraction between solute and membrane. Thick synthetic membranes are charged and they attract oppositely charged solutes, such as peptides. It is thought that this mechanism might contribute to cytokine removal and be potentially useful for treatment in sepsis [19].

In modern continuous renal replacement machines, blood flow, dialysate and ultrafiltration rates can be controlled with pumps. The processes of diffusion and convection can be combined. In the combined mode, both processes achieve small molecule removal. For larger molecules convection appears to be more important.

The interaction between the diffusive and convective processes may reduce the efficiency of each process. If dialysate flow rates are very low relative to ultrafiltration rates, the ultrafiltrate, which mixes with the dialysate, creates a ‘dialysate’ with

solute concentrations similar to those in plasma ultrafiltrate and consequently hardly any concentration gradient between the dialysate (slow flowing and overwhelmed by ultrafiltrate) and the blood.

Solutes such as bicarbonate or lactate will by design have a higher concentration in dialysate fluid than that in blood. These solutes move to blood through diffusion or by administration of fluid replacement for the ultrafiltrate.

Does it matter whether RRT is by diffusion or convection?

There is no level 1 evidence that supports one method of RRT over another. Convective therapy might be expected to be advantageous as it removes small and medium-sized molecules. However, this assumes that all these molecules are harmful. The advantage of convection over dialysis is that clearance is directly related to the ultrafiltration rate and therefore more predictable. Fluid balance is easily manipulated by the degree to which ultrafiltrate is replaced with physiological solutions. Diffusion alone does not allow fluid removal, and the solute clearance is biased towards the smaller molecules. In practice most clinicians use a combination of both to get maximum clearance.

When should you start renal support?

Traditionally renal replacement therapy (RRT) has been suggested when the urea level is greater than 35 mmol/l and that of creatinine is approaching 350 μmol/l. These end-points are loose, and most clinicians faced with a patient unlikely to regain urine output within a couple of days will start dialysis without reference to the measured end-points. If urine output is likely to pick up in less time, clinical end-points such as hyperkalaemia or metabolic acidosis can be managed for a short period with bicarbonate and techniques that reduce serum potassium, without recourse to RRT.

Many clinicians use RRT early, particularly when metabolic acidosis is part of the clinical picture. However, in the author's opinion the thinking behind this approach is occasionally confused. It is important to be aware that the development of metabolic acidosis resulting from acute oliguria alone is very slow—many hours or even some days—and that once it has initially been corrected with bicarbonate the bicarbonate requirements over the next 24 h should be only modest. However, if the source of metabolic acidosis is not only acute renal failure, but also hypovolaemia and shock, acid is produced both in large amounts and fast and is not easily dealt with by RRT. Many clinicians opt for rapid introduction of renal support for these patients, hoping to resolve metabolic acidosis, and are then surprised that this may not only take several hours but may also be followed by worsening of the condition. For this reason, any patient with metabolic acidosis, whether in renal failure or not, should in be managed in such a way as to ensure an effective cardiac output before dialysis is initiated [2]. It is possible to estimate whether cardiac

output is effective from clinical signs. Once the triad of normal blood pressure, warm feet and a heart rate below 100 is met then cardiac output for that patient can be assumed to be effective for global perfusion. If these end-points have not been met, resuscitation with fluids and inotropes and dilators should be used. Once the end-points are met and a base deficit remains, then a 100- to 200-ml 8.4% bicarbonate challenge should be given over 30 min to reduce the base deficit to normal. If urine output remains poor the base deficit will deteriorate. If base deficit deterioration is due solely to renal failure it will take several hours (assuming an effective cardiac output is being maintained).

If metabolic acidosis returns within 1 or 2 h, the clinician should not only look for persisting global or local ischaemia (gut, limb, liver ischaemia), but also should not expect RRT to resolve the problem without some additional measures. Failure to use resuscitation techniques to achieve an effective cardiac output and immediate use of dialysis in these circumstances can potentially cause further renal injury with a longer period for recovery. Using the bicarbonate challenge approach for patients with metabolic acidosis will ensure that many patients not only receive appropriate initial fluid management, but might also not need dialysis.

Common modes of RRT

Peritoneal dialysis (PD)

Dialysate fluid (1–3 l) is placed into the peritoneal cavity via a catheter and allowed to remain in situ for a predetermined period, after which it is allowed to decant. The dialysate fluid can be made hyperosmolar by means of varying sugar concentrations. Hyperosmolar solutions residing in the peritoneal cavity draw fluid from the circulation across the peritoneal lining. Movement of plasma water convects urea and other solutes. In addition, solutes in the blood follow their concentration gradients into the dialysate fluid. Dwell times in the peritoneal cavity vary between 30 min and 3 h. The longer the dwell time the greater the clearance by both diffusion and convection (with hypertonic dialysates). However, the efficiency of clearance is greatest in the first 40 min (50% of clearance occurs within this time, rising to only 70% by 2 h and 90% by 4 h). Consequently, the most effective way of clearing urea is through short cycles of about 1 h with dwell times of 30–40 min, rather than longer dwell times. Clearance rates for urea are typically 8 ml/min. The cycling of peritoneal filling and emptying can be automated, reducing the need for nursing personnel and the risk of infection through handling. Peritoneal dialysis has the advantage of not needing vascular access or anticoagulation. In the acutely ill patient a simple catheter can be placed, but there is a risk of peritonitis after some days. For chronic management surgically placed twin cuffed peritoneal catheters are anchored in the rectus muscle and subcutaneous tissue. The associated fibrous tissue formation around these cuffs provides a barrier for organism migration and minimises the risk of infection.

Intermittent haemodialysis

Intermittent haemodialysis (IHD) is the most common method of dialysis for chronic renal failure management. It uses diffusion as its main method of clearance, with dialysate flows of 500 ml/min, which provide urea clearances of about 220 ml/min. However, IHD is typically done in sessions of 4 h and is performed three times a week, equating with a mean urea clearance of 15 ml/min over a 7-day period.

Continuous RRT

The earliest method of CRRT used arterial pressure to drive blood through a filter system for ultrafiltration and convection and was dependent on patient haemodynamics. This method was unreliable owing to the considerable variability in blood pressure, and it is now rarely used. The introduction of dialysis machines with pumps allowed the use of a central venous based system with large-calibre double-lumen catheters.

Venous blood taken from the patient through one of these lumens is anticoagulated and diluted with a balanced physiological solution prior to passage through the haemofilter. Blood is cleared of solute by convection and/or diffusion and returned to the venous system through the adjacent lumen.

Continuous venovenous haemofiltration (CVVH) relies entirely on convection for solute clearance. With ultrafiltrate loss rates set at 1 l/h and equal volume replacement with a physiological solution, urea clearance rates are in the order of 15 ml/min. Overall fluid balance can be controlled by adjustment of fluid replacement rates, which are set by the clinician and automated by the machine.

Continuous venovenous haemodialysis (CVVHD) relies entirely on diffusion for urea clearance. With dialysate flow rates of 1 l/h, clearance rates are also in the order of 15 ml/min.

Continuous venovenous haemodiafiltration (CVVHDF) combines the effects of convection and diffusion to achieve urea clearance rates of 30 ml/min. These clearances assume dialysate and filtration flow rates each of 1 l/h.

Slow continuous ultrafiltration (SCUF) is similar to CVVH except that ultrafiltration rates are kept low to provide a slow continuous removal of fluid, particularly where the aim is to reduce circulating volume and oedema rather than solute clearance. There is no fluid replacement. Urea clearance tends to be low: in the order of 2 ml/min.

Does the dose of dialysis matter?

The aim of dialysis is first to return extracellular fluid composition and volume to normal and then to maintain clearance of the by-products of metabolism. By convention, the dose of dialysis required to achieve the composition targets has been based on blood urea clearance. Urea, a small molecule, is the principal by-product of protein catabolism and is distributed throughout the body water.

Ideally, urea clearance by haemodialysis should match its production. Whilst continuous renal replacement techniques are able to maintain relatively steady concentrations of urea, HD reduces urea concentrations for the short periods of dialysis only and is followed by a slow return to the previous elevated concentrations.

Table 3 outlines the urea clearance achieved by different modes of dialysis. The known adverse effects of uraemia include immunosuppression, impaired phagocytosis, defective lymphocyte and monocyte activity, reduced platelet stickiness, ileus and a tendency to gastrointestinal bleeding. Therefore there might be some advantage in minimising the baseline urea concentrations and the other molecules that are thought to contribute to these adverse effects.

Table 3. Clearance characteristics of differing modes of dialysis

	IHD	CVVH	CVVD	CVVHDF	PD	SCUF
Urea clearance	D	C	D	D, C	D, C	C
Approx urea clearance ml/min[a]	220 (during) 15 when averaged[b]	15	15	30	8	negligible

C convection, *D* diffusion, *IHD* intermittent haemodialysis, *CVVH* continuous venovenous haemofiltration, *CVVHD* continuous venovenous haemodialysis, *CVVHDF* continuous venovenous haemodiafiltration, *PD* peritoneal dialysis, *SCUF* slow continuous ultrafiltration

[a]Based on 1 l/h dialysate rate for CVVD, CVHDF, PD and haemofiltrate rates 1 l/h for CVVH, CVVHF

[b]Based on 4 h per day for 3 days and clearance averaged for 7 days

In the National Cooperative Dialysis Study among end-stage renal failure patients, patients whose target urea concentrations were 36 mmol/l had a slightly higher morbidity than those whose target was 18 mmol/l [20].

It has recently been suggested that among patients with acute renal failure, the outcome 15 days after stopping CVVH is better after higher doses of haemofiltration (35 ml kg^{-1} h^{-1}) than after lower doses (20 ml kg^{-1} h^{-1}) [21]. In addition, there were more survivors among those who were started on CVVH with lower urea values although this was not significant.

It is, however, unclear whether all-cause hospital mortality is altered by dosage of dialysis. In a randomised study of intermittent haemodialysis (HEMO study) in which both dialysis dose and flux across the filter membrane were varied there was no differences in all-cause mortality or complications between four possible dialysis methodologies [22].

Does it matter which dialysis membrane is used?

Membranes for dialysis are either cellulose based (usually for IHD machines), such as cuprophan, haemophan or cellulose acetate, or made from synthetic polymers. The latter include polysulfone, polyacrylnitrile (PAN), AN69, polyamide or polymethacrylate. These membranes have differing flux characteristics and are variably biocompatible. The cellulose-based membranes are poorly biocompatible, tend to be cheap and have low flux characteristics, while synthetic membranes are more biocompatible and have higher flux.

Recovery from acute renal failure has been reported as quicker, and mortality lower, among patients dialysed with synthetic rather than cellulose membranes. The mechanism is thought to be related to inflammatory cell activation and to stimulation of proinflammatory cytokines, complement and platelets [23–25]. In addition, synthetic membranes have been reported to adsorb activated complement fragments and cytokines. However, studies have failed to distinguish between the effects of flux (synthetic membranes allow more medium-sized molecules to pass) and biocompatibility.

Filters used for continuous RRT are usually synthetic.

How should the extracorporeal circuit be anticoagulated?

When blood comes in contact with a foreign material the coagulation pathway is activated; therefore, patients undergoing IHD normally receive unfractionated heparin to avoid clotting in the circuit. The risks of bleeding are low, as the therapy lasts for only a short period. However, for patients needing continuous RRT, the issue of anticoagulation can be problematic. Normally anticoagulation of the circuit can be achieved with continuous infusion of 200–1,000 U of unfractionated heparin, which is given with the aim of keeping the circuit's activated partial thromboplastin time no more than 50 s. It is possible, with pump rates above 140 ml/min and prefilter dilution sets, to run circuits successfully without heparin, but circuit clotting tends to occur earlier than in heparinised circuits at the same settings.

Ingenious methods have been devised to provide circuit anticoagulation with agents which reduce the risk of bleeding or use methodology that reverses the anticoagulation before the blood returns to the patient. These methods include prostacyclin, regional heparin and protamine, low-molecular-weight heparin, sodium citrate, orgaran and recombinant hirudin. A large number of critically ill patients have some degree of auto-anticoagulation or platelet function altered by uraemia. This degree of hypocoagulability can allow many patients to receive RRT without heparin. Early clotting (within 24 h) of the circuit should always arouse the suspicion that venous access is the problem. The ease of aspiration (there should be no cessation or hesitation in blood flow from either port; the ease of flushing is not relevant) should be checked before heparin is introduced or the dose increased. Patient movement for nursing procedures or spontaneous movements by the

patient commonly lead to temporay obstruction to venous access lines, which if left unattended causes a rise in venous access pressure and filter clotting.

A special problem is heparin-induced thrombocytopenia, which increases the risk of bleeding [26]. Orgaran, a low-molecular-weight glycosaminoglycan, has been used with mixed success in the management of patients [27].

Which buffer solution should be used for dialysis/replacement?

The most common dialysate fluids contain lactate as a buffer. Lactate is usually present in a higher concentration in the dialysate fluid than in the patient. Consequently, it enters the patient both through diffusion and when given as replacement fluid for the ultrafiltrate. Lactate is metabolised to bicarbonate and sugar in the liver based Cori cycle, replenishes buffer base and helps restore normal acid base status. Note that bicarbonate is being lost from blood by the process of convection and by diffusion into bicarbonate-free dialysate. However the lactate supplied as buffer base more than restores bicarbonate. In patients in whom generation of acidosis is less of a problem it is not uncommon to see aggressive dialysis causing a metabolic alkalosis due to lactate metabolism. For the majority of patients, lactate buffer solutions are more than adequate to restore the acid–base balance and they are cheap, which is a consideration when over 100 l dialysate fluid is used per day on a patient.

Lactate solutions can, however, be a problem in patients with hepatic failure. Hepatic lactate metabolism to bicarbonate and sugar is limited, so that lactate from dialysate fluids will accumulate and will be associated with a base deficit. Additionally, normal endogenous lactic acid production from muscle is also not metabolised by the liver. In addition, haemodiafiltration will remove bicarbonate from blood by convection and diffusion (no bicarbonate in lactate dialysate fluids). When these processes all combine it is easy to see that hyperlactataemia becomes associated in these liver patients with a large base deficit.

The readily available bicarbonate dialysate solutions make management of hepatic patients much simpler. However, RRT with such solutions is not sufficient to deal with acidosis generated over and above that due to acute renal failure. Patients who develop ischaemic hepatitis or any other form of ischaemia will remain acidotic until the primary problem is resolved. Hyperlactataemia during lactate dialysis in nonhepatic disease patients is of little consequence [28]. However, some clinicians find hyperlactataemia distracting if serum lactate concentrations are used as their major indicator of perfusion, and for this reason they use bicarbonate-containing dialysate fluids in spite of their extra cost. Poorly controlled acidosis with bicarbonate dialysate solutions should always be a reason to seek a cause of metabolic acidosis other than renal failure.

Does it matter which RRT is used?

In European and Australian critical care units continuous RRT is preferred to IHD for renal support. This might be because these countries have closed units, which are directed by intensive care specialists and have a self-reliant culture. These units will tend to start treatment without consulting or relying on nephrology dialysis departments. In the USA the reverse is largely true: dialysis is provided by nephrology personnel, who choose to use IHD because they are more familiar with it and perhaps because it requires less bedside attendance than CVVH.

In the early years of continuous arteriovenous techniques solute clearance was inadequate compared with that yielded by the more powerful intermittent machines. However, modern continuous venovenous machines offer many advantages over IHD, including ease of use, lack of need for special water supplies, greater urea clearance [29] and the facility to remove fluid gradually, thus avoiding hypovolaemic insults. IHD has the potential disadvantage of causing convective hypovolaemia and a disequilibrium syndrome. Convective hypovolaemia is thought to be due to rapid solute removal from the circulation, which results in an osmolarity-driven fluid shift from the intravascular space into interstitium and cells. This occurs even when no fluid has been removed from the patient. Disequilibrium syndrome follows extraction of solute from the vascular compartment faster than solute replenishment from the interstitium and cells into the vascular space. This results in an osmotic gradient promoting water movement into cells and thus causing swelling. Patients complain of headache and may have signs of cerebral oedema. These phenomena are not apparent with continuous techniques.

The additional effects of intentional fluid removal may confound convective hypovolaemia and cause significant hypotension following IHD. Many patients become hypotensive soon after starting IHD, and amongst other things this might be related to the clearance of inotropes. Continuous therapy avoids such changes and in general makes it easier to manage nutrition and other obligate fluid administration. The consequences of inadvertent hypotension/hypovolaemia may lead to new ischaemic lesions and possibly to delayed recovery [30, 31].

Unfortunately, venous access problems are a consistent reason for failure to achieve smooth running of continuous therapy over long periods; in truth, it is often an intermittent therapy lasting 24–36 h unless the patient is heavily sedated. Patient movement or nursing procedures often inadvertently kink femoral lines and internal jugular lines. The repeated clotting of a filter is frequently assumed to be an anticoagulation problem rather than one of venous access. This may lead to patients receiving more anticoagulants than necessary, with consequent problems. IHD machines appear to be less sensitive to venous access problems and in addition do not require 24-h anticoagulation. For these reasons it might be preferable to use IHD once patients are more stable and relatively mobile.

Although there is no evidence that mortality is altered by the choice between intermittent or continuous modes, there is some evidence that the time to renal recovery is shorter with CVVH than with IHD [32].

Does the removal of inflammatory and anti-inflammatory markers make a difference?

There has been much interest in the use of CVVH for clearing inflammatory mediators. This has led to the development and use of high-flux membranes with high-volume haemofiltration to maximise mediator clearance [24, 33–35].

Initial animal studies suggested that high-volume cytokine clearance led to tangible improvements, such as better myocardial function. However, controlled trials in patients have failed to support significant clearance of cytokines by RRT. In a randomised study among septic patients with normal native renal function there was no difference in circulating cytokines between those who received CVVH at 2 l/h and those who remained unsupported. In addition there were no improvements in objective measures of oxygenation or need for inotropic support [36]. In another recent study, although cytokines (IL-6 and TNF) were measured in the ultrafiltrate CVVH had no impact on blood concentrations [37]. However, there is some evidence that high-flux membranes (pore size greater than 60 kDa rather than 30 kDa) provide better medium molecule clearance and that peripheral blood mononuclear cells become more responsive when exposed ex vivo to an endotoxin [38–40]. Although increasing the pore size improves the clearance of cytokines it also leads to albumin losses.

Although CVVH cytokine clearance is conceptually attractive it is interesting to note that reducing cytokine levels by other methods, e.g. by means of monoclonal antibodies, has produced a series of negative trial results [41–43]. This evidence together with that from high-volume haemofiltration trials suggests there is probably little mileage in mediator modification.

Does renal replacement therapy alter mortality?

Acute oliguric renal failure will result in 100% mortality in the absence of spontaneous recovery or RRT. Any form of RRT will prevent a large number of deaths from the immediate complications of hyperkalaemia and progressive metabolic acidosis.

It is often argued that RRT has not influenced outcome over the years, or in other words that renal support in renal failure does not reduce mortality to that among patients without acute renal failure (ARF). However, it cannot be denied that RRT is used in older and sicker patients and has therefore facilitated more aggressive and successful treatments.

In the acutely ill, mortality increases by approximately 20% with acquisition of each supported organ failure [44, 45]. Clermont et al. examined the details of 1,530 patients admitted to critical care over 10 months in order to determine the impact of renal dysfunction on outcome. Among the 1,530 admissions 20.7% had renal impairment, 6% had acute renal failure not needing support, 11% needed dialysis and 3.7% had end-stage renal disease (ESRD), and all of these required dialysis [46]. Fifty percent of those with ARF were admitted with ARF while the rest developed

it in ICU. They observed an overall ICU mortality of 23% for patients with ARF, but 57% among those requiring dialysis. The mortality among those without renal failure was only 5%. Among those with ESRD mortality was 11%. They found no difference in outcome between patients who had ARF at the time of ICU admission and those who developed ARF in the ICU. They concluded that an acute decline in renal function was associated with a mortality that was not well explained simply by loss of organ function. The majority of ARF patients who did not require dialysis still had a considerably higher mortality than the ESRD patients, all of whom required dialysis.

This data sits well with evidence that when allowances are made for co-morbidity RRT-supported renal dysfunction has an attributable mortality [13, 46–49]. Table 4 lists some recent studies and associated mortality rates in ARF supported by dialysis.

Table 4. Hospital outcomes associated with patients in acute renal failure and needing renal replacement therapy in the intensive care unit

Author	Year	Hospital mortality (%)
Chertow [50]	1995	70
Hamel [51]	1997	73
Silvester [52]	2001	46.8
Metnitz [49] §§	2002	62.8

The failure of renal support to reduce mortality rates to the rates enjoyed by patients without renal failure suggests that renal failure probably intrinsically alters immunocompetence or the ability to control the inflammatory response. Some parallels can be made with ventilator supported acute respiratory failure.

Conclusions

Acute renal failure is common and easily supported. The mechanics of renal support management are well understood, but why the mortality rate associated with renal failure, even when supported, does not decline to baseline levels remains largely unexplained.

Perhaps no significant progress will be made until attempts to retain renal function are more successful.

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Chapter 12

Acute liver failure

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Acute liver failure is a relatively uncommon clinical syndrome caused by severe hepatocyte dysfunction in the absence of pre-existing liver disease.

Hepatic failure leads to a well-recognised pattern of clinical signs and symptoms; there is no specific therapy and the mortality rate is high (up to 80%) [1]. It results from severe impairment and/or necrosis of liver cells, which ultimately triggers multi-organ failure. Haemodynamic instability, renal failure, coagulopathy, profound metabolic disturbances and susceptibility to infections are common clinical features.

Hepatic encephalopathy with cerebral oedema is the key event that defines the prognosis, since death can occur even when the liver has begun to recover. Even though spontaneous liver regeneration is sometimes possible, it is, however, unpredictable; therefore, liver transplantation is the only therapeutic intervention of proven benefit.

Classification

The term "fulminant hepatic failure" was first introduced by Tray and Davidson in 1970 to describe "a potentially reversible condition where hepatocellular dysfunction is so severe that encephalopathy occurs within eight weeks of appearance of the first symptoms in the absence of pre-existing liver disease" [2].

In the early 1990s, according to data from the Liver Unit at King's College Hospital in London, O'Grady et al. [3] suggested a further subclassification based on the time interval between the onset of jaundice and the appearance of encephalopathy. They also included features such as incidence of life-threatening cerebral oedema and prognosis without liver transplant, which are useful to identify patients who would be appropriate candidates for liver transplantation.

The three classes proposed (Table 1) were:

a) Hyperacute liver failure: the appearance of the encephalopathy is recorded within 7 days after the onset of jaundice. These patients have a high incidence of cerebral oedema, but they are the most likely to survive with appropriate medical treatment (more than 30% survival without liver transplantation).

b) Acute liver failure: encephalopathy appears within 8–28 days after the onset of jaundice. There is still a high incidence of cerebral oedema (56%), but unlike the previous condition the outcome of acute liver failure is poor without liver transplantation (only 7% survive).

c) *Subacute liver failure*: encephalopathy develops 4–12 weeks after the onset of jaundice, and the condition is characterised by a poor prognosis despite the low incidence of cerebral oedema.

Table 1. Clinical features of subtypes of acute liver failure

Feature	Hyperacute	Acute	Subacute
Interval between jaundice and encephalopathy (days/weeks)	0–7	8–28	4–12 weeks
Cerebral oedema	Common	mmon	Rare
Renal failure	Early	Late	Late
Ascites	Rare	Rare	Common
Coagulation disorders	Marked	Marked	Modest
Prognosis	Moderate	Poor	Poor

Aetiology

Whilst the aetiology of acute liver failure is heterogeneous (Table 2), viral hepatitis remains the most common identifiable cause. All hepatotropic viruses can cause the syndrome [4, 5].

Table 2. Causes of acute liver failure

Hepatitis viruses	**HAV, HBV, HDV, HCV, CMV, herpes simplex 1 virus, EB virus**
Drugs: in a dose-dependent manner and for idiosyncratic reaction	Paracetamol, ecstasy, phenitoin, isoniazide, MAO inhibitors, alothane
Toxins	α-Amanitin from Amanita phalloides
Chemicals	Fluorinated hydrocarbons trichlorethylene and tetrachlorethylene (sniffing glue)
Miscellaneous	Acute fatty liver syndrome, HELLP syndrome, Budd-Chiari syndrome, hepatic artery thrombosis, graft nonfunction
Cryptogenic	—

Acetaminophen overdose and idiosyncratic drug reactions account for the majority of other cases. The overall mortality of paracetamol-induced ALF is ~40%.

Ingestion of toxins found in *Amanita phalloides* is among the most common causes in Italy.

Acute liver failure resulting from Wilson's disease bears to a high mortality without transplantation; Reye's syndrome is rare, as are other syndromes that can cause ALF in the third trimester of pregnancy (fatty liver of pregnancy, HELLP syndrome).

Pathophysiology

The liver is a multifunctional organ that has an important role in metabolism, biosynthesis, excretion, secretion and detoxification. These processes require energy, making the liver a highly aerobic oxygen-dependent tissue. It thus becomes clear that an impairment of its function will have significant haemodynamic, respiratory, metabolic and haemostatic consequences.

The extent of liver cell damage depends on the nature, duration and severity of the initial trigger event. In addition, there is secondary damage caused by the release of cytokines and cytotoxic mediators from activated cells of the reticuloendothelial system (Kupfer cells).

Further damage arises from the release of large amounts of free radicals and proteases as a result of interaction between neutrophil granulocytes and sinusoid endothelium. The activation of sinusoidal endothelial cells leads to lipid peroxidation of cell membranes, abnormalities in intrahepatic microcirculation with vasoconstriction and perfusion failure, tissue hypoxaemia and, ultimately, cell death.

Haemodynamic changes and tissue oxygen debt

In some ways, circulatory disturbances mimic septic shock, with a hyperdynamic pattern sustained by the release of toxic substances from injured hepatocytes. In the early stage of the syndrome, microcirculatory disturbances along with abnormal oxygen transport are responsible for the low peripheral oxygen utilisation despite the initial adequate blood pressure and arterial oxygen saturation.

Circulatory abnormalities tend to worsen during the course of the illness: and the loss of autoregulation of vascular tone results in a generalised vasodilatation and reduction in systemic vascular resistance; hypotension is the rule; tachycardia and an increase in cardiac output are the most common compensatory consequences (Table 3).

Table 3. Haemodynamic and oxyphoretic profile

	Acute liver failure	Normal values
CI	n or ↓ ↓	2.5–4 l min^{-1} m^{-2}
FC	↓ ↓	60–80 bpm
SVRI	↓ ↓ ↓	1200–2400 dyn s^{-1} cm^{-5} m^{-2}
DO2I	↑ ↓ or ↓	400–600 ml min^{-1} m^{-2}
VO2I	↓	120–160 ml min^{-1} m^{-2}
O2 Extraction	↓ ↓	22–30%
SvO2	↑ ↑	60–80%

Although delivery of oxygen to the tissues is often adequate, there is a decrease in its uptake, resulting in low arterio-venous oxygen content difference.

Activation of platelets together with increased adhesion of leucocytes to endothe-

lium predispose to microthrombi and circulatory plugging, with shunting of blood (through low resistance vessels) away from active metabolic tissues. Consequently, the oxygen extraction ratio and oxygen consumption are decreased, anaerobic metabolism ensues and lactic acidosis develops (oxygen debt).

Tissue hypoxia caused by severe peripheral hypoperfusion, and low blood pressure contribute to the development of multiorgan failure, which is associated with a very poor prognosis.

Clinical features

Early clinical presentation includes nonspecific symptoms such as sickness, anorexia, nausea and vomiting; more specific ones are jaundice and abdominal pain. Hepatic encephalopathy and coagulopathy typically define the syndrome. Other clinical manifestations are lacking as the liver is usually not palpable and there are no signs of chronic liver disease such as portal hypertension, spider naevi or ascites.

Careful history taking and accurate clinical examination of the patient make it possible to distinguish the altered mental status with this feature from neurological impairment resulting from other causes; laboratory biochemistry and clotting pattern help in the diagnosis of acute liver failure. Progression of hepatic dysfunction determines the involvement of the whole body with haemodynamic changes, metabolic disturbances and multiple organ failure.

Encephalopathy

Both vasogenic and cytotoxic mechanisms have been invoked in the pathogenesis of hepatic encephalopathy [6]. It has been demonstrated that many toxic substances released from the damaged liver can alter the autoregulation of cerebral blood flow (CBF) and increase the permeability of the blood–brain barrier, thus leading to cerebral oedema.

Failure of biotransformation and excretion of toxins normally processed by the liver is the main mechanism involved in cerebrovascular derangement. Ammonia is a nitrogenous molecule derived from the deamination of aminoacids; the two major sources are catabolism of endogenous proteins and gastrointestinal absorption, since resident bacteria split urea to produce ammonia. In the brain, ammonia detoxification occurs inside the astrocytes, where it is converted into glutamine by the enzyme glutamine synthetase. The accumulation of glutamine in the astrocytes induced by hyperammonaemia produces osmotic stress and causes them to swell; other chemicals, such as mercaptans, fatty acids, aromatic chain aminoacids, benzodiazepine-like substances and γ-aminobutyric acid, are also involved. The swelling of the astrocytes is an important mechanism in the increase of cerebral volume and ICP.

While CBF is sometimes reduced in the first stage of ALF (local cerebral vasoconstriction in response to reduction of mean systemic arterial pressure), it tends to increase in the subsequent stage as hyperammonaemia decreases cerebral

arteriolar tone. Despite vasodilatation in the systemic and splanchnic beds, cerebral vessel resistance may increase, so that cerebral perfusion pressure may be preserved. When in the course of illness cerebral vascular tone is no longer effective, vasodilatation develops and rapidly becomes poorly responsive to carbon dioxide stimulation. The loss of autoregulatory tone is responsible for excessive CBF (vasogenic oedema). Prolonged hyperaemia may worsen brain swelling and cerebral oedema. Brain oedema further aggravates the critically reduced cerebral perfusion, leading ultimately to marked cerebral ischaemia [7, 8].

Severity of hepatic encephalopathy is classified in four grades (I–IV; see Table 4), based on the progression from a normal mental status to deep hepatic coma. Brain oedema is a frequent and serious complication, occurring in up to 80% of patients with grade IV encephalopathy, and is a major cause of death.

Table 4. Staging of hepatic encephalopathy

Grade	Intellectual function	Neuromuscular function	EEG	Outcome (% survival)
I	Impaired attention, irritability, slowness of mentation, disturbed sleep	Incoordination, apraxia	Usually normal	70%
II	Drowsiness, inappropriate behaviour (confusion, euphoria), sleep disorders	Tremors, slowed or slurred speech, ataxia	Generalised slowing	60%
III	Marked confusion and disorientation, somnolence to semistupor but still arousable, amnesia, can follow simple commands	Hypoactive reflexes, nystagmus, clonus and muscular rigidity	Severe slowing	40%
IV	Stupor and coma	Dilated pupils and decerebrate posturing, absence to painful stimuli	Severe slowing with frequencies in the theta and delta ranges	20%

One of the earliest signs of encephalopathy reflects the involvement of higher cortical functions: patients may be agitated and exhibit aggressive behaviour and changes in personality; they usually experience a change in sleep pattern (wakefulness at night and drowsiness during the day). The EEG is usually normal.

Stage II is characterised by an exaggeration of these cortical manifestations, with more drowsiness and lethargy, and by the appearance of movement disorders that reflect increasing involvement of the descending reticular system or other neurological structures. These movement disturbances include tremors and incoordination. An EEG performed in stage II usually shows slower rhythms than normal. Spontaneous hyperventilation is common and can result in significant respiratory alkalosis.

Progression to stage III is defined as increasing obtundation though the patient

is still arousable: tremors may no longer be evident, leading to a generalised increase in muscle tone; hyperreflexia and muscle rigidity become evident, right up to the full decerebrate posture of stage IV. The EEG shows severe slowing in frequencies in the theta and delta ranges.

These neurological manifestations are generally symmetrical, and the appearance of focal neurological motor or sensory abnormalities should always prompt investigation for other causes of neurological disease, such as intracerebral haemorrhage.

Even though the clinical features may be fully reversible, either spontaneously or by transplantation, grade IV encephalopathy is always a manifestation of advanced liver disease and is associated with a poor long-term prognosis.

Coagulopathy

Coagulopathy is the second important hallmark of ALF. The liver has a central role in coagulation: it is responsible for the synthesis of the clotting factors and most of the inhibitors of coagulation and fibrinolysis; it also clears activated clotting factors from the bloodstream.

Coagulation disturbances include thrombocytopenia with abnormalities in aggregation and adhesion, and low circulating levels of fibrinogen and factors II, V, VII, IX and X. This causes prolongation of the prothrombin time, which together with factor V level is widely used as an indicator of the severity of hepatic injury. In contrast, factor VIII, which is produced by endothelial cells and not by the liver, is usually increased. At the same time, coagulation inhibitors AT III, protein C and protein S are reduced, but this phenomenon fails to have a corrective effect on the coagulopathy [9, 10]. Fibrinolysis is enhanced, as manifested by an increase in fibrin degradation products, poor clot formation and a certain degree of disseminated intravascular coagulation [11].

Bleeding occurs in as many as 75% of patients, usually from gastric mucosal erosions, but also from the nasopharynx, lungs, retroperitoneum, kidneys and skin puncture sites.

The prophylactic administration of fresh-frozen plasma in patients not suffering from bleeding has not been shown to reduce morbidity or mortality [11], and management with blood products is indicated only in the presence of manifest bleeding or to promote coagulation during invasive procedures.

Other laboratory data

Other laboratory data include elevated serum aminotransferases, hyperbilirubin, hypoglycaemia, hyperammonaemia, elevated lactate and, often, electrolyte abnormalities such as hyponatraemia, hypokalaemia and hypophosphataemia.

Metabolic acidosis becomes evident late in the course of the illness even though it is an early sign of a poor prognosis in the case of acetaminophen overdose.

Renal failure

Renal impairment occurs in up to 60–70% of cases and indicates a poor prognosis [12]. The usual form is a functional failure, but acute necrosis is also found [13].

Renal blood flow is reduced because of intense renal arteriolar vasoconstriction; renin and aldosterone levels are, in fact, increased [14, 15]. No structural damage to the renal parenchyma occurs if hepatic cells recover or if liver transplantation is performed. Acute tubular necrosis can result either from systemic hypotension or from a direct toxic effect of acetaminophen [16], antibiotics and contrast agents. The urinary sodium excretion in acute tubular necrosis is usually >20 mmol/l, and the urinary sediment often shows cellular casts.

Serum creatinine is a better index of renal function than blood urea, since urea synthesis is greatly decreased in these patients (with the risk of underestimation of the severity of renal dysfunction).

Renal support is often required, preferably in the form of continuous techniques rather than intermittent haemodialysis. Continuous renal replacement methods are indicated particularly in the case of elevated ICP: they are, in fact, associated with greater cardiovascular stability and higher cerebral perfusion pressures than are standard intermittent techniques [17–20]. The rapid water shift provoked by intermittent haemodialysis is responsible for the poorer neurological outcome than is seen with the slow fluid exchange when the continuous technique is applied [21].

Other indications for continuous replacement methods include uncontrolled acidosis, hyperkalaemia, fluid overload and oliguria.

Metabolic changes

The main metabolic disorders are hypoglycaemia and hyperlactataemia.

Low blood glucose levels result from impaired gluconeogenesis, inability to mobilise glycogen stores and inadequate hepatic uptake of insulin with augmentation of circulating levels. Blood glucose should be monitored frequently, as clinical signs of hypoglycaemia can be masked in the presence of established encephalopathy. Hypoglycaemia may sometimes precede the onset of encephalopathy, with a precipitous deterioration of the mental status.

Hyperlactataemia is common, with a reported incidence of approximately 80% [22].

Increased blood lactate is usually due to decreased hepatic clearance of systemically produced lactate by the Cori cycle and to increased lactate formation; increased production is sustained by microcirculatory shunting, which is responsible for generalised tissue hypoxia.

Susceptibility to infections

An increased susceptibility to infections in ALF relies on impaired phagocytic function and reduced complement levels. Sepsis enhances macrophage activation and cytokine release, which worsen circulation disturbances and tissue hypoxia, thus contributing to the development of multiorgan failure.

Bacterial infections affect almost 80% of patients, whilst fungal diseases (predominantly candidiasis) occur in 30%. Pneumonia accounts for 50% of infective episodes, and urinary infection for 20–25% [23].

Clinical signs of infection, such as fever and leucocytosis, are often absent. A high index of suspicion and close microbiological surveillance are always recommended to increase the likelihood of identifying subclinical infectious processes.

Therapeutic suggestions

While patients with minor hepatic injury can be well cared for on a medical ward, patients who rapidly deteriorate require close monitoring in an ICU setting to allow careful observation and detection of any progression of the syndrome. Rapid deterioration is a particular feature of acute liver failure; patients with no neurological or circulatory disturbances may worsen rapidly, thus requiring inotropic support for hypotension and/or mechanical ventilation.

As soon as the patient's condition starts to worsen (if possible not in a higher stage of encephalopathy than II), early contact should be made with a transplant centre to acquire information both on appropriate treatment and on whether a transfer is indicated.

Once the patient is in the ICU aggressive support of failing organs may improve his or her condition while winning time until the availability of an organ for transplantation, which is the only therapy of proven benefit at present.

Intubation and mechanical ventilation are indicated when the patient drifts into grade III encephalopathy, when marked confusion, stupor and muscular rigidity arise and the pharyngeal reflexes are no longer capable of protecting the patient against aspiration and pulmonary damage.

Sedation and assisted ventilation are useful for cerebral oedema, since they reduce cerebral irritation and rising ICP during nursing. Head elevation up to 20–30° and administration of mannitol should be considered, while thiopental, even if effective in protection of the CNS (by reducing the cerebral metabolism, decreasing cerebral blood volume and ICP), may increase the risk of cardiovascular instability and infection.

Hyperventilation, whilst effective in reducing blood flow and oxygen consumption, can precipitate cerebral ischaemia.

According to Nemoto et al., mild hypothermia could be adopted as a protective strategy, since it reduces the cerebral metabolic rate [24].

Indirect information about CBF can be obtained from transcranial Doppler of the middle cerebral artery [25] and/or with SjO_2 monitoring [26]. Continuous invasive ICP monitoring is possible with epidural, subdural or intraparenchymal transducers. While these may help in the identification of rapid intracranial pressure variations, their insertion has to be balanced against the risk of bleeding.

Intravascular fluid assessment and optimal fluid balance are highly recommended, since relative hypovolaemia and splanchnic venous pooling are the rule.

Volumetric monitoring with Pulsion PiCCO and a pulmonary artery catheter

allow for better titration of volume replacement. Vasopressors or inotropes might be required to increase mean arterial pressure, thus preserving renal and cerebral perfusion.

Use of blood products should be restricted to patients who are actively bleeding or are undergoing invasive procedures.

Prostanoid derivatives, even though widely used in the past, are now no longer employed; in fact, any favourable microcirculatory influence on tissue oxygenation have yet, to be confirmed.

Broad-spectrum antibiotics and antifungal prophylaxis are recommended.

Early antibiotic therapy reduces the incidence of infective episodes to 20% and the overall mortality to 44% [27].

Other recommendations include blood glucose level control and correction of electrolyte imbalances. Nephrotoxic medications, such as aminoglycoside antibiotics and nonsteroidal anti-inflammatory drugs, should be avoided.

As previously stated, continuous renal replacement therapy must be adopted in case of renal failure. Continuous replacement techniques are mandatory when fluid retention might exacerbate cerebral oedema.

Specific medical therapy

Specific treatments are currently recommended for ALF when its aetiology is definitely known.

N-Acetylcysteine (NAC), for example, has been introduced as a specific antidote for paracetamol overdose, since it may prevent progression to full-blown ALF. It has been shown to enhance tissue oxygenation and oxygen extraction while improving haemodynamics. Since acetylcysteine increases the synthesis and availability of glutathione, it is particularly indicated in this setting, where oxidative stress is accentuated.

The King's College group [28] suggest its use in all cases of ALF syndrome regardless of aetiology, even though other authors have not observed [29] clinically relevant improvement after its administration.

Fulminant hepatic failure resulting from herpesvirus benefits from aciclovir, while acute fatty liver of pregnancy requires rapid delivery of the fetus [30].

In acute decompensation of Wilson's disease, large amounts of fresh-frozen plasma have been shown to help in correcting the excessive retention of copper [31].

Liver-assisting devices

Artificial hepatic support should provide metabolic, synthetic and detoxification functions, allowing time for recovery and regeneration of the host organ or for transplantation. Various liver-assisting therapies have been introduced since the early 1960s, but none has yet led to a significant clinical improvement, since it is still impossible to reproduce the unique and complex architecture of the liver.

Basically, extracorporeal liver support systems are divided into biological,

nonbiological (or artificial) and bioartificial (hybrid technique) devices.

Biological methods: with these approaches liver support-detoxification was achieved by whole portal and artery perfusion through animal or human livers. They are no longer applied.

Artificial devices: the main aim of these is to detoxify the patient by means of dialysis-derived techniques: plasma exchange, haemofiltration, haemodialysis (HD), albumin-dialysis, plasma adsorption, the Prometheus® system.

Two of the most widely applied are:

MARS (molecular absorbent recirculating system), which is based on the principles of dialysis, filtration and adsorption. The patient's blood is brought into contact with an albumin-coated membrane which is capable of removing some toxins such as ammonia, bilirubin and aromatic aminoacids. The membrane adsorbs and holds the toxins for a time, but they are then released (following their concentration gradient) and are carried to the other side of the membrane, where dialysis against the albumin-rich dialysate removes the toxins from the membrane [32].

PAP (plasma adsorption perfusion) is another nonbiological device by which plasma is first separated from blood and then passed through a filter where toxins (especially bilirubin) are adsorbed.

The artificial support systems are useful mainly for detoxification of some substances (ammonia, aromatic aminoacids, and bilirubin) and water-soluble toxins. Improvement of systemic haemodynamics and reduction of cerebral oedema and ICP have been demonstrated, but nothing has been reported relating to the promotion of liver synthetic function. Evidence of any benefit on survival is still lacking, since the removal of toxins, mediators, cytokines and other pro-inflammatory factors can be associated with the simultaneous removal of regenerating growth factors.

Bioartificial devices: with this approach biological tissues are combined with nonbiological materials; the aims of these devices are to provide both excretory and biotransformational functions and to remove cytokines and other toxins. The patient's blood passes through columns containing cultured hepatocytes (porcine cells for the BAL [bioartificial liver] and human hepatoblastoma cells for the ELAD [extracorporeal liver-Assisting device]).

While the bioartificial systems have yielded real advantages in terms of neurological function and detoxification, serious drawbacks have nonetheless consistently limited their adoption, such as the risk of porcine retrovirus infections, graft-versus-host reactions, complement activation, activation of the clotting cascade, thrombocytopoenia, drug-induced cytopoenia (DIC), haemodynamic instability and higher costs.

Auxiliary heterotopic liver transplantation is applied with satisfactory results in some centres [33]. Intraportal hepatocyte transplantation has even been performed, but for selective indications [34]; its benefit in ALF has yet to be confirmed.

Artificial and bioartificial extracorporeal liver-support systems are still far from being incorporated into clinical routine; they should, however, be considered as a "bridge" while patients are waiting for transplants, which is the only definitive choice in most cases.

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INFECTIONS AND SEPSIS

Chapter 13

Pneumonia in ventilated patients. Severe Gram negative infections; the impact on mortality and its prevention

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The critically ill patient treated in the ICU is characterised by failure of one or more vital organ systems. The severity of the underlying disease in combination with the intensive monitoring and treatment (i.e. mechanical ventilation, etc.), however, often results in major infectious complications. The two main infections associated with increased mortality are: pneumonia and septicaemia.

This pneumonia related to mechanical ventilation and critical illness, i.e. ventilator-associated pneumonia (VAP), continues to be a significant cause of morbidity and mortality in critically ill patients. VAP is the leading cause of mortality related to nosocomial infections, with a crude mortality rate ranging from 50% to 70% [1–7]. The attributable mortality from VAP is lower, but may nonetheless be as high as 25% [2–4].

VAP increases the duration of both intensive care and hospitalisation, thus resulting in increased medical costs.

Micro-organisms causing infections in the critically ill

Surveillance cultures have demonstrated that only a limited range of micro-organisms cause infections in the critically ill. Approximately 15 potential pathogens, 6 in previously healthy hosts and 9 in patients with underlying disease, are responsible for pneumonia and septicaemia (Table 1).

Table 1. Micro-organisms by pathogenicity and colonisation site

'Community' micro-organisms	Oropharynx and gut	Streptococcus pneumoniae; *Haemophilus influenzae*; *Moraxella catarrhalis*; *Escherichia coli*; *Staphylococcus aureus*; *Candida* spp	Gram+ve and Gram–ve, potentially pathogenic micro-organisms
'Hospital' micro-organisms	Oropharynx and gut	*Klebsiella*, *Proteus*, *Morganella*, *Enterobacter*, *Citrobacter*, *Serratia*, *Pseudomonas*, *Acinetobacter* spp., MRSA	

These 15 potential pathogens are aerobic micro-organism, and they are normally present in the throat and gut in low concentrations. In contrast, anaerobes are carried in hig concentrations (10^8/ml of saliva and 10^{12}/gram of faeces.) The physiological phenomenon that the normal, mainly anaerobic flora, is required to control these 15 aerobic potential pathogens was recognised soon after the introduction of antimicrobial agents. Antibiotics that are active against anaerobes and are excreted in the gut may suppress the normal indigenous anaerobic flora. These flora-suppressing antimicrobials promote yeast overgrowth (defined as more than 10^5 micro-organisms) following the excretion of microbiologically active antibiotic concentrations into the throat and/or gut via saliva, bile and mucus. The outgrowth of Gram-negative bacteria is also promoted once resistance to colonisation fails as the consequence of antibiotic use and underlying severity of disease.

Aerobic Gram-negative bacteria, i.e. *Escherichia coli, Klebsiella, Proteus, Morganella, Enterobacter, Citrobacter, Serratia, Pseudomonas*, and *Acinetobacter* spp., are the responsible causative micro-organisms in over 50% of cases.

Pathogenesis of VAP

Many risk factors and risk groups of patients for VAP have been identified [8]. However this understanding has not led far in the direction of an integrated approach to a decreasing incidence of Gram-negative VAP and its related mortality, because of lacking perceptions about the essential components in the pathogenesis of VAP.

An observation published by Stoutenbeek et al. made it possible for three pivotal components to be distinguished in the pathogenesis of VAP: exogenous route to infections, and primary endogenous and secondary endogenous route to infections [9]. This understanding is crucial when it comes to the prevention of VAP.

The prevention of exogenous infections and of primary and secondary endogenous infections follows from this understanding. Each one of these infections requires a different set of preventive measures. Exogenous infections can be prevented by respecting the laws of sterility; primary endogenous infections can be prevented by a short course of systemic antibiotics anticipating on the carrier state of the patient; and secondary infections that might otherwise result from pathologic Gram-negative colonisation of oropharynx and intestine can be prevented by decontamination [9].

Exogenous versus endogenous pathogenesis

The pivotal step in the pathogenesis of primary and secondary endogenous infections is pathologic colonisation. Under healthy conditions resistance to pathologic colonisation maintains a “normal” carrier state in oropharynx and intestine.

It was recognised soon after the introduction of anti-microbial agents [10] that

the normal, mainly anaerobic, flora is required to control the abnormal aerobic potentially pathogenic micro-organisms (PPM). Antibiotics that are active against anaerobes and are excreted via the gut may suppress the normal indigenous flora. The need to preserve the normal indigenous flora has also been acknowledged with reference to the control of overgrowth of *S. aureus* and aerobic Gram-negative bacteria (AGNB) [11, 12]. Prior antibiotic administration lowers the infecting doses of high-level enteric pathogens *Salmonella* spp. and *Clostridium difficile* [13, 14].

In 1971 van der Waaij quantified the physiological phenomenon of the normal flora controlling the abnormal flora in challenge experiments in mice [15]. He defined colonisation resistance as the concentration of the bacterial challenge strain expressed by the log of colony forming units (CFU) per millilitre required to result in abnormal carriage in half the animals. Generally, healthy animals possess a high colonisation resistance of 10^9, as they clear high doses of 10^9 AGNB including *Pseudomonas aeruginosa, Klebsiella pneumoniae* and *Enterobacter cloacae* contaminating their drinking water. Antimicrobials including cephradine and cefotaxime did not promote establishment of abnormal flora and were labelled as ecologically friendly or 'green' antibiotics [16]. The abnormal carrier state was ascertained in 50% of the animals receiving such antibiotics as ampicillin and flucloxacillin after being challenged with $<10^5$ PPM. These agents decreased the resistance of mice to colonisation to <5 and were considered to be 'red' as they disregard the animal gut ecology. Amoxicillin was found to be 'orange', as only high doses lowered the colonisation resistance of mice. These antimicrobials were subsequently tested in healthy volunteers, also in challenge studies [17–19].

Vollaard demonstrated that none of the antimicrobials were found to be completely ecologically friendly [19]. They invariably impacted on colonisation resistance. He argued that the balance of the gut ecology is extremely fragile and very susceptible to antimicrobial agents. However, there were still major differences amongst antimicrobial agents in terms of their influence on the indigenous flora. In the volunteer studies, the failure of ampicillin and amoxicillin to take account of the ecology was significantly worse than that of cephradine and cefotaxime. Abnormal carriage was more frequent and lasted longer during ampicillin and amoxicillin administration than when cephradine and cefotaxime were given. The colonisation resistance is mainly based on Clostridium species amongst the indigenous anaerobes [20]. Ampicillin and amoxicillin are intrinsically more potent against Clostridium species compared with cephalosporins. Additionally, both antibiotics reach bactericidal concentrations in the faeces following excretion via bile. This combination of factors may explain why the indigenous flora is more affected by ampicillin and amoxicillin than by cephradine and cefotaxime. It was argued that the effect on colonisation resistance was an important criterion in the selection of antimicrobials.

In 1969, Johanson showed that disease influences carriage, independently of antibiotic intake [21]. Varying proportions of patients with such chronic underlying diseases as diabetes, alcoholism, chronic obstructive pulmonary disease and liver disease carry abnormal AGNB in the throat and gut [21–24]. Two studies in patients requiring treatment on the intensive care unit [ICU] subsequently showed a correlation between abnormal AGNB and the severity of their illness [25, 26]. One

third of ICU patients with an acute physiology and chronic health evaluation (APACHE) II score ³15 were abnormal carriers of AGNB. This increased to 50% in a population with an APACHE II score ³27. In general, abnormal carriage develops early, within the first week of admission to the ICU, when the patient's illness is most severe and the associated immunodepression tends to be highest [27]. Severity of illness is the most important factor in the conversion of the 'normal' into the 'abnormal' carrier state. This may be due in part to increased availability of AGNB-receptor sites on the digestive tract mucosa in illness. It is uncommon for the abnormal AGNB to be carried in the oropharynx and gastrointestinal tract of healthy individuals [28]. This is because of the efficacy of the carriage defence, defined as the individual's overall defence mechanism based on seven innate host factors aimed at clearance of AGNB: (1) intact anatomy of mucosal cell lining preventing adherence; (2) physiology including pH of saliva and stomach; (3) motility, maintained by actions of chewing, swallowing and peristalsis; (4) mucosal cell turnover, resulting in sloughing of cells and adherent micro-organisms; (5) the presence of secretory immunoglobulin A, preventing adherence by coating AGNB; (6) the washing effect and stasis prevention by the quality and quantity of secretions such as saliva, bile, gastric fluid and mucus; and (7) the indigenous flora, providing colonisation resistance, constituting the microbial factor of the carriage defence.

The indigenous anaerobic flora is thought to operate in four ways:

1. The predominant anaerobes form a 'living wallpaper' and occupy the mucosal receptor sites, inhibiting the incoming abnormal bacteria from adhering.
2. The anaerobes 'starve' the AGNB as they consume huge amounts of nutrients.
3. They produce toxic substances and volatile fatty acids to 'knock out' AGNB.
4. They contribute to the clearance of abnormal bacteria via their role in promoting physiology including motility and mucosal cell renewal.

Most importantly, the healthy state implies the absence of receptors on the digestive tract mucosa for adherence of AGNB. As a hypothesis, it has been suggested that the fibronectin layer covering the mucosal cell surface protects the host from adhering AGNB. Significantly increased levels of salivary elastase have been shown to precede carriage of AGNB in the oropharynx in postoperative patients [29]. It is probable that in individuals suffering both chronic and acute underlying illness, circulating populations of activated macrophages release elastase into mucosal secretions, thereby denuding the protective fibronectin layer. It is thought that this hypothetical mechanism is a deleterious consequence of the inflammatory response encountered during and after illness.

Currently, the flora shift from normal to abnormal AGNB in individuals with underlying disease is thought to be due to the severity of their illness. The use of antimicrobials that impair the microbial factor of the carriage defence further promotes overgrowth of abnormal flora [30]. The most profound effects on patients' ecology and disruption of colonisation resistance have been seen with extended-spectrum beta lactam antibiotics such as amoxicillin and clavulanic acid, piperacillin and tazobactam, and ceftriaxone. Aminoglycosides have only minor effects on the indigenous gut flora. Fluoroquinolones—albeit limited in their activity against anaerobes—promote yeast overgrowth [31]. Elimination of faecal

AGNB following i.v. ciprofloxacin lowers the rate of molecular oxygen consumption, permitting an increase in the pO_2 of lumen contents from 5 to 60 mmHg; under such conditions strictly anaerobic micro-organisms can no longer survive, even though they may not themselves be sensitive to ciprofloxacin, and yeast overgrowth may subsequently develop owing to an impaired microbial factor of the carriage defence. The most logical approach to minimising the risk of PPM overgrowth in the digestive tract is simple, but unfortunately is not often given much consideration when decisions on antibiotic treatment have to be made [32].

Surveillance cultures were crucial in the observation that most infections originated from the patients own flora (i.e. development of endogenous infections).

In 1969 Waldemar Johanson showed that the oropharyngeal flora is the major source of lower airway infections in both mechanically ventilated and nonventilated patients [21]. Again regular surveillance cultures were the only technique that made it possible to show that oropharyngeal carriage is the initial step in the development of lower airway infections.

Link between effective eradication of carriage and infection prevention

Up to the mid-1970s carriage was not considered a pivotal step in the pathogenesis of infections in the critically ill. On the contrary, the general consensus at that time was that carriage was not an indication for starting antibiotic therapy to prevent and treat carriage associated with infection in the critically ill. The Groningen group readily appreciated that eradication of the carrier state is essential for the elimination of pneumonia and septicaemia. This working hypothesis was evaluated in an elegant study conducted in four stages to assess the impact of enteral and parenteral antimicrobials on pneumonia [35]. This study was underlaid by strict definitions of the three types of infections and of the 15 potential pathogens. In the early 1980s Stoutenbeek et al., in their efforts to control pneumonia and septicaemia during mechanical ventilation in the critically ill, discovered that enteral administration of nonabsorbable antibiotics reduced urinary tract infections but did not prevent pneumonia [35]. Analysis of their data based on surveillance cultures suggested that both normal (e.g. *Pneumococci*, *Haemophilus influenzae*) and abnormal flora (*Klebsiella, Pseudomonas*) caused lower airway infections. In this study, all efforts to decontaminate the oropharyngeal cavity using sprays, lozenges, oral washes and rinses failed to eradicate potential pathogens, and especially Gram-negative bacteria, from the oropharynx and to cure the subsequent lower airway infections. Their introduction of an oropharyngeal paste was very successful in the eradication of abnormal oropharyngeal pathogens, and Gram-negative infections especially (usually secondary endogenous infections) were prevented. Subsequent lower airway infections caused by flora normally present remained unaffected but were successfully eliminated by the addition of a short course of systemic antibiotics (e.g. cefotaxime).

The successful eradication of aerobic Gram-negative bacilli underlined the effectiveness of the vehicle used (Orabase®) and the selected antimicrobials (PTA). The paste guaranteed a proper contact time between the abnormal salivary micro-

organisms and the antibiotic agent. The antibiotic mixture of polymyxin and tobramycin was chosen for synergistic activity against AGNB, in particular *Pseudomonas* spp., their respect for the normal anaerobic flora and their moderate inactivation by saliva.

The careful selection of these antimicrobials and the use of paste were pivotal and innovative in the control of infections in the critically ill. The addition of a short course of a parenteral antimicrobial agent virtually prevented further lower airway infections. These infections were predominantly primary endogenous pneumonias due to bacteria carried by the patient on admission to the unit.

Prevention of Gram-negative VAP in the ICU

In the ICU setting it was noticed as long ago as in the early 1970s that predominantly Gram-negative micro-organisms were causing pneumonia in mechanically ventilated patients, with a subsequent high mortality. A high mortality of 64% due to Gram-negative infections was reported by Feeley [36]. The topical administration of nebulised polymyxin B to prevent Gram-negative VAP resulted in a reduction from 11% to 4%. *Pseudomonas*-related VAP was eliminated but was replaced by *Proteus* spp. that are intrinsically resistant against polymyxine [36].

Another attempt to prevent Gram-negative VAP was reported by Klastersky, who instilled gentamicin endotracheally. This intervention led to selection of resistant Gram-negative strains [37].

A different approach to controlling the onset of especially Gram-negative VAP and treating it was published by Stoutenbeek et al. [33–35]. Their intervention was based on the treatment and prevention of the abnormal carrier state in oropharynx and gut to prevent the infections that usually develop after acquisition, carriage and outgrowth of micro-organisms using nonabsorbable antibiotics in the mouth and intestine, thereby taking account of the fact that carriage in the oropharynx carriage was pivotal in the continuum of acquisition, carriage outgrowth and infection of the respiratory tract.

Selective decontamination of the digestive tract (SDD) is probably the most-investigated clinical intervention in critically ill patients treated in the ICU. Several meta-analyses have been published underlining its efficacy and significance in reducing the frequency of infection in critically ill patients, and especially of Gram-negative VAP and bloodstream infections, with reported mortality reduced by 20–40% [38–40].

Conventional approach

The prevailing opinion in the early 1980s required restricted antibiotic administration. This meant that only microbiologically confirmed infections were treated with antimicrobials and carriage was not treated. Infection prevention was predominantly focused on strict adherence to hygiene and isolation.

Prophylactic antibiotics were not recommended, because of the fear that resistance would develop [41].

An exponentially increasing number of studies report the problem of antimicrobial-resistant infections in the critically ill patient as the result of the traditional approach to the control and treatment of infections in the ICU, and these fears were also transferred to the use of SDD.

However, the increasing number of publications dealing with the problem of resistance describe resistance that has occurred predominantly with the use of solely systemic antibiotics. This resistance problem is a major challenge for the intensive care specialist.

In clinical practice there are several stages in the development of carriage of resistant micro-organisms. Firstly, it has been known for the past 30 years that critical illness is the most independent risk factor for acquisition and carriage of abnormal, often resistant, bacteria [42–44], whilst in the critically ill but previously healthy (i.e. trauma) patient carriage will develop [45, 46]. Secondly, for carriage of abnormal flora to occur the patient must have been exposed to the abnormal micro-organisms. Patients may carry abnormal flora on admission (import) or the flora may have been normal on admission and abnormal flora subsequently acquired in the ICU (acquisition). Thirdly, following exposure critically ill patients may develop carriage, i.e. persistent presence, of PPM in throat and gut. Healthy individuals do not become sustained carriers of potentially pathogenic micro-organisms.

This abnormal carriage leads to overgrowth of abnormal flora in the ICU patient. Overgrowth presents a serious problem in the ICU for three reasons namely:

- Overgrowth is required for the carriage of resistant strains amongst the sensitive population.
- Overgrowth is required for the endogenous supercolonisation/infection of individual patients.
- Overgrowth of resistant microbes promotes dissemination throughout the ICU on the hands of the care staff.

The conventional way of controlling antibiotic usage, and thereby the onset of resistance, in this condition (VAP) is firstly to increase the specificity of the diagnosis of VAP by invasive methods and secondly to apply scheduled changes in antibiotic classes.

However, in a French study comparing protected specimen brush versus tracheal aspirate for the diagnosis of VAP, the resistance problem was virtually identical: 61.3% versus 59.8% despite a significant reduction in the use of antibiotics in the PSB group [49].

Changing antimicrobial classes may be temporarily effective. However after 4–6 weeks intestinal overgrowth of MR strains will again lead to carriage with MR strains and to subsequent organ site infections [50].

In spite of these measures the success rate of the treatment of Gram-negative pneumonia, usually VAP, in the ICU is disappointingly low with microbiological cure rates and onset of resistance [51–53].

Isolation with the aim of infection prevention does not prevent infections of endogenous origin, but delays the onset of exogenous infections [54].

A potential link between antimicrobial resistance and SDD is suggested [42]. The ten meta-analyses and the 54 randomised controlled studies (RCTs) available, however, do not provide data for such a suggestion. A Dutch RCT demonstrated that carriage of AGNB resistant to imipenem, ceftazidime, ciprofloxacin, tobramycin and polymyxin occurred in 16% of SDD patients, as against 26% of control patients [55]. This is in line with an earlier French RCT [56] showing that the addition of enteral to the parenteral antimicrobials controls carriage and infection owing to extended-spectrum beta lactamase producing *Klebsiella* species.

Conclusions

Gram-negative infections in the ICU are still a substantial problem. The major explanation for this structural problem is explained mainly by failure to appreciate the effects of solely systemic antibiotics on resistance to colonisation resistance and acquisition, and the role of carriage and overgrowth in these infections.

Measures aimed at the treatment of pathologic colonisation in throat and intestine (i.e. SDD) reduce the incidence of Gram-negative infections and mortality rates.

There are five manoeuvres that have been shown to control mortality in the ICU (SDD, corticosteroids, small tidal ventilation, intensive insulin therapy and activated protein C). SDD is the only manoeuvre supported by two RCTs of adequate sample size providing a grade A recommendation based on level 1 evidence.

Only one trial is available for the other four, giving them a grade B recommendation. Additionally, SDD can be applied to all patients at high risk of infection, whilst the other four interventions have only been assessed in particular subsets of the ICU population. Finally, none of these four manoeuvres can exert an impact on the resistance problem. In contrast, SDD is highly likely to contribute to the control of the growing problem of antimicrobial resistance, especially of Gram-negative micro-organisms.

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Chapter 14

Gram-positive ventilator-associated pneumonia: impact on mortality

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Ventilator-associated pneumonia (VAP) is defined as an infection of the lung parenchyma developing during mechanical ventilation, usually after at least 2 days of positive-pressure ventilation delivered via an endotracheal tube [1, 2]. This time criterion aims to exclude pneumonias caused by infectious agents already present or incubating before mechanical ventilation is started [1]. The diagnosis of VAP is usually based on clinical, radiographic, and microbiological criteria. However, the accuracy of data on the epidemiology of VAP is limited by the lack of a gold standard for its diagnosis [3]. In most reports the incidence of VAP ranges from 8% to 28% [3]. The lower incidence is reported in studies where quantitative cultures of protected specimen brushes were used to define pneumonia [4]. The incidence seems to rise from 5% for patients receiving mechanical ventilation for 1 day to 69% for those receiving mechanical ventilation for more than 30 days, with an incremental risk of pneumonia of around 1% per day [2, 5, 6]. Some authors report that, although the cumulative risk of developing VAP increases over time, the daily hazard rate decreases after 5 days of mechanical ventilation; these authors estimate the risk per day at 3% for the first 5 days of mechanical ventilation, 2% between days 5 and 10 of mechanical ventilation and 1% between days 10 and 15 of mechanical ventilation [7]. VAP is, then, a common complication of long ICU stays. Among the causative pathogens of VAP, Gram-positive strains are common and are associated with a high mortality. The aim of this paper is to review the impact of Gram-positive VAP on mortality.

Epidemiology of Gram-positive VAP

The link between VAP and the duration of mechanical ventilation is important not only for epidemiological purposes, but also for microbiological and prognostic studies. Since the first studies on VAP, a distinction has been made between an early–onset type, which occurs during the first 4 days of mechanical ventilation, and a late-onset type, which develops 5 or more days after the start of mechanical ventilation [2]. Early-onset VAP is usually caused by different micro-organisms and has a better outcome than late-onset VAP [1, 2, 8]. Pathogens causing VAP differ according to the population of patients in the ICU, the duration of hospital and ICU stay and the specific diagnostic method used [3]. Moreover VAP is a

polymicrobial infection in 40% of cases [6]. The high incidence of Gram-negative strains in VAP has been documented repeatedly, and several studies have indicated that more than 60% of VAP are caused by a Gram-negative strain [6, 9]. Recently, however, Gram-positive VAP have become more frequent, and Kollef et al., in a retrospective analysis of two randomised double blind studies, found that 48% of VAP were caused by Gram-positive strains [10]. Data from 24 studies conducted in ventilated patients, in which bacteriological studies were restricted to uncontaminated specimens, suggested that the most frequent Gram-positive strain responsible for 20% of VAP was *Staphylococcus aureus* [3]. In Kollef's recent study, *Staphylococcus aureus* was found to have caused 40% of VAP and accounted for 83% of the Gram-positive strains isolated in VAP [10]. Even more worryingly, 41% of *Staphylococcus aureus* strains turned out to be methicillin resistant [10]. At least four factors have been considered to influence the causative micro-organism of VAP: the underlying disease, the duration of mechanical ventilation and the duration of hospital stay before VAP onset, and the use or not of antibiotic therapy before the development of VAP [3] (Table 1).

Table 1. Factors influencing the microbiology of ventilator-associated pneumonia (VAP)

Underlying disease
Duration of mechanical ventilation
Duration of hospital stay before VAP onset
Antibiotic therapy before VAP onset

As far as the underlying diseases are concerned, chronic obstructive pulmonary disease (COPD) may predispose to infection with specific organisms, including *H. influenzae*, *Moraxella catarralis* and *Streptococcus pneumoniae* [8, 11]. *S. aureus* infections are more common in patients with malignancy, cystic fibrosis, trauma, ARDS and neurological diseases and those who have undergone abdominal and cardiovascular surgery [12]. Pseudomonas infection is more common in patients with ARDS, cystic fibrosis, malignancy and abdominal surgery [13]. Neurosurgery, head trauma, and large-volume aspiration are risk factors for VAP caused by *Acinetobacter baumanii* [14].

With reference to the duration of mechanical ventilation preceding VAP, early-onset VAP (VAP after no more than 4–7 days of mechanical ventilation) is often caused by *H. Influenzae*, *S. pneumoniae*, MSSA or susceptible Enterobacteriaceae, whereas late-onset VAP is usually caused by *P. aeruginosa*, MRSA, *Acinetobacter* and other multi-resistant strains [8, 15, 16]. Not all studies have confirmed this distribution pattern, however: for example, Ibrahim et al. [17] found in 2000 that the most common pathogens associated with early-onset VAP were similar to those associated with late-onset VAP: *P. aeruginosa* (25%), MRSA (18%) and *Enterobacter* (10%). These findings suggest that other factors, including prior hospitalisation and use of antibiotics, may decrease the microbiological and prognostic value of the distinction between early- and late-onset VAP [3]. This distinction would

maintain only a temporal relationship with the start of mechanical ventilation remains if the other factors mentioned are disregarded.

With increasing duration of hospital stay the incidence of VAP caused by antibiotic-resistant strains rises; MRSA and *Enterococci* give particular cause for concern. Prior use of antibiotic drugs has the same effect. Rello et al. performed a prospective study in which there were 129 episodes of nosocomial pneumonia documented by protected specimen brush [18]. They considered the pathogens responsible in patients who had received antibiotic therapy before VAP. The rate of pneumonia caused by antibiotic-resistant strains was significantly higher in patients who had received antibiotics [18]. However, the incidence of multiresistant pathogens is also closely related to local factors and varies from one ICU to another. All these considerations and rates referred to the incidence of specific pathogens must also be seen in the light of local epidemiological data.

Impact of VAP microbiology on mortality

The microbiological picture of VAP has an important impact on its mortality. Crude ICU mortality rates of 24–76% have been reported for VAP at a variety of institutions [3]. It has to be said that the contribution of VAP to mortality is not clear in many studies, and some authors report no increase in mortality when VAP occurs in specific populations of patients (e.g. patients with ARDS) [13, 19]. Factors that complicate the evaluation of VAP's contribution to mortality are the difficulty in establishing a firm diagnosis and its common association with severe underlying diseases that themselves carry a high mortality [3]. Among seven case-control studies, five have yielded the conclusion that VAP is associated with significant attributable mortality that can be estimated at 25%, with a relative risk of death of 2 [20–26]. Analysis of the studies investigating the impact of VAP on mortality shows that many other important factors, besides just the development of VAP, influence outcome and mortality in patients with VAP. These factors include the severity of the underlying disease, the responsible pathogens and the antibiotic therapy, if any, that has preceded it [3] (Table 2).

Table 2. Determinants of mortality from Gram-positive VAP

Severity of the underlying disease
Responsible pathogens
Antibiotic therapy

Turning now to the impact of the underlying disease on mortality in patients with VAP, a growing bulk of data suggests that VAP increases mortality only in the subset of patients with underlying disease of intermediate severity [27]. Probably patients with a less severe underlying disease develop low-severity early-onset VAP and experience an excellent outcome, while on the other hand patients with very severe illness would die anyway even if they did not develop VAP, so that in these

patients VAP does not bring about any significant increase in mortality. It has been estimated that among patients with moderately severe underlying disease the mortality is between 20% and 30% higher in those who develop VAP [3].

The role of the causative pathogens in the mortality associated with VAP is an important one, many studies revealing high mortality rates for VAP caused by aerobic Gram-negative bacilli [6]. For VAP caused by *Pseudomonas* species a mortality rate ranging from 70% to more than 80% has been reported [3, 6, 21]. In the previously cited study by Kollef et al., Gram-positive VAP was associated with a mortality rate ranging from 20% to 30% [10]. High mortality rates of up to 86% have also recently been reported for VAP caused by Gram-positive strains when these were antibiotic resistant [28]. In particular, a study comparing VAP caused by methicillin-resistant *Staphylococcus aureus* (MRSA) with VAP caused by methicillin-sensitive *Staphylococcus aureus* (MSSA) found mortality directly attributable to pneumonia in 86% of the former cases, as against only 12% of the latter, with a relative risk of death of 20.7 for MRSA-induced pneumonia [28]. Early-onset VAP attributable to such antibiotic-sensitive organisms as *Haemophilus influenzae* and *Streptococcus pneumoniae* has an excellent prognosis compared with late-onset VAP, which is often caused by antibiotic-resistant organisms [3].

Impact of antibiotic therapy on mortality of Gram-positive VAP

Antibiotic therapy can dramatically change the impact of VAP on mortality. The studies by Luna et al. [29] and Kollef et al. [10] confirm that an adequate antibiotic therapy significantly lowers the mortality attributable to VAP. With an inadequate antibiotic therapy mortality ranges between 40% and 90%, whereas with an appropriate antibiotic therapy it ranges between 25% and 40% [3]. The antibiotic therapy should be not only appropriate, but also early, to give the greatest benefit in terms of mortality [3]. Moreover, the definition of an appropriate antibiotic therapy is under continuous revision. Pharmacological research together with careful use of the drugs by the clinicians can provide further significant improvements in terms of mortality attributable to VAP. Gram-positive VAP provides a sound example of how antibiotic therapy can change the impact of VAP on mortality. As previously stated, mortality from Gram-positive VAP is largely due to antibiotic-resistant strains such as MRSA [28]. Vancomycin has long been accepted as the most useful drug against this pathogen, although it has some pharmacokinetic flaws when used in VAP because of its poor lung penetration; the result, earlier, was that VAP caused by MRSA continued to have an attributable mortality of at least 40% [30]. The introduction of linezolid, a new molecule that is active against MRSA and which reaches higher concentrations in the lung tissue than in the plasma, has decreased the attributable mortality of VAP caused by MRSA to 16% [10, 30]. Therefore some authors consider that vancomycin can no longer be recommended as a therapeutic option for pulmonary infections caused by MRSA [10, 30]. However, every new antibiotic triggers the development of specific antibiotic resistance in the target micro-organism, and this will decrease its efficacy. The only way to give to an

antibiotic a long life is to use it cautiously, with due consideration for the balance between its benefits and the risks of its overuse. This conservative strategy is particularly important for drugs for which no alternative is available, such as linezolid, and could be changed when other drugs, such as tigecycline, have also been demonstrated to be efficacious.

Conclusions

Gram-positive VAP carries a mortality ranging from 86% to 12%, depending on the severity of the underlying disease, the antibiotic resistance of the pathogen responsible and the antibiotic therapy adopted. Although recent improvements in antibiotic therapy seem to have decreased the attributable mortality of Gram-positive VAP to 16%, the impact of Gram-positive VAP on mortality should be managed not least by exploiting another important strategy, that is to say prevention, since sooner or later any antibiotic will become ineffective [30]. With this in mind, the combination of antibiotic rotation, restricted use of antibiotics and increasing compliance with hygiene measures is an important strategy with proven efficacy. This strategy is particularly useful because when the mortality rate of Gram-positive VAP is decreased to its minimum (which is probably not much lower than the present level of 15–20%), the only way to reduce the number of individuals who die from Gram-positive VAP will be to decrease the number who develop it.

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Chapter 15

Fungal infections in the ICU

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Data collected over the past 10–20 years clearly show that invasive fungal infections, far from being observed in immunocompromised hosts only, are increasingly recognised as a growing problem in critically ill nonimmunocompromised patients and in subjects undergoing major surgical procedures [1–3]. While *Candida* spp. are the most common cause of severe fungal infections in the ICU, mould infections are so far rare, but the problem is rapidly rising due to the increased spectrum of patients at risk for aspergillar infections [4]. According to Vanderwoude [5], this particular group of patients has recently been categorised into different risk classes: *high risk* (allogeneic bone marrow-transplanted patients, neutropenic and haematological patients); *intermediate risk* (autologous bone marrow-transplanted patients, subjects suffering from malnutrition, under corticosteroid therapy, with diabetes or underlying pulmonary diseases) and *low risk* (patients suffering for cystic fibrosis and connective tissue disease). Cases of invasive pulmonary aspergillosis have been reported in apparently nonimmunocompromised COPD patients [5].

Invasive Candida infections: the definitions

Even if not strictly defined in the critically ill nonimmunocompromised host, invasive candidiasis (IC) usually includes two specific entities [1]: candidaemia (isolation of *Candida spp* in the blood) and systemic or disseminated candidiasis (tissue invasion demonstrated by culture or histology at nonadjacent, normally sterile sites). *Proven* invasive Candida infections include candidaemia, the histopathological evidence of tissue invasion and the positive fungal culture from a usually sterile site. The definitions of *probable* or *possible* Candida infection in nonimmunocompromised, nonneutropenic hosts have not been validated so far. The term *invasive* is sometimes referred to the infection that follows host colonisation [1]. IC is associated with elevated morbidity (40% of ICU admissions in a recent European survey on candidaemia) and very high crude (50%) and attributable (30–38%) mortality [6, 7]: ICU stay is significantly prolonged and healthcare costs are increased, being as high as US$ 44,000 per episode [8].

Epidemiology

In the U.S., Candida is reported to be the fourth leading organism responsible for nosocomial bloodstream infection [9], candidaemia representing 10–20% of all cases of candidiasis: in unselected critically ill patients cared for in ICUs, the incidence of candidaemia usually ranges from 0.5% to 2%, or 1–4/1000 patient-days [3, 10].

In Europe, in the mid-1990s Candida infections were reported to account for 17% of hospital-acquired infections in ICU patients (EPIC study) [11]. In a more recent survey conducted in a large sample of the European ICU population [12], *Candida* spp. accounted for 9–10% of the isolates, with invasive candidiasis very often associated (39%) with severe sepsis/septic shock.

In a multicentre study conducted in French ICUs [13], the frequency of IC was reported to be 3 per 1000 admissions (range 0–13), the highest figures recorded in units accepting haematological patients. Forty percent of the patients had major surgery and postoperative complications; mechanical ventilation and central venous lines were in use in more than 80% of these patients, and total parenteral nutrition (TPN) in 33%. The incidence of candidaemia (70% of all cases of IC) was 2 per 1000 ICU admissions. Very long ICU stays (median 25 days) and a very high mortality rate (60%) characterised the group of patients affected by candidiasis [13].

The frequency of *Candida* BSI in the Italian hospital population seems to range between 2% and 5%: in a recent study on candidaemia in North Italian hospitals, Luzzaro was able to demonstrate an overall incidence rate of 4.9% for *Candida* spp. isolation [14]. In a retrospective study dealing with 20 years' ICU activity, Tortorano et al. recorded candidaemia in 0.6% of the patients (2.6/1000 admissions) [6]; among ICU patients, the incidence of candidaemia ranges from 2 to 16 per 1000 admissions, with a rate 1–8 per 1000 patient-days. Close to 5% is the rate of candidaemia recorded in a large group of Italian ICUs (GiViTi, unpublished data, 2005), whilst when reviewing candidaemia episodes during the period 2003–2005 in our hospital we found a total of 108 episodes: 23% were recorded in the ICUs (median rate 7.8/1000 admissions, range 4–10): the frequencies recorded on medical (40%) and surgical (37%) wards were similar. C. albicans was the pathogen isolated in 53% of these cases, *C. glabrata* and *C. parapsilosis* accounting for 18% and 13%, respectively (courtesy of G. Gesu, MD, and G. Ortisi, MD, unpublished data). These data, including the species distribution, largely reflect those reported by Tortorano [15] in the most recent survey on candidaemia in tertiary European hospitals: the candidaemia rate ranged from 0.2 to 0.4 per 1000 hospital admissions. Candidaemias were more frequently recorded in surgical patients (43%), a consistent proportion of whom were cared for in the ICUs (40%). *C. albicans* was responsible for more than half of the cases, except those occurring in haematological patients [15]. These data confirm the Swiss report on the Candida secular trend (2.9% of all bloodstream isolates) [16].

The most recent data recorded in the ICU setting indicate that *Candida* spp. are responsible for 1–5% of bloodstream infections and 4–5% of surgical site infections.

In spite of the small number of cases, the influence of IC on the final outcome is impressive. Among patients with severe candidiasis, candidaemia has a definite impact on the outcome, the crude mortality ranging from 40% to 60%, with no major changes over the last two to three decades. The variations in crude mortality reported in the literature probably reflect the wide variation in the severity of the underlying disease [1].

Risk factors

A comprehensive list of risk factors predisposing to severe candidiasis is reported in Table 1: recent abdominal surgery, gastrointestinal tract perforation, dialysis, broad-spectrum antibiotic therapy, and *Candida* colonisation are considered to be conditions that increase the risk [3].

Table 1. Risk factors predisposing to the development of severe candidiasis. (Modified from [21])

High risk factors	Nonspecific risk factors
Colonisation of several body sites	Age (young and old)
Broad-spectrum antibiotics	Diabetes
Immunosuppression	Renal failure
Neutropenia	Recent surgery
Burns >50%	Urinary catheter
Perforation of the digestive tract	Vascular access
Major abdominal surgery	Prolonged ICU stay (> 5 days)
Urinary tract surgery in presence of candiduria	Multiple transfusion
Major trauma (ISS>20)	
Total parenteral nutrition	
Haemodialysis/haemofiltration	
APACHE II >20	
Central venous catheter	
Candiduria if $>10^5$ CFU/ml	

Among the factors that can predict fatal outcome are extremes of age, severity of the underlying morbidities, duration of positivity of blood cultures, absence of antifungal treatment and presence of infected catheters: since these two latter variables are potentially under clinical control, they should be implemented in the form of strategies able to influence the outcome [1]. In fact, *exogenous* acquisition of *Candida* has been proposed in cases of patients bearing intravascular devices and receiving TPN: catheter-related candidaemia was particularly common in the case of *C. parapsilosis* infections. In the ECMM study, 80% of the cases had an intravascular catheter, which, when cultured, yielded in 65% of the cases the same

Candida species found in the blood, the catheter serving as portal entry for the fungi. The role of the biofilm produced by *Candida* spp. is an important contributing factor in the susceptibility to invasive fungal infection [17].

As already underlined, in the nonimmunocompromised, nonneutropenic population the surgical patient seems to be at particular risk for fungal infection: in the European study chaired by Alberti, a consistent proportion of patients affected by severe sepsis/septic shock and cared for in ICUs for IC (mainly candidaemia) were accepted from the surgical wards after complicated major abdominal surgery [12]. In the NEMIS study, risk factors for candidaemia were abdominal surgery, and presence of CVC and TPN. Patients with acute renal failure, DIC and shock had a significantly higher rate of CBSI, while, contrary to results from other studies, the presence of antifungal drugs was associated, at least in univariate analysis, with a decreased risk of CBSI [10]. In a consensus conference held in 1997 and dealing with management and prevention of severe *Candida* infections [18], complicated abdominal surgical procedures and *Candida* spp. isolates from at least two sites (so-called *Candida* colonisation) were considered together with CVC, hyperalimentation and prolonged ATB therapy (>14 days), risk factors for invasive candidiasis and appropriate conditions for starting an antifungal prophylaxis [19]. Among the many factors predisposing to IC, the leading risk factor for infection, when considered, is *Candida* colonisation, the true prerequisite for subsequent deep-seated infection [1, 10, 15]. According to Eggimann, *Candida* colonisation is the recovery of *Candida* spp. in one or more specimens other than blood cultures without any signs or symptoms of infection [1]. Mucous membrane colonisation has been demonstrated to precede candidaemia (endogenous origin): as reported by Tortorano in the 2004 ECMM study [20], 70–80% of patients with *Candida* spp. BSI (mainly *albicans, glabrata* and *tropicalis*) had colonisation of the alimentary tract with the same *Candida* species as was responsible for the fungaemia. "Heavy" colonisation of the peritoneal cavity strongly predicts the subsequent abdominal infections, while multiple site colonisation has been recognised as an independent risk factor for invasive infection [1]. To improve and optimise the level of predictive validity and specificity of the tests analysing colonisation, two indexes have been developed [1, 17, 21]. The *Candida colonisation index* (CCI) is the ratio of the number of distinct body sites positive for genotypically identical strains of *Candida*, divided by the total body sites tested: a value above the threshold of 0.5 was reported to correctly identify the infected patients in the original series studied by Pittet [1]. Although not validated in large prospective clinical trials, an increasing number of studies suggest the clinical usefulness of CCI [21]. The *corrected Candida colonisation index* is used to account the extent of *Candida* growth at each side. It was determined by multiplying the number of sites with *heavy Candida* growth colonisation by the value for the derived colonisation index [19, 21]. A corrected colonisation index (more difficult and in some ways less acceptable in clinical practice) above 0.4 has been found to be 100% specific and predictive with 100% accuracy [19]. Commenting on the predictive value of the colonisation index, Lipsett [22] acknowledged the strong negative predictive value of the absence of colonisation (in the absence of fungal colonisation, infection is unlikely, thus

underscoring the negative likelihood ratio); in contrast, the positive predictive value of the presence of colonisation in more than two sites was too low and could not be used to assess a patient's risk of fungal infection. It must be stressed, however, that different definitions of "colonisation" were used in the different studies (e.g. different sites tested, different number of tested sites), making the interpretation extremely difficult.

Currently, active and extensive investigation is focused on preventive strategies for invasive fungal infections. Antifungal prophylaxis has been demonstrated to reduce the incidence of invasive fungal infection in the immunocompromised, neutropenic host, but its place, role and benefits in the nonneutropenic critically ill patients are much less well defined. Surveillance fungal cultures were used to target specific clinical intervention in this setting. It has long been known that delay in initiating antifungal treatment in a critically ill patient at risk of fungal infection is associated with worse outcome [23].

Therapeutic strategies: from prophylaxis to pre-emptive therapy

Among the many strategies implemented to prevent severe candidiasis, pre-emptive therapy and targeted prophylaxis could play a relevant role. According to the definition given by Eggimann [23], *pre-emptive therapy* is the early administration of antifungal treatment to patients with evidence of substantial colonisation in the presence of multiple risk factors: the number of factors considered (usually two to four, but in some cases even one) differs in the various studies. Pre-emptive therapy should be given to patients with well-established risk factors, including a known degree of *Candida* colonisation [23]. According to Eggimann, in critically ill patients, in the case of worsening general conditions and multiple organ dysfunction, if IC is suspected (presence of known risk factors, fever in spite of broad-spectrum antibiotics, organ dysfunction), empirical antifungal therapy may be justified while the results of blood cultures are awaited [23]. A more problematic scenario could be the presence of risk factors but the absence of known colonisation: assessment of the degree of colonisation should allow earlier identification of subjects who might benefit from the treatment (pre-emptive in this case). The time needed for assessment of the degree of colonisation could be a limiting step.

Prophylaxis means the administration of antifungals to groups of patients known to be at high risk of candidal infection [23]: organ-transplanted patients (today with some limitation according to the type of organ transplanted, severity of illness, complexity of surgery), immunocompromised patients with expected long-term neutropenia; "nonimmunocompromised patients in whom *prophylaxis is known to be effective*" [24]. However it must be stressed that concerns have been raised about this latter definition, particularly in the case of complicated postsurgical patients, a category still deserving of further large and well-conducted clinical trials. Then, in critically ill, nonimmunosuppressed, nonneutropenic surgical or medical patients, prophylaxis should be considered for selected groups of patients in whom the risk of IC is sufficiently high to justify the intervention: a figure

considered in the literature is frequency of candidiasis higher than 10% in spite of aggressive use of infection control measures [23, 24]. In the recent IDSA guidelines for the treatment of candidiasis [24], expected long ICU stay (more than 3 days) and prolonged mechanical ventilation are indications for prophylaxis, because of a documented tendency towards a decreased rate of candidiasis [23–25]. In a very recent meta-analysis on antifungals for preventing fungal infections in nonneutropenic critically ill and surgical patients, Playford et al. concluded that fluconazole or ketoconazole prophylaxis was able to reduce fungal infection by one half and mortality by one quarter [3]. This makes antifungal prophylaxis at least attractive in this group of patients and confirms the statement of the IDSA document, in which antifungal prophylaxis in ICUs was endorsed as "A1 recommendation for carefully selected patients" in ICUs with high rates of fungal infections [24]. Conversely, in a low-risk population, the injudicious use of prophylaxis might lead to the selection of resistant organisms/strains. The core of the problem in ICU patients is then the diagnosis of colonisation, its correct definition and differentiating between colonisation and infection: while the futile use of antifungals has to be avoided, because it is potentially associated with changes in *Candida* spp. distribution (increased *C. non albicans* vs *C. albicans* species and increased azole-resistant *Candida* strains), the early ("timely") initiation of antifungal therapy in patients with IC is critical in improving outcome. In spite of the (sometimes) too wide use of extended antifungal prophylaxis with azoles (mainly fluconazole), the most recent analysis of a European multi-institutional survey on *Candida* BSI demonstrated a limited role of azole-resistant *Candida* species in the causation of BSI and a low proportion of cases with antifungal resistance [15]. Despite major progress in the definition of the approaches to treatment and variety of very active drugs available, the diagnosis of systemic candidiasis is problematic at best: in one fifth of candidiasis cases there is no fever; overt signs of inflammation are sometimes missed; in at least 20–30% of cases the diagnosis is made at the postmortem autopsy [21, 26]. The diagnosis of IC is still based on blood cultures in a substantial proportion of cases, a single positive blood culture being considered enough for a definitive diagnosis of candidaemia and then of IC. Unfortunately, blood cultures have quite a low sensitivity for *Candida* species (60%) [26]. In the absence of accurate tools for early nonculture diagnosis of candidiasis, strategies for starting anti-Candida treatments in nonneutropenic critically ill patients in a timely manner are desperately needed. In fact, fungal wall elements such as glucan, mannan and β 1–3 glucan or new PCR assays are still of only limited value [27], in contrast to the situation with *Aspergillus* spp., where high-resolution CAT scan and serological and molecular techniques seem to be more than promising and are already part of the early diagnostic procedure [4]. The "*Candida* score", a bedside scoring system recently proposed by the EPCAN Study Group [28], might help clinicians to decide whether early antifungal treatment is justified when invasive *Candida* infection is suspected in nonneutropenic critically ill surgical or medical patients. Surgery, multifocal candidal colonisation, TPN and severe sepsis were all predictors of proven *Candida* infection. A cut-off score of >2.5 (sensitivity 81%; specificity 76%) accurately selected patients who benefited from early antifungal treatment [28].

Conclusions

Several risk factors for IC are recorded in a large number of critically ill patients admitted to medical and surgical ICUs: a consistent proportion of them (ranging from 20% to 60%) become colonised during their hospital stay, but unlike immunocompromised neutropenic individuals, only a minority (1–5%) will develop IC. The strategy proposed for the critically ill at risk of or suspected of having IC, unlike that implemented for the immunosuppressed, neutropenic host, relies upon a quantitative definition of colonisation and the implementation of pre-emptive therapy or targeted prophylaxis, as indicated [23]. Even though not yet validated by prospective clinical studies, the proposed strategy differentiates between prophylaxis and pre-emptive therapy. Prophylaxis is considered for a selected group of patients in whom the frequency of candidaemia is high enough to make such treatment beneficial. Pre-emptive antifungal therapy, on the other hand, should be given to individuals with well-known risk factors and a known degree of *Candida* colonisation, clinical markers which expose to such a high risk of IC that "the benefit of immediate antifungal treatment outweighs potentially negative side effects including emergence of resistant strains" [23]. Last but not least, resistance profiles have to be periodically assessed in units where these strategies are applied.

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Chapter 16

Focus on the diagnosis and treatment of severe meningitis

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Meningitis is the most common worldwide infection of the central nervous system, and bacterial meningitis is a potentially life-threatening disease that requires immediate recognition and treatment. Community-acquired bacterial meningitis has an annual incidence of 4–6 cases per 100,000 adults, and *Streptococcus pneumoniae* and *Neisseria meningitidis* are responsible for at least 80% of all cases [1, 2]. In a surveillance study conducted in 1995 in USA, the incidence of bacterial meningitis was found to have declined dramatically [2]. This finding was a result of a vaccine-related decline in meningitis caused by *Haemophilus influenzae* type B vaccine; in the USA and in other industrialised countries, bacterial meningitis is now a disease predominantly of adults rather than infants and children. Moreover, conjugate vaccines against *S. pneumoniae* are expected to reduce the incidence of childhood pneumococcal meningitis significantly [3]. Bacterial meningitis is also an important problem in hospitalised patients. In a review of 493 episodes of bacterial meningitis in adults at a USA tertiary hospital from 1962 to 1988 inclusive, 40% of episodes were nosocomial in origin, with most cases (38%) caused by Gram-negative bacilli. In that study, the mortality rate remained high over time, and even in the 1980s, almost one quarter of adults with meningitis died, despite the advances in antibiotic therapy. In contrast, it was found that the mortality rate of Gram-negative bacillary meningitis had decreased since the advent of third-generation cephalosporins [4]. Patients with severe meningitis are often neurologically depressed and prone to seizures; in addition, intensive supportive care may be needed for septic shock or other complications. In a recent prospective study at a Spanish university hospital, almost 60% of 104 patients with community-acquired meningitis were admitted to the intensive care unit (ICU) over a 6-year period [5].

Microbial agents and antibiotic resistance

Among adult patients with community-acquired meningitis most cases are caused by *S. pneumoniae*, *N. meningitidis*, and *Listeria monocytogenes*.

S. pneumoniae remains the most frequent cause of bacterial meningitis in adults. Pneumococcal meningitis is a severe form of disease that often leaves neurological sequelae in survivors (in up to 30%) and is fatal in 19–30% of patients. The proportion of isolates of *S. pneumoniae* that are not susceptible to penicillin and cephalosporins has been increasing in frequency during the last decade in the

USA and also in many Asian and European countries [6–8]. In 1994, 27% of sterile-site isolates from children in Atlanta were nonsusceptible to penicillin, and 13% were nonsusceptible to cefotaxime [9]. Indeed, meningitis treatment failures attributed to cephalosporin resistance have been reported. Therefore, both the American Academy of Pediatrics and the Infectious Diseases American Society recommend vancomycin in addition to a third-generation cephalosporin (either ceftriaxone or cefotaxime) for the treatment of suspected pneumococcal meningitis [10, 11]. On the other hand, a recent European study confirmed that the rate of penicillin-nonsusceptible *S. pneumoniae* was high in Spain (61.9%) and France (47.6%) but remained substantially lower in Austria (4.4%), Germany (6.0%), Belgium (11.5%), Switzerland (17.3%), Portugal (19.0%) and Italy (13%) from 2001 to 2003 [12].

N. meningitidis is mainly responsible for community-acquired bacterial meningitis in young adults. The mortality and morbidity for meningococcal meningitis are lower than those for pneumococcal meningitis, with fatality rates of 3–13% and morbidity rates of 3–7%. In the case of *N. meningitidis* isolates, the majority are susceptible to penicillin, although strains with reduced penicillin susceptibility have been reported in Europe (particularly Spain, Greece, Switzerland, Romania, France, Belgium, United Kingdom, Croatia, and Turkey), Malawi, South Africa, Canada and the United States of America. The clinical significance of these isolates is unknown at present, since many patients with meningitis caused by such resistant strains respond to high doses of penicillin; however, isolated reports of treatment failure have been published [13]. As a consequence, third-generation cephalosporins are likely to emerge as the first-line treatment for patients with meningococcal meningitis in the future [14].

L. monocytogenes causes meningitis preferentially in neonates, adults older than 60 years, alcoholics, cancer patients, those receiving long-term treatment with corticosteroids and immunosuppressive drugs and pregnant women. *Listeria* meningitis accounts for approximately 8% of all cases of bacterial meningitis and carries a mortality rate of 15–29%. Therapy should consist of ampicillin or penicillin G, since third-generation cephalosporins are inactive against *L. monocytogenes* [15].

Spontaneous Gram-negative bacillary meningitis is a rare complication of bacteraemia, occurring mainly in neonates and in neutropenic and debilitated patients. In a recent French study on Gram-negative bacillary meningitis [16] it seemed the severity of predisposing underlying diseases might explain why patients admitted to the ICUs had such a poor prognosis (mortality 38%) despite the early use of third-generation cephalosporins.

Clinical features and prognostic factors

Meningitis is the most likely diagnosis in patients who show the classic triad of fever, headache and a stiff neck, which is present in at least 80% of patients. Symptoms and signs of community-acquired bacterial meningitis included headache (87% of episodes), neck stiffness (83%), fever (77%), and a change in mental

status defined by a Glasgow Coma Score below 14 (69%) in a study of 696 Dutch adults observed from October 1998 to April 2002 [1]. At least two of the four signs were present in 95% of these patients; in addition, patients with pneumococcal meningitis had more severe disease than did patients with meningococcal meningitis, showing a higher frequency of seizures and focal neurological deficits and a low level of consciousness.

Bacterial meningitis can be present in patients in whom the clinical diagnosis is not obvious. This is particularly true in small children and the elderly, in whom fever may be minimal and changes in mental status may be the most prominent symptom. Untreated bacterial meningitis is characterised by progressive loss of consciousness, seizures and focal deficits, followed by coma and death.

Despite the development of more effective antibiotics, bacterial meningitis continues to cause high mortality. The extent of mental status changes provides a clinical indication of the severity of the disease. Indeed, patients presenting in coma have a mortality rate of up to 50%. Systemic complications of the infectious disease include septic shock, disseminated intravascular coagulation (particularly with meningococcal infections) and acute respiratory distress syndrome.

In the Dutch prospective study on 696 episodes of community-acquired bacterial meningitis, the strongest risk factors for an unfavourable outcome (overall mortality rate of 21%) were those that were indicative of systemic compromise, a low level of consciousness, and infection with *S. pneumoniae* [1]. In a previous review of 493 bacterial meningitis episodes in adults at a single US tertiary hospital from 1962 to 1988, risk factors for death were older age ($\geq$60 years), seizures within the first 24 h and, again, an obtunded mental state on admission [4]. Another retrospective study on 269 adults with bacterial meningitis episodes in four hospitals in Connecticut from 1970 to 1995 showed that the following baseline clinical features were independently associated with adverse clinical outcome (death or neurological deficit at discharge): hypotension (defined as systolic blood pressure plain $\leq$90 mmHg or a $\geq$40-mmHg decrease in systolic blood pressure), altered mental status (defined as lethargy, disorientation, or coma), seizures and age [17]. According to a recent review article on community-acquired bacterial meningitis in adults [18], monitoring in an ICU is recommended so that changes in the patient's consciousness and the development of any new neurological signs can be recognised, monitoring for subtle seizures is possible and severe agitation can be treated effectively. In addition, concomitant septic shock or pulmonary infiltrates are other conditions that should prompt the patient's admission to the ICU (Table 1).

Table 1. Criteria for admission of patients with bacterial meningitis to the intensive care unit

- Glasgow Coma Score below 10
- Neurological deterioration
- Shock
- Pulmonary infiltrates
- Seizures

Delay in the initiation of antimicrobial therapy can result in a poor outcome of community-acquired bacterial meningitis. In the Connecticut study, the median delay between arrival at the emergency department and the administration of antibiotics was 4 h; indeed, among patients whose clinical condition worsened in the emergency department an association was found between the time of start of antibiotic therapy and outcome [17]. Another retrospective Canadian study on community-acquired bacterial meningitis found an independent association between delays of longer than 6 h after arrival in the emergency room before antibiotics were administered and death [19]. Significant delays in the administration of antibiotics have also been assessed by others [20], and such delays were most frequently due to the performance of cranial imaging before diagnostic lumbar puncture and the transfer of patients to another hospital. Indeed, in the Canadian study the second most common diagnostic-treatment sequence was computerised tomography of the head followed by lumbar puncture followed by antibiotics, a sequence found to confer a 5.5-fold likelihood that over 6 h would elapse between arrival in the emergency room and administration of antibiotic treatment [19]. Cranial imaging should precede lumbar puncture in patients who have new-onset seizures, an immunocompromised state, clinical signs that are suggestive of space-occupying lesions or moderate to severe impairment of consciousness. If cranial imaging has to be performed before lumbar puncture (Table 2) antibiotic therapy should be initiated before the patient is sent for neuroimaging; in patients who have not undergone prior imaging and in whom disease progression is apparent antibiotics should be started directly after lumbar puncture, as they should in all patients with cloudy cerebrospinal fluid [18].

Table 2. Indications for performing cranial imaging before lumbar puncture

- Glasgow Coma Score below 10
- Severely immunocompromised state
- New onset of seizures
- Signs of brain shift: papilloedema, focal neurological signs not including cranial nerve

Management and outcome of severe meningitis

Bacterial meningitis is a neurological emergency, and appropriate therapy should be initiated as soon as possible after the diagnosis is considered likely and cerebrospinal fluid samples, or at least blood samples, have been obtained for culture. The choice of empirical antibiotic therapy is based on the most common bacteria causing the disease according to the patient's age and the clinical setting and on current patterns of antimicrobial susceptibility. Since the prevalence of penicillin-resistant *S. pneumoniae* has risen dramatically during the past decades in USA and in other countries, most experts recommend the combination of vancomycin plus either ceftriaxone or cefotaxime is recommended for adults with suspected community-acquired bacterial meningitis [11, 18]. In a USA population-based surveillance study, cefotaxime-nonsusceptible pneumococcal meningitis was not associa-

ted with increased mortality, prolonged length of hospital or ICU stay, requirement for intubation or oxygen, neurological deficit or admission to an extended-care facility; however, most such patients received the combination of cefotaxime and vancomycin [21]. On the other hand, the empirical treatment of suspected pneumococcal meningitis may depend on third-generation cephalosporins alone in Italy and in a number of European countries where the rate of penicillin-nonsusceptible *S. pneumoniae* is basically low [12]. In patients older than 50 years or with other risk factors for *Listeria* infection, ampicillin should be use in combination with a third-generation cephalosporin, with or without vancomycin (Table 3).

Table 3. Recommendations for empirical antimicrobial therapy in adults with bacterial meningitis

Predisposing factors	Common bacterial pathogens	Antimicrobial therapy
Age 16–50 years	N. meningitidis, S. pneumoniae	Third-generation cephalosporin + vancomycin
Age >50 years	*S. pneumoniae*, *N. meningitidis*, *L. monocytogenes*, Gram- bacilli	Third-generation cephalosporin + vancomycin + ampicillin
Risk factors for Listeria	*S. pneumoniae*, *H. influenzae*, *L. monocytogenes*	Third-generation cephalosporin + vancomycin + ampicillin
Basilar skull fracture	*S. pneumoniae*, *H. influenzae*, group A β-hemol. streptococci	Third-generation cephalosporin + vancomycin
Penetrating head trauma	*S. aureus*, *S. epidermidis*, Gram- bacilli including *P. aeruginosa*	Vancomycin + (cefepime or ceftazidime or meropenem)
Post-neurosurgery status	*S. aureus*, *S. epidermidis*, Gram- bacilli including *P. aeruginosa*	Vancomycin + (cefepime or ceftazidime or meropenem)
Cerebrospinal fluid shunt	*S. epidermidis*, *S. aureus*, Gram- bacilli including *P. aeruginosa*, *Propionibacterium acnes*	Vancomycin + (cefepime or ceftazidime or meropenem)

In experimental meningitis studies, outcome is correlated with the severity of the subarachnoid space inflammatory response. Attenuation of this inflammatory response may be effective in decreasing many of the pathophysiological consequences of bacterial meningitis, such as cerebral oedema, increased intracranial pressure, altered cerebral blood flow, cerebral vasculitis and neuronal injury, including deafness and other symptoms [22, 23]. Since treatment with steroids reduces inflammation in the subarachnoid space, several trials have assessed these drugs as adjuvant therapy in children with bacterial meningitis. In 2003, a Cochrane Review showed a beneficial effect of steroids on severe hearing loss both in children with bacterial meningitis caused by *H. influenzae* type B, and in meningitis caused by bacteria other than *H. influenzae* [24]. A recent randomised, placebo-controlled trial of adjunctive steroid therapy in 301 adults with acute bacterial meningitis showed that early (before or with the first dose of antimicrobial therapy) treatment with dexamethasone improves outcome [25]: overall mortality was reduced from

15% to 7%, and in patients with pneumococcal meningitis mortality was reduced from 34% to 14%. The benefit was greatest in patients with intermediate disease severity, as defined by a score of 8–11 on the Glasgow Coma Scale on admission, and in those with pneumococcal meningitis, in whom the rate of unfavourable outcome declined from 52% to 26%. Although no significant beneficial effect was seen in the meningococcal subgroup, a beneficial effect could not be ruled out, since the number of patients in this subgroup was small. In addition, the benefits of dexamethasone were not offset by any apparent side effects of steroid treatment. In a recent systematic review of this topic that included five clinical trials [26], treatment with steroids was associated with a significant reduction in mortality (relative risk 0.9; 95% confidence interval 0.3–2.1) and in neurological sequelae (relative risk 0.5; 95% confidence interval 0.1–1.7), and with a reduction of case fatality by 21% in pneumococcal meningitis (relative risk 0.5; 95% confidence interval 0.1–1.7). In meningococcal meningitis mortality and neurological sequelae were both reduced, but not significantly so. None of the adverse events, including gastrointestinal bleeding, differed in frequency between the treatment and the placebo groups. According to this review, routine steroid therapy with the first dose of antibiotics is justified in most adult in whom acute community-acquired bacterial meningitis is suspected. On the basis of the available evidence on the use of adjunctive dexamethasone, steroids should be initiated in all adult patients with suspected or confirmed pneumococcal meningitis; adjunctive dexamethasone should not be given to patients who have already received antimicrobial therapy [11, 18]. Moreover, adjunctive dexamethasone can be harmful in patients with history of hypersensitivity to steroids, recent head injury and cerebrospinal fluid shunt (nosocomial meningitis). Patients with septic shock and adrenal insufficiency benefit from steroids in physiological doses (i.e. hydrocortisone 50 mg q.i.d. and fludrocortisone 50 μg q.d.) and for longer than 4 days. Although there are no controlled studies on the effects of corticosteroid therapy in patients with both meningitis and septic shock, the use of low doses of steroids, as given by Annane et al. [27], seems reasonable at present. Table 4 summarises the indications for steroid therapy in adult patients with suspected community-acquired meningitis [18].

Table 4. Recommendations for adjunctive dexamethasone therapy in adults with bacterial meningitis

- Dexamethasone: 10 mg, 4 times daily for 4 days, before or with the first dose of antibiotic
- Low dose of steroids (i.e. hydrocortisone 50 mg, 4 times daily, and fludrocortisone 50 μg, once daily) if concomitant septic shock
- No use of dexamethasone if one or more of the following applies: pretreatment with parenteral antibiotics, hypersensitivity to steroids, recent head injury, cerebrospinal fluid shunt
- Caution with steroid use: history of peptic ulcer

Although bacterial meningitis is still a serious disease and may require specific management in an ICU, to date studies focused on adult patients admitted with acute community-acquired bacterial meningitis are scarce. In a prospective study

at two ICUs within a Spanish university hospital [5], the overall mortality rate of 62 adults was 10.9% and the rate of adverse clinical outcome (death or severe neurological deficit) was 17.1%. The most common pathogen was *S. pneumoniae* (39%); some degree of resistance to cefotaxime was found in each of three isolates (12%), which shows that the combination with vancomycin may be adequate as initial empiric therapy in Spain. All patients were empirically treated with third-generation cephalosporin, and dexamethasone was used in 40 cases (62.5%). After a multivariate analysis, only the severity of the disease (APACHE II >13) on admission to the ICU was independently associated with adverse clinical outcome. In a retrospective study conducted in an ICU of a French tertiary-care hospital [28], in-hospital mortality of 80 adults with pneumococcal meningitis was 25% and the adverse clinical outcome rate (death or any neurological defict at discharge) was 65%. The overall prevalence of drug-nonsusceptible *S. pneumoniae* was 24%, but the number of nonsusceptible strains had increased over time. Systemic corticosteroids were administered to 27% of the cohort on admission. Multivariate analysis indicated that only SAPS II was independently associated with an adverse clinical outcome. Moreover, three variables remained independently associated with in-hospital mortality: thrombocytopenia, mechanical ventilation and an arterial pH >7.47. With adjustment for the identified prognostic factors, corticosteroids significantly reduced the risk of death. In this study the conclusions reached were that in intubated patients with *S. pneumoniae* meningitis, nonsusceptibility to penicillin G was not associated with a worse outcome; that high-dose corticosteroids may be beneficial in the most severely ill patients; and that hyperventilation should be used with caution.

In conclusion, bacterial meningitis, and particularly pneumococcal meningitis, continues to be a major cause of mortality and morbidity, especially in patients requiring admission to the ICU. The strongest risk factors for an unfavourable outcome are those indicative of systemic compromise, impaired consciousness, and infection with *S. pneumoniae*. Now that routine dexamethasone therapy has been implemented, complication and sequelae are expected to decline [18]. Finally, the role of granulocyte colony-stimulating factor [29] and other cytokines attenuating the proinflammatory cytokine response is promising and justifies further clinical trials.

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Chapter 17

Plasma filtration in sepsis: a research protocol

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Sepsis is a major cause of morbidity and mortality in intensive care units (ICUs) worldwide [1]. The mortality rate in sepsis ranges from 20% to 70%, depending on the severity of the disease, the time treatment is started, the number of affected organs and the study design [2]. It has recently been described as the tenth most frequent cause of death in North America [3]. Septic shock, the most severe complication of sepsis, is characterised by a high rate of hospital mortality: 62.8% in the GiViTI (Gruppo Italiano per la Valutazione degli Interventi in Terapia Intensiva) cohort in 2004 [4], which is in line with that reported in other European series [5].

Sepsis and septic shock are important risk factors for acute renal failure (ARF) [6]. It has been demonstrated that the presence of renal failure increases with the severity of the infection, rising from 19% in sepsis, through 23% in severe sepsis to 51% in septic shock [7]. For this reason, extracorporeal therapies for the treatment of renal failure have become widespread in ICUs [8]: membranes with highly hydraulic permeability achieve increased ultrafiltration rates and solute removal in the range of 5–50 kDa [9].

Sepsis generally develops as a result of an inflammatory process mediated by the host's immune system [10]. Such severe systemic inflammation appears to be due mostly to the local and systemic effects of circulating "mediators" with pro-inflammatory and anti-inflammatory effects [11]. When the inflammatory process that characterises the systemic response to infectious pathogens becomes self-sustaining and progressive, organ dysfunction ensues. A complex cascade of inflammatory mediators, extra- and intracellular cell signalling pathways is activated. These processes result in tissue hypoperfusion and biochemico-physical alterations culminating in multi-organ dysfunction syndrome (MODS) [12].

Genetic predisposition is almost certainly relevant in up-regulation of the expression of inflammatory mediators, thereby having an adverse influence on the anti-/pro-inflammatory balance [13, 14]. Although several therapeutic interventions have targeted specific components of the pro-inflammatory septic cascade, no improvement in survival has been obtained in large-scale clinical trials focusing on specific molecules [15]. The possibility of removing a wide spectrum of molecules with the use of extracorporeal therapies represents a new rationale for the treatment of severe sepsis. Techniques include diffusive (haemodialysis), convective (haemofiltration), and mixed (haemodiafiltration), with the use of adsorption or plasma filtration, through an intermittent or a continuous approach. The effi-

ciency of the treatments appears to be tied to removal of inflammatory mediators, even though no difference in mortality between specific treatments has been confirmed in the literature.

More specific approaches have been proposed, such as high-volume haemofiltration and continuous plasma filtration [16, 17], in order to remove several pro- and anti-inflammatory mediators and to overcome the limitations of conventional continuous renal replacement therapy (CRRT) (i.e., low volume exchange and low sieving coefficients for sepsis-associated mediators).

In order to improve the efficacy of a blood purification system in the critically ill septic patients, unselective adsorption onto a cartridge was added to plasma filtration and conventional diffusion/convection in a newly designed extracorporeal device called coupled plasma filtration–adsorption (CPFA) (Fig. 1).

CPFA is a specific method for the treatment of sepsis. The equipment it requires is as follows (Fig. 2):

1. A plasma-filter (polyethersulfone 0.45 m^2 with a cut-off of approx 800 kDa)
2. A haemofilter (polyethersulfone 1.4 m^2)
3. A cartridge (containing approximately 140 ml of hydrophobic styrenic resin)

The kit is lodged in the Bellco 'Lynda' machine (Bellco, Mirandola, Italy).

The treatment consists in separation of plasma from the whole blood with adsorption of the inflammatory mediators and cytokines from the plasma, and a subsequent purification step accomplished by way of a haemofilter.

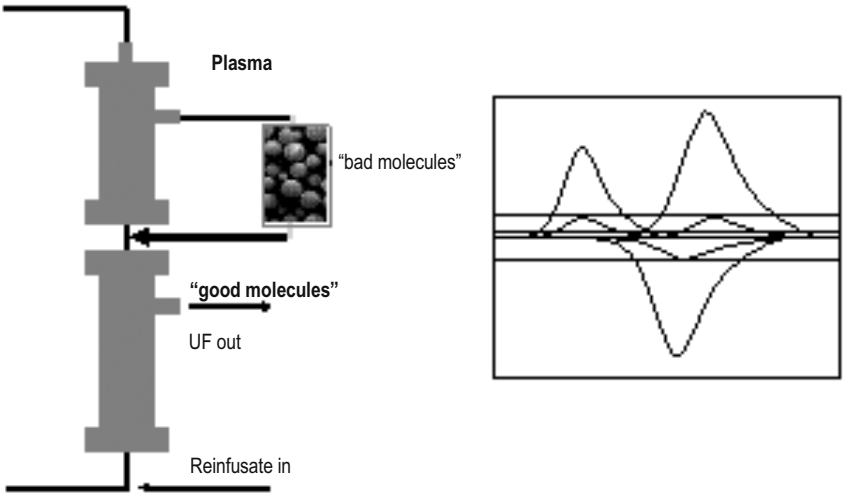

Fig. 1. The peak concentration hypothesis suggests that nonselective control of the peaks of inflammation and immunoparalysis may help to restore immunohomeostasis

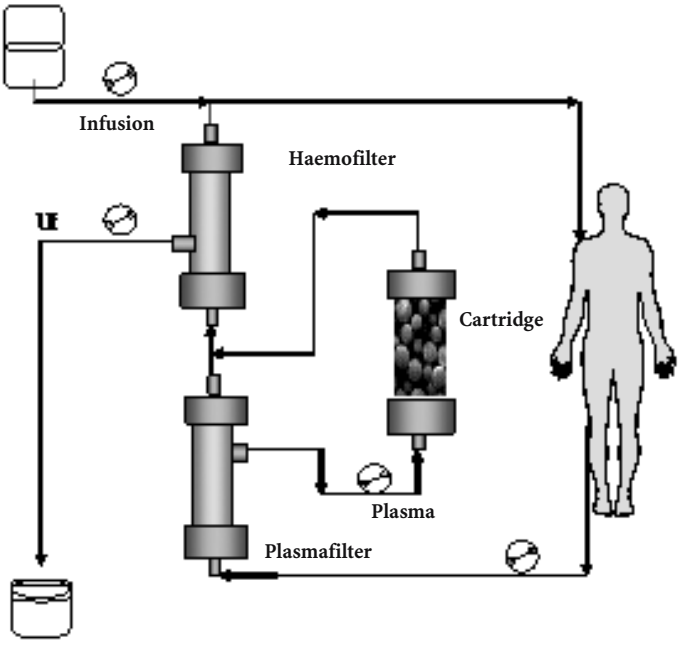

Fig. 2. Scheme of coupled plasma filtration–adsorption

The life of the cartridge, as demonstrated by in vitro experiments, is 10 h, which corresponds to the mean expected treatment duration.

In recent years resins and charcoals have been used because of their capacity and ability to remove toxic substances from blood, but the medical applications were often counterbalanced by safety concerns, such as leaching of metals, release of small microparticles and poor homogeneity and biocompatibility. Haemoperfusion through ion/cation exchange resins was first proposed in 1948 for the treatment of renal failure, but several variations followed. Early experience and treatments were complicated by pyrogenic reactions, electrolyte disturbances and haemolysis.

In fact, the use of more sophisticated technologies to coat resins reduces the problems that result from loss of efficiency, poor reproducibility and mixed outcomes. Extracorporeal applications require that resin is defined in terms of the chemical nature of the resin, particle size, porosity and surface area. Resins must be also tested for the release of microparticles, heavy metals and other toxic substances. The resin test is done in real conditions similar to those obtaining during a patient application. The optimisation of flow and column geometry is a parameter that also greatly influences adsorption efficacy. There is a balance between the volume of plasma being treated and the time plasma is in contact with the resin [18].

Using an experimental model of acute endotoxaemia in rabbits, Tetta et al.

studied whether nonselective adsorption from plasma of cytokines and other pro-inflammatory mediators known to be produced in excess during sepsis could reduce 72-h mortality. Cumulative survival was significantly improved in rabbits treated with CPFA, and cumulative survival of the resin with the lipopolysaccharide (LPS) group was not significantly different from that of the control group (Fig. 3) [19].

Human studies are limited, but promising: Ronco et al. compared CPFA against haemodiafiltration by measuring homodynamic and immune responsiveness in ARF patients in septic shock. These authors observed that the haemodynamic was significantly better with the use of CPFA than with haemodiafiltration. They also observed significantly higher leucocyte responsiveness after CPFA treatment [20].

Another clinical study was conducted by Formica et al. The authors examined the effect of repeated applications of CPFA on haemodynamic response in septic patients with and without renal failure. In this long-term study, the authors showed CPFA to be a safe and feasible treatment leading to significant improvements in haemodynamic stability, vasopressor requirement, pulmonary function, and 28- and 90-day survival (Fig. 4). The 28-day survival rate was 90%, which was quite unexpected considering an APACHE II-predicted mortality of about 40% for these patients [21].

On the grounds of these experiences it was also expected that early therapy would hamper the inflammatory cascade.

In the light of these remarks, GiViTI decided to launch a collaborative randomised controlled trial for formal evaluation of the efficacy and clinical safety of CPFA in septic shock. The main study objective is to clarify whether the implementation of CPFA in addition to the current clinical practice can reduce mortality of septic shock patients in ICU. The second objective of the study is to determine

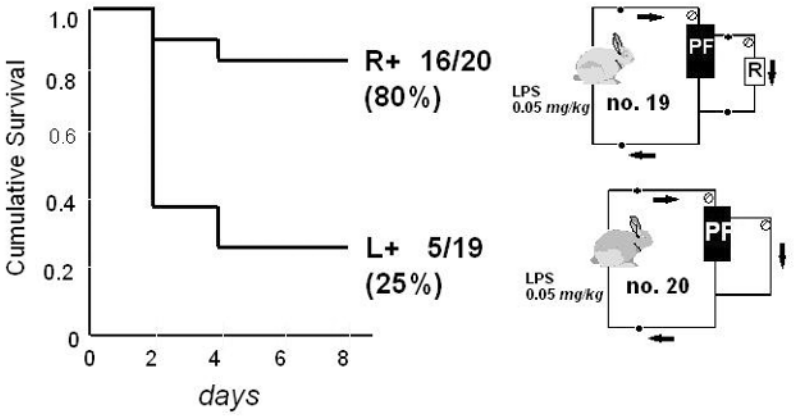

Fig. 3. Coupled plasma filtration–adsorption in a rabbit model of endotoxic shock

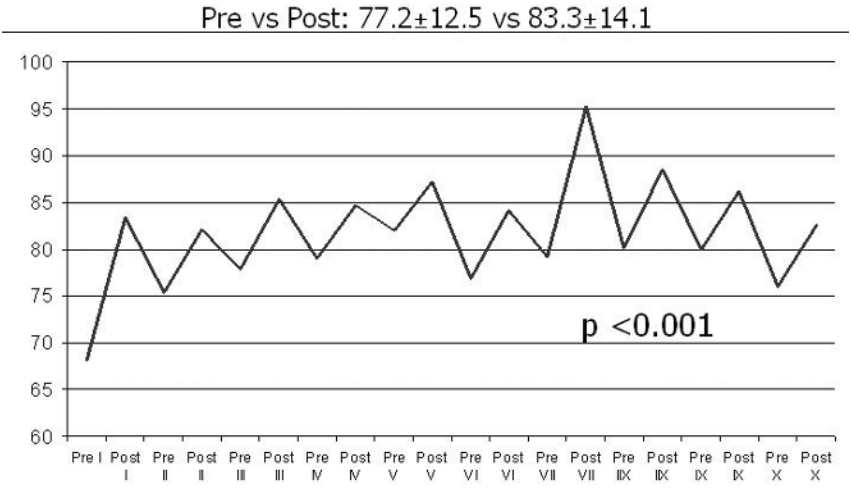

Fig. 4. Trend in mean arterial pressure (MAP) throughout the first ten sessions (each *point* is the mean of the measure at that time for all patients). Statistical significance is related to the difference between all 100 pre- vs posttreatment measurements

whether CPFA can reduce the incidence of organ dysfunction and length of stay.

The study will involve Italian, adult, general ICUs affiliated to the GiViTI group, in which CPFA is regularly used in the treatment of septic shock. The study is restricted to ICUs that, based on the promising but still incomplete evidence available, have already introduced CPFA into their routine practice. In other words, we ask the staff at these centres to use CPFA within a research programme that will yield information on the real efficacy of the treatment.

All patients who are admitted to the ICU in septic shock or who develop septic shock while in the ICU will be eligible. The definition used for septic shock is that provided by the international literature [22, 23]. Patients will be considered eligible for the study only if it will be possible to initiate CPFA in less than 6 h either from admission to the ICU for patients admitted in septic shock, or from the diagnosis of septic shock for the others.

There are some exclusion criteria that make patients not eligible for the study; these concern age, pregnancy, cerebral coma, metastatic cancer, cardiopulmonary resuscitation, life expectancy, etc. Eligible patients will be identified upon admission or during the stay in the ICU and randomised. Patients randomised to the control arm will be treated according to the current clinical practice in the ICU. Patients randomised to the experimental arm will also be treated according to the ICU's current clinical practice, but with the addition of CPFA.

The CPFA treatment will be applied intermittently (10 consecutive hours followed by a 14-h break or CVVH for patients with renal failure) for 5 days following randomisation. The cartridge must be changed after 10 h; previous experience has shown saturation of the resin after this.

The clinical follow-up starts on the day of randomisation and finishes at

discharge from the ICU. During the ICU stay, information on compliance with the four A-level recommendations of the *Surviving Sepsis Campaign* [24], and the daily SOFA score (Sequential Organ Failure Assessment) [25] will be recorded. The vital status will be recorded at ICU discharge, at hospital discharge and at 90 days from randomisation. For patients transferred to other hospitals, "vital status at hospital discharge" will be intended as the vital status at discharge from the latest hospital in which the patients stayed.

In agreement with the study rationale, lower mortality is expected in patients treated with CPFA than in patients treated according to standard practice only. In the light of these considerations, the following primary and secondary end-points were chosen:

- Mortality at hospital discharge. For patients transferred to other hospitals, it will be intended as mortality at the discharge from the latest hospital in which the patients stayed.
- Mortality within 90 days of randomisation. With this end-point it will be possible to evaluate whether a possible benefit obtained in the short term (hospital discharge) is maintained afterwards.
- Proportion of patients who develop one, two, three and four new organ failures during their ICU stay. A new organ failure is defined as a change in SOFA score from 0, 1 or 2 to 3 or 4 in any of the systems considered [26]. This end-point will determine whether CPFA can reduce the risk that organ failures will develop.
- Days not spent in the ICU during the first 30 days after randomisation. With this end-point it will be possible to determine whether CPFA can reduce the complexity of these patients' care.

Data previously published by GiViTI show a hospital mortality rate of 63% in septic shock patients. The study is designed to reveal a 25% relative improvement in hospital mortality with the use of CPFA. For it to have a power of 80% to find out such a difference with 5% type I error, it is necessary to enrol 155 subjects in each arm. Increasing this estimate by approximately 5% to prevent possible problems in compliance with the protocol yields a number of patients needed of 330. This sample allows detection of a 29% difference with a power of 90%.

The trial will be monitored with the Bayesian approach. As known, the Bayesian approach combines a prior distribution and the gathering of the experimental evidence into a posterior distribution. The posterior distribution will be the basis on which to decide whether to interrupt the trial or not. Hence, this analysis requires a probabilistic formalisation of two conflicting hypotheses: one sceptical and one enthusiastic. The trial will be interrupted earlier than planned when the patient's benefit is achieved (i.e., demonstration of treatment efficacy), when sceptics are convinced of the treatment efficacy or, in other words, when the posterior distribution deriving from a prior sceptical hypothesis acknowledges the achieved benefit. Conversely, the trial will be interrupted earlier than planned in case of treatment's futility (i.e., demonstration that the treatment is futile) when a prior enthusiastic approach is curbed by the treatment uselessness or, in other words, when the posterior distribution deriving from a prior

enthusiastic hypothesis acknowledges the unchanged conditions.

Before enrolment, all patients will be given information on the study's objectives, procedures and correlated risks.

If any patient is not able to give consent, the instructions provided by the International Commission on Harmonisation will be followed (ICH Guideline for Good Clinical Practice). We consider that this trial is extremely important, to prove the effectiveness of this technique in decreasing morbidity and mortality in septic shock. If we obtain a positive result we can conclude that sepsis can be treated by blood purification technology, but even if we do not, the study will still be important because its result will modify the current clinical practice in ICUs.

The trial has been registered with both the ClinicalTrials.gov (identifier NCT00332371) and the ISRCTN (24534559) registries.

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HIGHLIGHTS ON CIRCULATORY FAILURE, CPR AND TRAUMA

Chapter 18

The cell in shock

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'Cellular homeostasis' is any of the processes involved in the maintenance of an internal equilibrium within a cell or between a cell and its external environment. The physical and biochemical parameters of physiological equilibrium conducive to eukaryotic cell function include availability and maintenance of nutrients, oxygenation, temperature, pH, and osmolality, but exposure to conditions when these parameters are outside the physiological ranges is considered to cause stress to the cell, leading to macromolecular damage. Many types of environmental stress have been shown to cause deleterious changes in cells, including osmotic stress [1], thermal stress [2], heavy metal stress [3], ionising radiation [4], baric stress [5], oxidative stress [6], chemical genotoxin stress [7], mechanical injury stress [8] and hypoxia/ischaemia [9].

As a reaction to the threat of macromolecular damage from sudden environmental change or frequent fluctuations in environmental factors, the cell induces a stress response. This response has been described as an evolutionarily highly conserved mechanism of cellular protection [10]. The endpoints of stress events include quick responses, such as protein modifications (e.g. protein phosphorylation) [11], changes in Ca^{2+} concentrations [12], and slow responses, such as protein chaperoning and repair, transcriptional regulation, removal of damage proteins, DNA and chromatin stabilisation and repair, cell-cycle control, cell proliferation and apoptosis [13].

Cells respond to multiple opposing signals simultaneously, and the decision on whether to die or survive will depend on the intensity of the stress signal. An extreme condition of stress represents a cell in shock. The cells have a few tools for reversing shock before it goes too far. But all too often shock is so devastating, because the dose of stress exceeds the cell's capacity for maintaining integrity, that the cellular tools are driven to induce the death of the cell [14–16]. This process is physiological, since it serves to avoid the genesis of tumours and genetic instability of organisms [17].

Cellular stressors

Heat shock and the heart shock proteins

Ashburner and Bonner wrote the first review on the induction of gene activity by heat shock 27 years ago, describing how immediately after an increase in temperature all cells increase production of a certain class of molecules called heat shock proteins [18]. Subsequent studies have revealed that the same response takes place when cells are subjected to a wide variety of environmental insults, such as toxic metals [19], alcohols [20], and many metabolic insults [21].

Similar changes in gene expression provide a rapid and direct mechanism of cellular defence against so many different stress-induced damage that the term 'heat shock response' has been replaced by the more general term 'stress response', and the associated products are now referred to as stress proteins [22, 23]. Many stress proteins are also expressed in normal cells with the same function, such as control of protein synthesis, folding, and translocation into organelles [24]. And after cells have been exposed to a stress, these proteins are required to recognise unfolded proteins and either target them for removal, prevent their aggregation or assist in their refolding into their native, functional state. Five molecular chaperones represent the minimal stress proteome: DnaK/HSP70, DnaJ/HSP40, GrpE, HSP60, and peptidyl-prolyl isomerase (cylophilin). The proteins involved in cellular stress responses are the most highly conserved of all organisms [10]. In biology, chaperones are specific proteins that have the function of assisting other proteins in achieving proper folding. They were discovered as heat shock proteins, that is, proteins expressed in heat shock conditions. The reason for this behaviour is that protein folding is severely affected by heat, and chaperones therefore act to counteract the potential damage. Although most proteins can fold in the absence of chaperones, for a minority their presence is an absolute requirement.

Recent analysis has revealed that stress, rather than simply imposing destructive forces, leads to subtle changes in macromolecular structures, which result in a redirection of the cell energy to allow the synthesis of heat shock proteins, which themselves function in restoring homeostasis [25].

Cells that produce high levels of stress proteins are better able to survive the stress damage than cells that do not [26].

The major inducible heat shock protein is HSP70. The binding activity of HSP70 itself is involved in the regulation of apoptosis, where it may associate with pro-apoptotic proteins, thereby keeping these proteins in the inactive state, or play a part in the proteasome-mediated degradation of apoptosis-regulatory proteins [27]. However after a severe stress, when repair turns out to be impossible HSP 70 is involved in activation of the apoptotic programme and, in the extreme case, of cellular necrosis [28].

Oxidative stress

Oxidative stress is the cumulative production of 'reactive oxygen species' (ROS) and 'reactive nitrogen species' (RNS) through either endogenous or exogenous insults. Most endogenously formed ROS pass into mitochondria through a leak from a respiratory electron, resulting in the formation of superoxide anion radicals. Eventually these anion radicals are transformed into hydrogen peroxide and then into hydroxyl radicals, HO, which directly attack surrounding macromolecules, including lipids, proteins and DNA [29]. Most of this damage cannot be entirely repaired or removed by elements of the cellular degradative system, such as proteasomes, lysosome, cytosolic and mitochondrial proteases. Consequently, irreversibly damaged and defective structures accumulate within long-lived postmitotic cells, such as cardiac myocytes [30] and neurones [31], which explains why age-related changes occur in any aerobic organism, especially within long-lived postmitotic cells, even in an absolutely favourable environmental condition, leading to a progressively high probability of death [32]. It is also common in many types of cancer cell that are linked with altered redox regulation of cellular signalling pathways; the redox imbalance may consequently be related to oncogenic stimulation. DNA mutation is a critical step in carcinogenesis, and high levels of oxidative DNA lesions have been noted in diverse tumours, strongly implicating such damage in the aetiology of cancer. It appears that the DNA damage is linked predominantly with the initiation process [33].

Numerous stress response mechanisms are rapidly activated in response to oxidative insults. Some of the pathways are preferentially linked to enhanced survival, while others are more frequently associated with cell death. All cells have free radical scavenging systems to diminish and repair oxidative damage, and these include compounds such as glutathione, ascorbate, thioredoxin and various antioxidant enzymes [34].

Osmotic stress

The cellular response to osmotic stress ensures that the concentration of water inside the cell is maintained within a range that is compatible with biological function. Mammals limit osmotic stress by establishing an internal aqueous environment in which intravascular water and plasma electrolyte concentrations are subject to sensitive and dynamic, organism-based homeostatic regulation by the kidney, resulting in a homeostatic balance in which plasma osmolality does not normally vary by more than 2–3% [35]. During osmotic stress total osmolyte concentrations can vary by hundreds of millimoles.

Cells respond to osmotic stress by varying the concentration of osmolytes within the cell, in this manner eliminating any change in intracellular water concentration and the associated change in cell volume that might occur by osmosis. A direct cellular response to hypertonic stress takes place in seconds and involves increases in the intracellular concentrations of charged ions, such as

sodium, potassium and chloride, which are mediated by pre-existing ion transport systems [36–38].

Mammalian inner renal medullary cells are normally exposed to extremely high NaCl concentrations. This condition promotes DNA damage and inhibition of DNA repair. Under normal conditions, most cells in the body die when exposed to high NaCl, but these renal cells mostly survive and keep functioning both in vitro and in vivo [39]. The interstitial NaCl concentration in parts of a normal renal medulla can be 500 mM or more, depending on the species [40]. Several studies have shown protective adaptations for cellular survival and functioning in this extreme stress condition, including accumulation of large amounts of organic osmolytes, which regulate cell volume and intracellular ionic strength despite the hypertonicity of the high NaCl [41].

Endoplasmic reticulum stress

Correct functioning of the endoplasmic reticulum (ER) is essential for numerous aspects of cell physiology, including lipid and membrane biogenesis, vesicle trafficking and protein targeting and secretion. The ER is highly susceptible to alterations in homeostasis and exerts a strict quality control system to ensure that only correctly folded proteins transit to the Golgi. Unfolded or misfolded proteins are retained in the ER and conserved cell stress response. The aim of this, initially, was to compensate for the damage, but it can eventually promote cell death if ER dysfunction is severe or prolonged [43]. ER-initiated cell death is linked with several diseases, including hypoxia, ischaemia/reperfusion injury, neurodegeneration, heart disease, viral infection and diabetes, and it reflects an extreme condition of stress [42, 44, 45].

Persistent accumulation of unfolded proteins, interference with protein glycosylation by glucose deprivation, and changes in the redox or ionic conditions of the ER lumen can trigger programmed cell death. There are three known pro-apototic signalling pathways emanating from the ER that can be mediated by IRE1, caspase-12 and PERK/CHOP.

Under chronic ER stress, inositol requiring-1 (IRE1), an ER-resident transmembrane protein kinase, is activated, leading to the recruitment of JIK (c-Jun-N-terminal-inhibitory kinase), and TNF-receptor-associated factor 2 (TRAF2). TRAF2 activates c-Jun N-terminal protein kinase (JNK) and downstream proapoptotic kinases, such as apoptosis-signalling kinase 1 (ASK1), finally directing the activation of mitochondrial apoptotic protease-activating factor-1 (Apaf-1)-dependent caspase [46]. The mechanism underlying apoptosis via IRE1-JNK signalling has not yet been identified. On the other hand, the recruitment of JIK enables the activation of procaspase-12 located in the ER. Once activated, caspase-12 activates procaspase-9 to activate procaspase-3, the executioner of cell death [47].

Like IRE1, PKR-like ER kinase (PERK) is another sensor of reticulum stress. Activated PERK phosphorylates eukaryotic translation initiation factor-2 (eIF2α), which enhances translation of activating transcription factor-4 (ATF4) mRNA.

ATF4 induces transcription of the pro-apoptotic factor CHOP, a member of the C/EBP family of transcription factors. It has recently been shown that CHOP sensitises cells to ER stress transcriptionally, down-regulating the anti-apoptotic protein Bcl-2 [48].

Ischaemia/hypoxia

Cellular hypoxia occurs in various conditions, ranging from environmental exposures such as ascent to a high altitude to pathophysiological states with inadequate oxygen supply (hypoxia), which are usually caused by blood vessel constriction or obstruction (ischaemia). The basis of this disorder is the exhaustion of energy supplies. Therefore, human cells have evolved an ability to survive and adapt to reduction of oxygen pressure in the ambience [49]. Functionally, these adaptations include compensatory changes that allow cells to survive the hypoxic exposure itself, such as increases in anaerobic metabolism and initiation of a cell stress response, in addition to responses that are designed to increase local oxygen delivery, such as production of angiogenic factors and erythropoietin [50, 51]. Changes in gene expression have already been linked with the human cellular response to hypoxia [52]. At least three important mechanisms for altering gene expression during hypoxia have been identified: (1) changes in transcription mediated by well-described transcription factors, including hypoxia-inducible factor- (HIF-1); (2) stabilisation of hypoxia-sensitive RNA species, such as vascular endothelial growth factor (VEGF); and (3) translation through the internal ribosomal entry sites (IRES), which happens in a cap-independent manner of molecules such as VEGF even under severely hypoxic conditions [53].

HIF-1 is a transcription factor consisting of α- and β-subunits. HIF-1α expression is linked to cellular oxygen status, whereas the HIF-1β subunit is constitutively expressed. HIF-1α dimerises with HIF-1β in the nucleus and transcriptionally activates a number of genes by way of binding to hypoxia-responsive elements (HREs). The HIF-1α subunit is stabilised during hypoxia, but degrades rapidly via the ubiquitin pathway in normoxia. HIF-1 induces expression of proteins that might assist cell survival during hypoxia, such as VEGF [54].

In mammals hypoxia has been well documented, and this stressful situation elicits other stress conditions by the reduction of four different parameters: (a) body temperature, (b) heart rate, (c) respiratory rate and (d) blood pH. These decreases are associated with a protective physiological effect; however, a long period of hypoxia/ischaemia causes extensive damage [55, 56].

Stress-activated signalling cascades

Many distinct steps in the stress initiation process are widely regulated by molecular modifications, and particularly phosphorylation. The stress-activated signalling cascades in stressed cells are becoming clear. At the beginning of these signall-

ing cascades are the sensors of environmental stress: a family of serine/threonine kinases. This family includes: PKR, RNA-dependent protein kinase, which is activated by viral infection, ER stress, hypoxic stress, heat and UV irradiation [57, 58]; PERK (RNA-dependent protein kinase-like endoplasmic reticulum kinase)/PEK (pancreatic eIF2alpha kinase), resident ER proteins, are activated with the accumulation of unfolded proteins in the ER [59]; MAPKs p38, ERK and JNK are stress-responsive and are activated by oxidative stress, such as an increase in cellular H_2O_2 [60].

The end-points of signalling events include both quick responses, such as protein modifications, and slow responses, including transcriptional regulation, cell-cycle control, cell proliferation and cell death [13].

The endpoint of cell shock

Programmed cell death

The term 'programmed cell death' (PCD) was created to describe a physiological process that eliminates unwanted cells [61, 62], an active and controlled process of self-destruction [63]. Glucksmann was one of the scientists who discovered in 1951 that PCD was an integral part of normal embryonic development [64].

PCD can be defined as a sequence of biochemical and morphological alterations based on cellular metabolism and leading to cell demise, by which dying cells are removed in a safe, noninflammatory manner. In physiological conditions, PCD is tightly controlled and regulates the balance between proliferation and differentiation both in the course of development and during the optimisation of adult cell and tissue functions, in accordance with environmental stimulus. Alterations in the regulation of PCD have been implicated in a number of pathologies, including neurodegeneration and cancer [65–67].

PCD can be divided into four different types: apoptotic cell death, autophagic cell death, apoptosis-like PCD and necrosis-like PCD. What the various types of PCD have in common is that they are executed by active cellular processes and can be interrupted by interfering with intracellular signalling [68].

Apoptotic cell death or type I PCD. The main physical and biochemical hallmarks of apoptosis include loss of sialic acid, translocation of phosphatidylserine to the outer plasma membrane, cell shrinkage, nuclear condensation, chromatin aggregation, DNA fragmentation, membrane blebbing and formation of apoptotic bodies. Certain modifications that occur in the plasma membrane enable the recognition of apoptotic bodies by neighbouring cells or phagocytes, preventing an inflammatory reaction [69, 70]. Apoptosis can be considered a mild response of cells when stress exceeds cellular tolerance limits.

Apoptosis consists of at least two phases: initiation and execution. This apoptotic cascade can be initiated via two major pathways in mammalian cells: the extrinsic or death receptor pathway and intrinsic or mitochondrial pathways. Upon

triggering of either pathway, a specific family of cysteine proteases, the caspases, is activated to execute the programme. We have to keep in mind the significant cross-talk and feedback between the different pathways that regulate the apoptotic machinery and can promote amplification of the apoptotic stimulus [71].

The extrinsic apoptosis pathway is induced upon the binding of ligands (TNF, TRAIL, FasL etc.) to members of the TNFα receptor super-family, which are usually called the death receptors (Fas, also called CD95/Apo-1; TNF receptors; TRAIL receptors). Death receptors contain an intracellular globular interaction domain known as a death domain (DD) in the cytoplasm tail. Ligand-induced receptor multimerisation results in the formation of the death-inducing signalling complex (DISC) that includes the death receptor, intracellular adaptor proteins (TRADD, FADD, RAIDD) and initiator caspases (procaspase 8), leading to autocatalytic processing and activation of the initiator, caspase 9 [72].

The intrinsic pathway is initiated by the majority of apoptotic stimuli, including UV radiation, gamma irradiation, heat, DNA damage, the actions of some oncoproteins and tumour suppressor genes, viral virulence factors and most chemotherapeutic agents, irradiation, cytotoxic drugs, granzyme B and DNA damage. These stimuli lead to the loss of mitochondrial membrane potential, with the release of pro-apoptotic cell death proteins resulting in the formation of another multiprotein complex, the apoptosome, that includes Apaf-1, cytochrome-c, ATP/dATP and the initiator caspase, procaspase 9, promoting the autocatalytic activation of caspase-9 and subsequent effector caspases. Pro- and anti-apoptotic proteins of the Bcl-2 family regulate the release of pro-cell death mitochondrial proteins, while the activity of caspases is negatively regulated by the IAPs. Smac and Omi promote caspase activation by antagonising the inhibitory effects of the IAPs, while AIF and EndoG contribute to caspase-independent cell death [73].

The typical pathways of caspase activation during initiation include the 'death-receptor-mediated' recruitment of procaspase-2, procaspase-8 and procaspase-10 and a 'mitochondrial' pathway through which caspase-9 is activated via release of cytochrome-c. The two pathways converge, leading to activation of procaspase-3 and, further downstream, to activation of caspase-6 and caspase-7. All these pathways are associated with activation of caspase-activated DNase (CAD), and so also with 'typical' internucleosomal DNA fragmentation [74].

Autophagic cell death or type II PCD. Autophagy is characterised by the accumulation of autophagic vesicles (autophagosomes and autophagolysosomes) and depends on autophagy proteins. It is often observed when massive cell elimination is demanded or when phagocytes do not have easy access to the dying cells. The set of proteins (Atg5, Atg6, and Atg7) and the arrangement of autophagosomes involved in both autophagic cell death and autophagy that promotes cell survival are the same, but their regulation is substantially different during each of these processes [75]. The activation of autophagic cell death is common during tissue remodelling processes, such as metamorphosis in insects and organ morphogenesis during development, and is part of the cellular response to oxidative stress [76, 77]. Suppressing autophagosome formation by means of autophagy inhibitors, such as

3-methyladenine (3-MA) and wortmannin, or by silencing Atg5 and Atg6 inhibits this nonapoptotic form of cell death. These results suggest that autophagosome formation is required for cells to die after exposure to different cell stressors, proving the existence of this alternative death mechanism [78]. Investigation of autophagic death is still in its early stages, which is why information on the molecular basis of autophagic death is extremely limited.

Apoptosis-like, or type III, PCD. Apoptosis-like PCD involves caspase-independent mitochondrial pathways. Upon mitochondrial outer-membrane permeabilisation, AIF is released from the inter-membrane mitochondrial space. AIF is the best-characterised caspase-independent cell death regulator, and upon release it translocates to the nucleus, where it is associated with large-scale DNA fragmentation; however, chromatin condensation is less compact than in apoptosis [79]. The DNA-degrading capacity of AIF relies on recruitment of downstream nucleases, such as cyclophilin A [80], and the display of phagocytosis-recognition molecules occurs before lysis of the plasma membrane [68].

Necrosis-like, or type IV, PCD. In necrosis-like PCD, the cell-death programme is triggered by organelles other than mitochondria, such as ER, lysosomes, and the nucleus, and by proteases other than caspases, such as calpains and cathepsins originating from the ER and lysosomes, respectively. No chromatin condensation is observed. The molecular mechanisms of such PCD are less well understood, although it is believed that they represent 'alternative' death pathways when caspases are inhibited. Ca^{2+} and ROS can lead on to severe mitochondrial dysfunction and necrosis-like PCD with or without autophagy [81].

Both apoptosis and necrosis-like PCD are induced by chemotherapy, which causes cellular stress [82].

Necrosis

Necrosis is a more disorderly manner of cell death, which results from harsh circumstances outside the cell and is often called 'accidental' cell death, since it usually occurs as a result of unintentional traumatic injury, whether thermal, chemical or anoxic. It is characterised by DNA broken into randomly sized fragments, cellular oedema and disruption of the plasma membrane, leading to release of the cellular components and inflammatory tissue response [83]. Phosphatidil serine externalisation, an event previously considered unique for apoptosis, may also occur in cells undergoing necrosis [84].

Necrosis has a major role in neuronal cell death following neonatal hypoxia/ischaemia. Cytochrome-c release and caspase activation were also noted in various human breast carcinoma cells induced by a cytotoxic agent to undergo necrosis [83].

Apoptosis and necrosis have been shown to be more similar in their regulation than was previously believed, with several signalling pathways in common. There

is often a delicate balance between the two modes of death, yet outcomes and consequences for the organism can be totally different, depending on which pathway is followed after a cell stress.

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Chapter 19

Tissue partial pressure of carbon dioxide tension measurements and microcirculation visualisation. New techniques for the study of low flow states

G. Ristagno, W. Tang, M.H. Weil

Microcirculation is the ultimate determinant of the outcomes of circulatory shock states. Microcirculatory function is the prerequisite for adequate tissue oxygenation and therefore organ function. It transports oxygen and nutrients to tissue cells, ensures adequate immunological function and, during disease, delivers therapeutic drugs to target cells. It is made up of the smallest blood vessels: arterioles, capillaries and venules [1] (Fig. 1). The previous techniques used for studying microcirculation (microscopes, laser Doppler or plethysmography) were able to provide only a global measurement of microvascular blood flow; a measurement expressed as an average value of whatever was the diameter or direction of single vessels. Recent technological developments allow more precise and direct investigation of the tissue perfusion, and especially of the microcirculatory blood flow. The new techniques are basically noninvasive measurements of tissue carbon dioxide tension (PCO_2), for example at the oral cavity mucosa, and the orthogonal polarisation spectral (OPS) imaging techniques, which have allowed direct visualisation and monitoring of microcirculation at the bedside [2, 3] (Fig. 2).

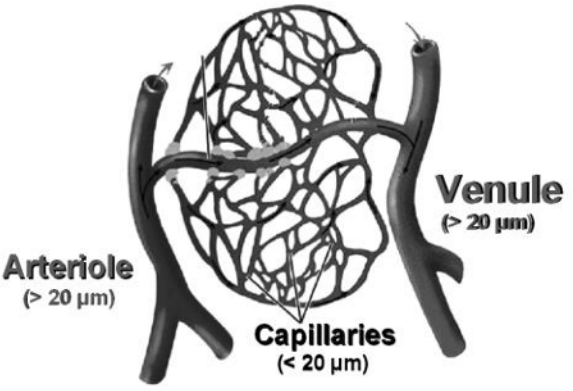

Fig. 1. Anatomy of microcirculation

Fig. 2. Orthogonal Polarization Spectral imaging camera: CYTOSCAN A/R (Cytometrics Inc., Philadelphia, PA).

Tissue CO_2 measurements

Tissue hypercarbia accompanies diverse states of perfusion failure, and it is recognised as a diffuse phenomenon during circulatory shock. It has in fact been observed in heart, stomach, liver, kidney and brain in conditions of haemorrhagic and anaphylactic shock [4–9]. Increases in tissue PCO_2 account for anaerobic production of CO_2. In fact, when oxygen delivery to the tissues is critically reduced, during circulatory failure states, anaerobic metabolism is triggered with consequent hydrogen ion production. This excess of hydrogen ions is buffered by tissue bicarbonate in such a way that CO_2 is generated [9, 10]. In the first measurements of tissue PCO_2, gastric tonometry was recognised as an early and clinically useful indicator of perfusion failure during low flow states [11]. Gastric tonometry is accomplished by way of a balloon incorporated in the distal end of a nasogastric tube, which is advanced into the stomach. The balloon is then filled with saline solution, and after an interval of 45–90 min of equilibration, the PCO_2 of the fluid sampled from the balloon is measured with a conventional blood gas analyser. This technique also provides for analyses of the gastric intramucosal pH (pHi), which is computed from simultaneous measurements of the PCO_2 in the saline and calculation of bicarbonate from arterial blood measurements of pH and PCO_2 based on the Henderson-Hasselbach equation. Several clinical studies have confirmed the validity and the utility of gastric tonometry. Close correlations between gastric pHi and mortality have been reported [12]. In 83 patients with acute circulatory failure, gastric pHi measured by tonometry was compared with adequacy of tissue oxygenation assessed by conventional methods (cardiac index, oxygen delivery and oxygen uptake). Only gastric pHi at 24 h proved to be an

independent predictor of outcome, predicting death with a sensitivity of 88% [13]. However, the tonometric method presented several limitations [14]. It was an invasive method, which required stopping feeding. The tissue PCO_2 measurements could be influenced by the PCO_2 of the gastric juice and by the PCO_2 generated in the gastric wall as a result of the neutralisation of hydrogen ions by the bicarbonate contained in the gastric juice or in the backflow of duodenal fluid. Therefore, this measurement required H_2-blockade. Gastric tonometry also presented relatively labour-intensive manipulations and a long time interval for equilibration of CO_2 between the saline in the tonometer balloon and the gastric wall. For all these reasons and also because we recognised that hypercarbia was a general phenomenon in perfusion failure, which was equally profound in the intraabdominal viscera and in extraabdominal sites in circulatory shock, we investigated diverse sites for measurement of tissue PCO_2 directly and in less invasive ways [6].

We had previously demonstrated a close correlation between gastric and oesophageal wall mucosa PCO_2 [5], and subsequently we established that sublingual fossa mucosa and buccal mucosa were sites that provided measurements of tissue PCO_2 comparable to those in the mucosa of both the stomach and the oesophageal wall. In fact, decreases in organ blood flow were closely associated with increases in PCO_2 in the sublingual mucosa and that of the buccal cavity [5–7, 15–17]. We also investigated the feasibility and predictive value of sublingual PCO_2 ($PslCO_2$) measurement as a noninvasive and early indicator of systemic perfusion failure on clinical settings. $PslCO_2$ was measured in five healthy human volunteers and in 46 patients with acute illness or injuries admitted to ICUs attached to emergency departments and to medical and surgical departments. $PslCO_2$ was approximately 45 torr in the healthy volunteers and approximately 81 torr in 26 patients who presented signs of circulatory failure. The initial sublingual mucosa PCO_2 of 12 patients who died without recovering from shock was approximately 93 torr, and this contrasted with the value of 58 torr ($p<0.001$) in hospital survivors. When $PslCO_2$ exceeded the threshold of 70 torr its positive predictive value for presence of physical signs of circulatory shock was 1.00. A value < 70 torr predicted survival with a predictive value of 0.93. Later, we demonstrated that the buccal mucosa tissue PCO_2 measurements could be used as sensitive indicators of systemic blood flow during haemorrhagic shock [16]. We induced haemorrhagic shock in five anaesthetised pigs weighing 35–40 kg. Blood was shed at a rate of 20 ml/min until the mean arterial pressure had declined to 55±5 mmHg. After 2 h the shed blood was reinfused at a rate of 100 ml/min and animals were observed for a further 2 h. Over the 2-h interval of shock, the buccal mucosa PCO_2 increased in parallel with the sublingual mucosa PCO_2, from 56 to 116 torr (Fig. 3). Increases in buccal tissue PCO_2 were accompanied by corresponding decreases in cardiac output and mean arterial pressure, and by increases in arterial blood lactate concentrations. Increases in buccal PCO_2 were accompanied by reductions in buccal mucosal flows, measured by microsphere techniques. These decreases in blood flow were closely related to those in the sublingual sites and to concomitant reductions in liver and kidney blood flow. After reinfusion of the shed blood, buccal and sublingual mucosa PCO_2 values were restored to baseline. There was a close correlation

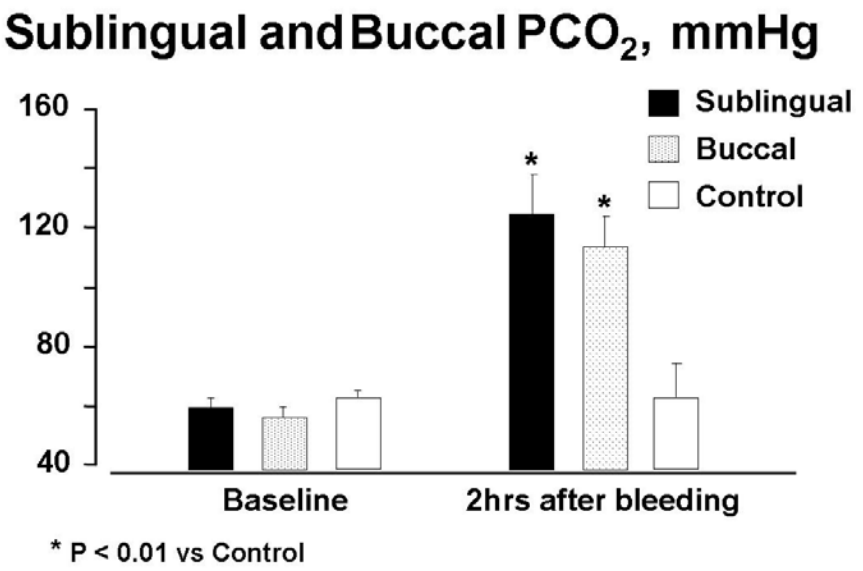

Fig. 3. Increases and decreases in sublingual and buccal mucosal partial pressure of carbon dioxide (PCO_2). * p <0.01 versus control

between buccal mucosa PCO_2 and sublingual mucosa PCO_2 measurements, and buccal PCO_2 measurement was a useful guide for diagnosis of circulatory shock states. In a more recent study on a rat model of haemorrhagic shock [17], our group investigated the buccal PCO_2 measurements to identify a threshold level that would predict the effects of volume repletion on survival and to confirm buccal PCO_2 as a better indicator of the severity of volume deficit than other commonly used standard measurements. Animals were randomised into four groups for bleeding, with losses equal to 25%, 30%, 35% and 40% of the estimated total blood volume over a period of 30 min. Thirty minutes after the end of bleeding, infusion of lactated Ringer's solution was started, in amounts corresponding to twice the volume of blood removed over 30 min. The standard measurements used for diagnosis and as a guide for therapy during haemorrhagic shock, such as mean arterial pressure, failed to distinguish between the four groups. Buccal mucosa PCO_2, however, did differentiate between the various degrees of severity of haemorrhage (Fig. 4). Moreover, during and after volume repletion, buccal mucosa PCO_2 was able to predict survival and neurological recovery in the various groups. During circulatory failure buccal mucosa tissue CO_2 was a noninvasive and rapid response indicator. Buccal PCO_2 was therefore confirmed as a useful guide to the diagnosis of circulatory shock and as a quantitative indicator of its severity. It also provided a rapid response for confirmation of the effectiveness of treatments.

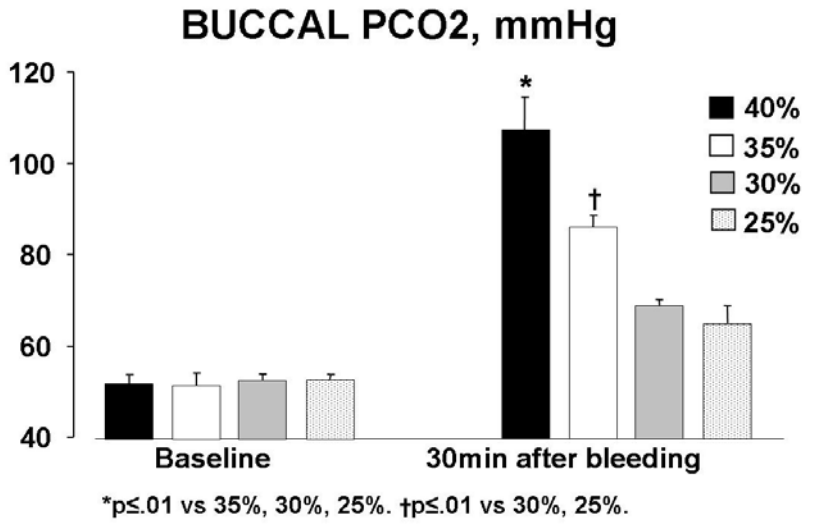

Fig. 4. Comparison of measurements of buccal PCO_2 among four groups at baseline and after bleeding

Monitoring of microcirculation with the OPS technique

The OPS imaging technology is a noninvasive method for direct visualisation of multiple conditions of the microcirculation and performance of quantitative measurements of the diameter of vessels, the velocity of red blood cells and functional capillary density [18]. This method uses a linearly polarised light to illuminate the area of interest. The light is reflected from the tissue source and forms an image of the illuminated region within the target of the video camera. The image is captured through a polariser, which is oriented orthogonally to the plane of the illuminating light [19]. This polarisation analyser allows only depolarised photons scattered within the tissue to pass the optical probe and generate the image [20]. This optical filtration eliminates the light reflected at the surface of the tissue to produce high-contrast reflected images of the microcirculation. Red blood cells appear dark, and white blood cells and platelets are sometimes visible as refringent bodies. The wavelength is chosen within the haemoglobin absorption spectrum, and both oxy- and deoxy-haemoglobin absorb equally. The vessels are visible only if they contain red blood cells. Several experimental and clinical studies have been performed on various tissues and under different conditions, and especially in settings of circulatory shock [21, 22]. Recent investigations in patients with chronic cardiovascular diseases [23] and with acute cardiocirculatory failure attributable to septic and cardiogenic shock documented characteristic reductions in microcirculatory blood flow that were largely independent from the macrocirculation [21, 24, 25]. These alterations

included a decrease in vessel density and an increase in the proportion of nonperfused or intermittently perfused capillaries. Flow in vessels under 20 μm in diameter was significantly decreased during septic shock, while in vessels with diameters over 20 μm perfusion was well preserved. In the presence of sepsis, multiple organ failure commonly occurs, even after restoration of a stable haemodynamic state; it is related to direct impairment of cellular function or cytopathic hypoxia and/or redistribution of blood flow between and within the organs at the microcirculatory level [21]. In a recent study in a rat model of sepsis and septic shock conducted by our group, we investigated simultaneous microcirculatory blood flow changes in buccal and gastric mucosa. In the same experimental setting we also continuously measured gastric and buccal mucosa tissue PCO_2 changes [26].

Sepsis was induced by ligation of the coecum in its distal tract and subsequent puncture to allow faeces to be expressed into the abdominal cavity. Measurements of the microcirculation were taken at baseline and then at hourly intervals until death and compared with measurements in sham-operated animals. We observed an early and progressive decrease in microcirculatory blood flow in vessels smaller than 20 μm (approximately 30% at 4 h before death and more than 80% at 1 h before death), whereas blood flow in vessels larger than 20 μm was well preserved during progression of sepsis. No significant abnormalities were observed in sham-operated control animals. Gastric and buccal tissue PCO_2 values also progressively increased after coecal ligation and puncture which terminated in death. The present study adds to the evidence indicating that microvascular abnormalities ultimately account for the fatal course of sepsis and septic shock and, even more importantly, that there is a close correlation between tissue PCO_2 and blood flow in vessels smaller than 20 μm, which means predominantly capillaries ($p<0.01$).

This dissociation between large pressure vessel flows and microcirculatory flows, with concurrent increases in tissue PCO_2, were also observed in a rat model of haemorrhagic shock (X. Fang, S. Sun, L. Huang et al., 2006, unpublished data).

Microcirculation during cardiac arrest and cardiopulmonary resuscitation

In cardiac arrest and cardiopulmonary resuscitation (CPR), changes in macrocirculatory haemodynamics and gas exchange, and especially coronary perfusion pressure (CPP) and end-tidal CO_2, have been extensively investigated as predictors of outcomes in the restoration of cardiac function [27–31], but the "microcirculation" has been the subject of little exploration. This prompted our group to investigate changes in the microcirculation accompanying this most severe form of circulatory failure and the effects of cardiopulmonary resuscitation [32]. In nine pigs we induced 5 min of untreated ventricular fibrillation (VF) prior to beginning closed chest cardiac compression and attempting electrical defibrillation. OPS imaging was utilised for visualisation of the sublingual microcirculation at baseline, during VF and CPR and after the return of spontaneous circulation (ROSC). We observed that there was a close correlation between microvascular blood flow and coronary perfusion pressure during CPR ($r=0.82$; $p<0.01$), and like that of coronary

perfusion pressure, the magnitude of microcirculatory blood flow was indicative of the effectiveness of the resuscitation intervention and of outcome. Microcirculatory blood flow decreased to less than one fourth within 0.5 min after the induction of VF. In animals that were resuscitated, microvascular flow was significantly greater after 1 and 5 min of chest compression than in animals in which resuscitation attempts failed ($p<0.05$ and $p<0.01$, respectively). After ROSC, microcirculatory blood flow returned to within 20% of baseline values within 5 min.

Recently we focused our attention on the investigation of cerebral microcirculatory changes during cardiac arrest and CPR [33]. We performed a craniotomy on each of five domestic male pigs and created a window over both left and right fronto-parietal surfaces of the cortex to allow for OPS imaging (CYTOSCAN A/R, Cytometrics Inc., Philadelphia, Pa.) so as to record the cerebral blood flow through the surface cerebral vessels at baseline, during VF and CPR and then after ROSC. Velocity of blood flow was graded from 0, i.e. "no flow", to 3, "normal" velocity, on the pial and penetrating vessels <20μm. After 3 min of untreated VF, animals were mechanically ventilated and precordial compression (PC) was performed for 4 min prior to defibrillation. Cerebral microcirculatory blood flow was continuously recorded. We observed that microcirculatory blood flow velocity started to decrease, but continued during the first minute of cardiac arrest ($p<0.01$ vs BL) and was promptly albeit only partially restored by chest compression. Following ROSC, we confirmed a rapid restoration of cerebral microcirculatory blood flow to normal levels (Fig. 5). Moreover, with the aid of these techniques for investigation of microcirculatory perfusion, we recently focused our attention on the effects on the small vessel blood flows consequent on the administration of vasopressor agents

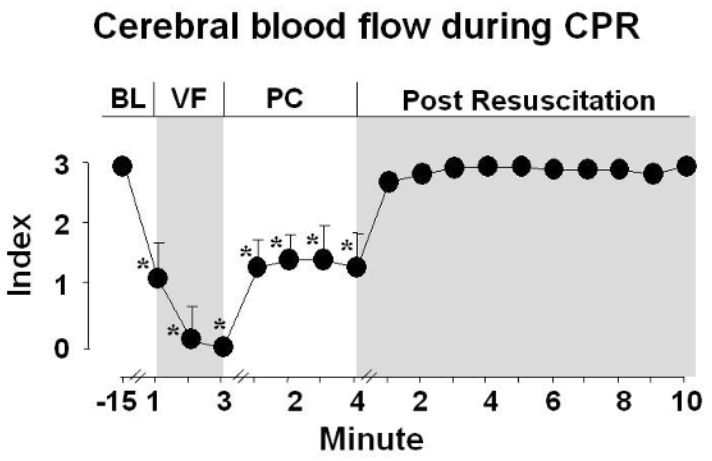

Fig. 5. Cerebral microcirculatory blood flow velocity at baseline and during ventricular fibrillation, chest compression and post-resuscitation. *BL*=baseline *VF*=ventricular fibrillation *PC*=precordial compression. * $p<0.01$ vs BL

during CPR, and especially after epinephrine. Epinephrine has been the preferred adrenergic amine for the treatment of human cardiac arrest for almost 40 years [34–38]. In cardiac arrest, re-establishing vital organ perfusion plays an important part in initial CPR. As a pharmacological intervention, the rationale for the administration of vasopressor agents during CPR is to restore threshold levels of CPP and, therefore, myocardial blood flow [39]. Pharmacological responses to adrenergic agents are mediated by a group of receptors, which are classified as alpha (including $alpha_1$ and $alpha_2$) and beta (including $beta_1$, $beta_2$ and $beta_3$) [40, 41]. The primary efficacy of epinephrine in CPR is due to its $alpha_1$ and $alpha_2$ adrenergic effects. This contrasts with its beta-adrenergic actions, which are inotropic, chronotropic and vasodilatory. Accordingly, beta-adrenergic actions prompt increases in myocardial oxygen consumption, ectopic ventricular arrhythmias and transient hypoxaemia due to pulmonary arteriovenous shunting. We previously demonstrated that a beta-adrenergic blocking agent, when administered during CPR, significantly improved initial cardiac resuscitation, minimised postresuscitation myocardial dysfunction and increased the duration of postresuscitation survival [42, 43].

$Alpha_1$-adrenergic receptors, which, like beta receptors, mediate increases in both inotropic and chronotropic responses, also augment myocardial oxygen requirements and thereby increase the severity of global ischaemic injury [44]. When $alpha_1$-adrenergic receptors were blocked by either a selective or a nonselective alpha-adrenergic blocker, myocardial function was significantly improved after acute myocardial infarction [45]. We have shown that combining $alpha_1$- and beta-adrenergic blockade, the equivalent of selective $alpha_2$-vasopressor agonists, resulted in better postresuscitation cardiac and neurological recovery [39]. In addition, $alpha_1$-adrenergic agonists may constrict coronary arteries in such a way that there is a superimposed reduction in myocardial function. Accordingly, selective $alpha_2$-agonists are as effective as epinephrine for initial cardiac resuscitation but do not increase myocardial oxygen consumption and therefore result in strikingly better postresuscitation myocardial function and survival [46–48]. In addition, $alpha_2$-adrenergic agonists increase endothelial nitric oxide production, therefore counterbalancing the $alpha_2$-adrenergic vasoconstrictor effects in coronary arteries [49].

A recent observation, in a porcine model of cardiac arrest and resuscitation [50], of reductions lasting more than 5 min after ROSC and in the sublingual microcirculation after the administration of epinephrine during CPR, prompted us to investigate the effect of this vasopressor on the cerebral microcirculation [51]. Our study, performed in an established porcine model of cardiac arrest and resuscitation, is based on 3 min of VF and 4 min of chest compression and ventilation (with a compression/ventilation ratio of 15 : 2), before defibrillation is attempted. Our preliminary results were obtained in eight domestic male pigs weighing 40±2 kg, in which we performed a craniotomy and created a window over the fronto-parietal surface of the cortex to allow for OPS imaging (CYTOSCAN A/R, Cytometrics Inc., Philadelphia, Pa.) so as to record cerebral blood flow through the surface cerebral vessels. The velocity of blood flow was graded from 0 ("no flow") to 3 ("normal") in the pial and penetrating vessels μm, which are predominantly

capillaries. Before cardiac arrest was induced the animals were randomised to receive epinephrine (30 μg/kg) or saline placebo over 10-s intervals, beginning 1 min after the onset of CPR. The results were consistent with those previously obtained in the vasculature of the sublingual mucosa. The cortical microcirculatory blood flow was significantly lower in pigs treated with epinephrine than in the saline placebo group. These effects persisted for more than 5 min after resuscitation (Fig. 6).

In the setting of CPR, it is important to give more emphasis to the cerebral aspect. Cerebral recovery depends on numerous factors related to the duration of arrest and of CPR and to the efficacy of the basic, advanced and prolonged life support [52]. There are still many gaps in our knowledge about optimising support for better outcomes in cerebral function, and more studies and trials are needed to enhance our understanding of its management. We believe that this new OPS technique, which allows direct monitoring of organ perfusion, and particularly brain perfusion, represents an exciting instrument for use in ongoing research and will facilitate substantial advances in the field of resuscitation.

Conclusions

Our inadequate understanding of the microcirculation is a significant gap in our present knowledge base. In contrast to intraarterial pressure, and even more the noninvasive cuff technique, sublingual/buccal PCO_2 discriminated between short-

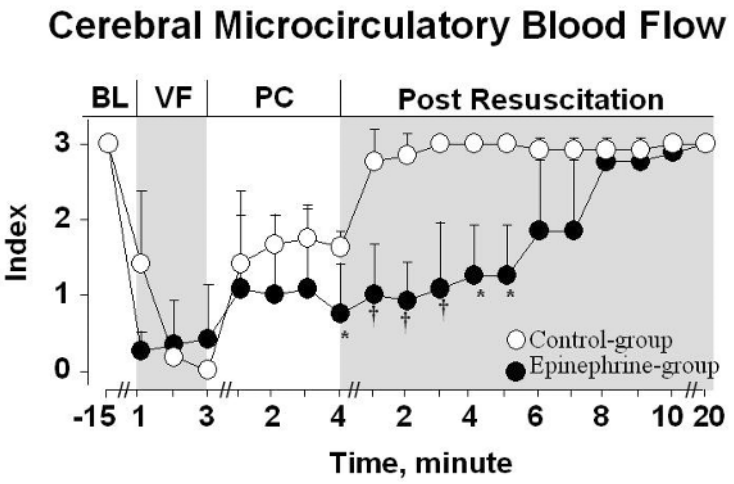

Fig. 6. Cerebral microcirculatory blood flow velocity at baseline and during ventricular fibrillation, chest compression and post-resuscitation. *BL*=baseline *VF*=ventricular fibrillation *PC*=precordial compression. * $p < 0 = 0.05$; † $p < 0.01$ vs saline placebo group

and long-term survival after large-volume blood loss. Tissue ischaemia reflected in increases of arterial blood lactate and tissue PCO_2 are now explained by selective decreases in blood flow in microvessels corresponding to capillaries, which can be detected with the aid of OPS imaging. In settings of cardiac arrest OPS measurements of microvascular flow were predictive of resuscitability, and they also open up new opportunities for better understanding of CPR. Moreover, initial observations on the effects of adrenergic vasopressor agents on the microcirculation once again prompt reexamination of the rationale for routine administration of vasopressor drugs for the management of diverse shock states.

Buccal PCO_2 and microvascular flow investigations, therefore promise to be practical clinical measurements for diagnosis, triage and treatment during low flow states.

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Chapter 20

Ventricular fibrillation and defibrillation: contemporary understanding of mechanisms

R.D. White

Before proceeding with a discussion of contemporary transthoracic defibrillation and the transition to biphasic waveforms, I will review the mechanisms of ventricular fibrillation (VF) and defibrillation. Though they are complex, much insight has been gained into these mechanisms, which facilitates an understanding of why defibrillation with well-designed biphasic waveforms has emerged from experimental observations into clinical practice.

The electrophysiological mechanisms that initiate VF are still not well understood. As with descriptions of mechanisms of defibrillation, new terminology is used with traditional terms to describe electrical activity that launches and sustains VF. Regions undergoing transition from excitable to refractory states are referred to as 'wavefronts'. The term 'rotor' is used to define a rotating wave of electrical activity in the absence of an obstacle to conduction. Rotors can also be described as vortex waves, spiral waves, or functional re-entry [1–3]. Circus movement re-entry is a commonly understood form of electrical activity that is a rotor. The excitable region in a re-entrant circuit is referred to as the 'excitable gap'. Once initiated, VF is sustained by the incessant recirculation of re-entrant activation fronts moving along randomly changing pathways at varying conduction velocities. Excitable (nonrefractory) myocardium in their path assures their survival and therefore sustained fibrillation. The unstable and fragmented activation characteristic of VF can be understood to be the consequence of wavefronts that have been disrupted by interaction with refractory tails of other waves. As these wavefronts fracture, some may propagate unchanged until they are annihilated by random collision with other waves, whereas others can create new vortexes. The final result would be fragmentation into multiple daughter wavelets, which in turn can lead to formation of new vortexes and wavebreaks [4, 5]. In this manner, the 'pernicious stability' of VF is sustained, despite its erratic nature. Indeed, VF may not be a totally random arrhythmia, as previous descriptions have suggested. Although re-entry (i.e. the multiple wavelet hypothesis) is well accepted as the mechanism of VF, rapidly discharging foci (the focal source hypothesis) may be the mechanism in some forms of VF [6]. Re-entry also can be understood within the recently developed concept of virtual electrode polarisation (VEP). Because this is a hypothesis that can explain both successful and failed defibrillation shocks, and the greater efficacy of biphasic shocks, VEP and the mechanisms by which VEP can lead to re-entry are discussed later in detail.

What seems certain is that VF is sustained by re-entrant wavefronts dependent on excitable tissue in their path. To terminate VF, a defibrillation shock must extinguish most or all fibrillatory wavefronts, and at the same time, it must not itself induce VF. The mechanisms by which this can be achieved are discussed in the next section.

Defibrillation: hypotheses and electrophysiological mechanisms

Fibrillation and defibrillation are very complex processes that are still poorly understood. Several hypotheses have been proposed as mechanisms of defibrillation. These include the critical mass, the upper limit of vulnerability (ULV) hypothesis, the extension of refractoriness hypothesis and the progressive repolarisation hypothesis [7–14]. A detailed description of each of these hypotheses is available in a recent chapter [15].

Most descriptions of defibrillation have emphasised the critical role of depolarisation in shock success. For monophasic shocks, repolarisation must be overcome to achieve depolarisation. At least in part, this is accomplished because depolarised tissue will depolarise adjacent repolarised zones [16]. If sodium channels have been sufficiently recruited in repolarised areas, a new action potential can be induced, resulting in extension of refractoriness. Biphasic shocks, however, can 'exploit' the repolarised areas by depolarising them during the second phase of the shock [17]. Thus, biphasic shocks can prolong refractory periods at lower shock intensities because repolarisation during the first phase 'conditions' the cells by sodium channel recruitment for optimal depolarisation during the second phase. This extended refractoriness will then abort excitation by incoming VF wavefronts.

Finally, the 'virtual electrode polarisation hypothesis' of the mechanisms of both successful and failed shocks has recently been introduced. Because this proposal embraces new terminology and concepts, it is described in detail in the next section.

Most of what is known about VF and defibrillation has been derived from a wide variety of animal models. The complexity and duration of commonly present underlying structural heart disease in human VF, the typical substrate for arrhythmogenesis, makes extrapolation from these experimental studies challenging and means it must not be done except with caution. Even in experimental settings VF rapidly undergoes electrophysiological deterioration with time (Fig. 1). In longer duration human VF, these adverse changes are certain to be accentuated. It can be anticipated that advances in waveform design and energy delivery will increase the likelihood that human VF can be terminated with longer durations and various underlying myocardial substrates.

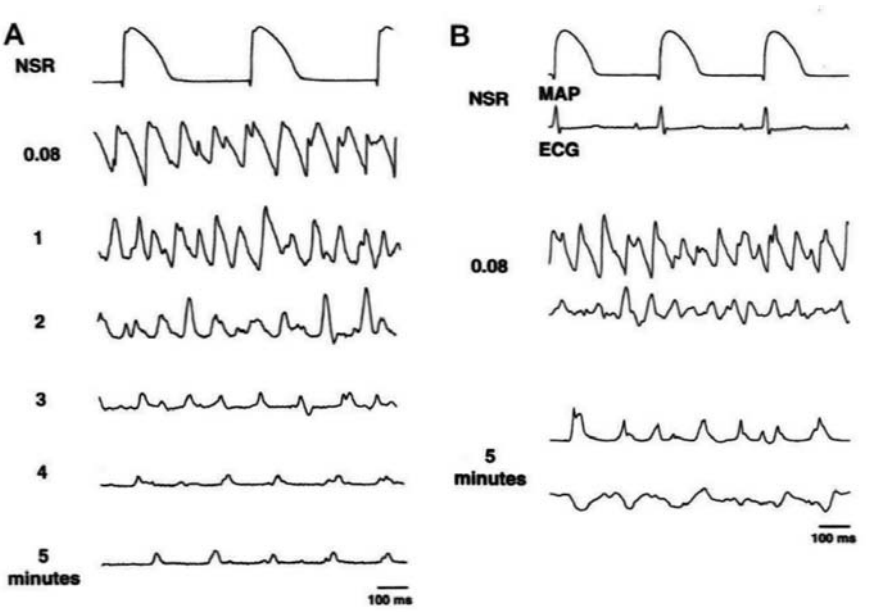

Fig. 1. **A** Monophase action potentials (*MAP*) recorded during normal sinus rhythm (*NSR*) and over the course of 5 min of induced ventricular fibrillation (*VF*). **B** The electrocardiogram (*ECG*) is shown below the action potentials in a different preparation. Electrophysiological deterioration occurs over this time period, with prolonged diastolic intervals and increased cycle lengths. The ECG reflects this electrophysiological degeneration

Virtual electrode polarisation

The hypothesis of 'virtual electrodes', also known as 'virtual electrode polarisation' (VEP), describes a complex global myocardial polarisation characterised by the simultaneous presence of positive and negative areas of polarisation adjacent to each other [18–24]. In virtual electrode terminology, 'negative polarisation' describes repolarisation (hyperpolarisation) and 'positive polarisation' describes depolarisation. Shortening of action potential duration by negative polarisation is referred to as 'de-excitation', which can be understood to be equivalent to repolarisation. Thus, in essence, 'excitation' describes shock-induced depolarisation of de-excited (repolarised) tissue.

VEP is a result of redistribution of charge between neighbouring areas of myocardium. Re-entry can develop because of the proximity of areas of shock-induced positive and negative polarisation.

The complexity of the data describing mechanisms of monophasic and biphasic waveform defibrillation, and their apparently conflicting interpretations, have been put into perspective by Ideker et al. [6], who pointed out that most of the studies and proposed mechanisms of defibrillation may be in part correct, and yet

all may be partially incorrect because they are incomplete. Many of these proposed mechanisms will be unified and at the same time be rendered increasingly applicable to human fibrillating hearts because of investigations that closely mimic the human heart with underlying structural disease. At this time, all the available data provide a clear picture of what VF is and how it is terminated by the application of electric shocks, both monophasic and biphasic.

Mechanisms of superior efficacy of biphasic shocks

Despite the several different hypotheses set up in attempts to define the mechanisms of defibrillation, it is agreed that optimal biphasic shocks have greater efficacy than monophasic shocks. Sufficiently strong monophasic shocks are also capable of defibrillation, and these shocks invoke similar mechanisms to achieve defibrillation. The greater efficacy of biphasic shocks resides in the ability of the second phase to achieve defibrillation more easily by creating a homogeneous distribution of postshock transmembrane voltage.

Shocks induce both positive and negative polarisation (depolarisation and repolarisation) simultaneously. To create uniform depolarisation, monophasic shocks must be of sufficient intensity to depolarise the repolarised tissue. In VEP terminology, the positively polarised areas must excite the de-excited areas and also bring them to a state of positive polarisation. The voltage gradient, or driving force, and the areas of de-excitation must be of sufficient magnitude to enable rapid propagation of postshock excitation before recovery of adjacent tissue permits re-entry to develop. During the first phase of biphasic shocks, similar simultaneous positive/negative polarisation is induced. In myocardial tissue experiencing de-excitation, sodium channels are recruited, rendering this tissue more susceptible to excitation (depolarisation; i.e., the de-excited areas are more easily re-excited and thus fully depolarised).

The second phase of a biphasic shock (the countershock) exploits these readily excitable repolarised areas with rapidly propagating postshock excitation and fully depolarises them, while having minimal effect on previously depolarised areas. Because these activations traverse the excitable gap rapidly, the adjacent positively polarised tissue has not recovered from the refractoriness. Defibrillation is achieved when rapid excitation of de-excited (repolarised) areas brings about uniform depolarisation, or positive polarisation. Although there are differences among the various hypotheses, this explanation seems fundamentally consistent with the ULV hypothesis, the extension of refractoriness hypothesis, the progressive depolarisation hypothesis, and the VEP hypothesis. The VEP hypothesis emphasises the global pattern of these events and the critical role that de-excitation plays in the process of anti-arrhythmia. The graded response hypothesis, which proposes that biphasic shock-induced lengthening of repolarisation time and increase in refractoriness might prevent propagation of re-entrant wavefronts, also seems to be fundamentally consistent with these concepts. All investigators agree that optimally designed biphasic waveforms, with optimal first-phase/second-phase current (or

charge) delivery ratios, are more effective in terminating VF (and other re-entrant arrhythmias) than are monophasic waveforms.

In 1996, the first approved biphasic waveform was incorporated into an automated external defibrillator (AED) marketed as the ForeRunner™ (Philips Medical Systems, Seattle Wash., USA). It is an impedance-compensated biphasic truncated exponential (BTE) waveform, which delivers a fixed energy of 150 J [25, 26]. Since then, other biphasic waveforms have been approved for clinical use, most of them utilising a BTE design. Compensation for impedance is typically achieved by extending the phasic durations and adjusting the tilt of the first phase [25]. Maximum total duration is limited to 20 ms. An example of a BTE waveform is shown in Fig. 2. Some of these incorporate escalating energy protocols, with energy capability up to 360 J.

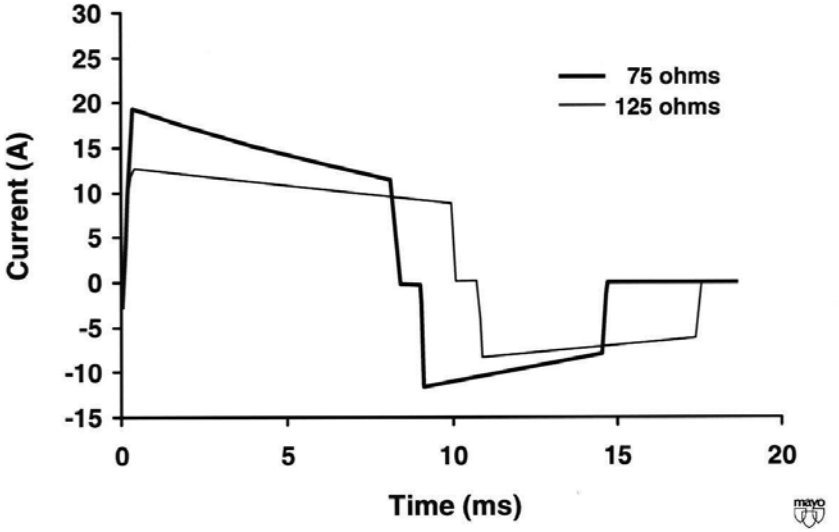

Fig. 2. Biphasic truncated exponential waveform delivering 150 J. The figure depicts current versus time, and waveform morphology for discharge into two impedances is shown. This waveform compensates for increasing impedance by extending the phasic duration. (Phillips Medical Systems, Heartstream Operation, Seattle, Wash.)

Another biphasic waveform is the rectilinear biphasic waveform (RBW) (Zoll Medical Corporation, Chelmsford, Mass., USA) [27, 28]. This waveform maintains a relatively constant current during the first phase, based upon the rationale that it is first-phase current that primarily accounts for defibrillation, though with high impedance and 200 J selected energy the waveform acquires a BTE morphology with a first-phase tilt. Impedance compensation waveform is achieved by increasing the energy delivered while the phasic durations remain fixed (6 ms for the first phase and 4 ms for the second phase). This biphasic waveform is shown in Fig. 3. Because of this mechanism to obtain impedance compensation, delivered energy is typically higher than the energy selected (Fig. 4).

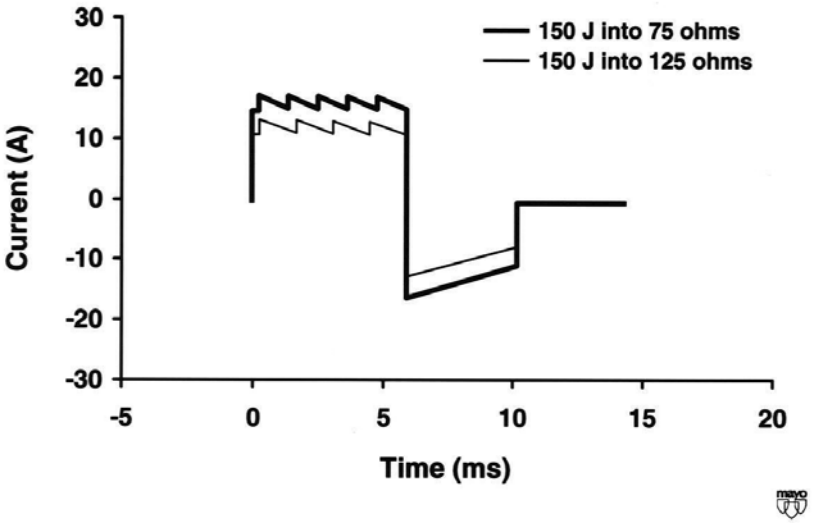

Fig. 3. Rectilinear biphasic waveform. Current is plotted against time for discharge into two impedances. Durations of the first and second phases remain constant (6 and 4 ms, respectively). A relatively constant current is maintained during the first phase, although there is some droop with high impedances and high-energy settings

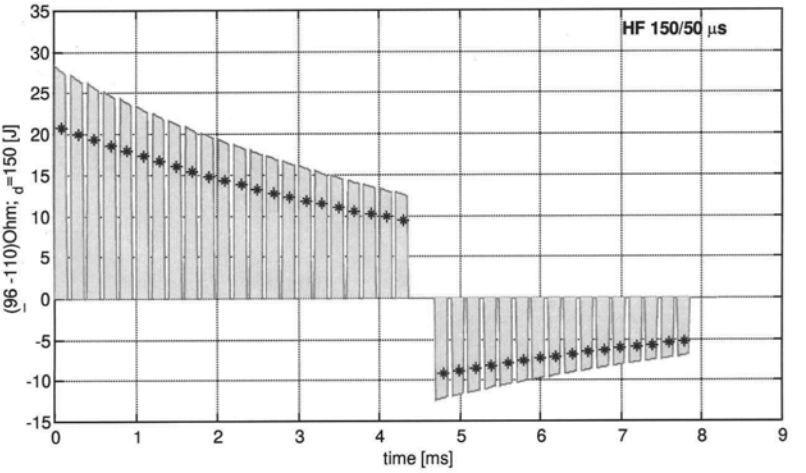

Fig. 4. Pulsed biphasic waveform. Current is plotted on the *vertical axis*. The maximum delivered energy (150 J) and impedance of 100 Ω are shown. The *stars* represent average current during each duty cycle of the pulses. (Schiller Medical, Wissembourg, France)

Yet another biphasic waveform that has been approved for clinical use in Europe and is awaiting approval for use in the United States is a biphasic pulsed waveform. Chopping the waveform at high frequency is intended to achieve high shock efficacy with very low energies, e.g. 90–130 J. At this time there are no peer-reviewed published studies defining the performance of this waveform when applied for VF in out-of-hospital cardiac arrest. This pulsed waveform is shown in Fig. 5.

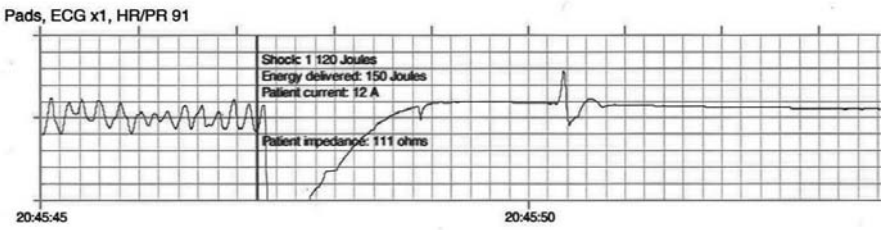

Fig. 5. A 120-J selected energy shock with the rectilinear biphasic waveform. Impedance compensation for 111 Ω results in delivered energy of 150 J and an average current of 12 amp. Thus, the selected energy is 30 J less than that delivered

Biphasic waveforms, regardless of design and of delivered energy, have replaced non-impedance-compensated monophasic waveforms for external defibrillation. Clinical experience with several of these waveforms has been published and confirms the high shock efficacy in terminating VF [29–35]. At this time there is no certain clinical evidence of superiority of one type of biphasic waveform over another. Currently available research indicates that biphasic shock energies, regardless of waveform, for initial shocks of 150–200 J are also safe and effective. However, very limited data are available on 300- to 360-J biphasic shocks, because of the very high efficacy (90%) of initial shocks with energies in the range of 150–200 J.

The 2005 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care and the European Resuscitation Council ILCOR Guidelines state that for the first shock using a BTE waveform 150–200 J is safe and effective and 120 J selected energy is safe and effective with the RBW. If additional shocks are needed to terminate persistent VF the same (nonescalating) or a higher (escalating) dose can be used. There is no unequivocal evidence that escalation is needed. If VF recurs after initial termination the energy dose that terminated the VF should be used [36, 37].

While there is experimental evidence of at least transient myocardial dysfunction after high-energy shocks, there are no reports of shock-induced myocardial dysfunction in clinical settings in which higher energies (300–360 J) are used [36, 38]. Of course it would be difficult to identify such shock-induced myocardial injury in a clinical setting of cardiac arrest without immediate preshock data and with all the other variables that influence myocardial function during cardiac arrest and

resuscitation. Certainly the trend appears to be a transition towards lower energies for defibrillation, which will render the question of myocardial injury a non-issue.

Conclusions

The transition of biphasic waveforms from ICDs to external defibrillators constitutes a significant technological advance for transthoracic defibrillation. Impedance compensation has enabled the delivery of defibrillation current adapted to each patient and to each shock in the same patient. Optimally designed biphasic waveforms have been shown clinically to have greater efficacy than monophasic waveforms in the termination of VF, and because peak current delivery is less these waveforms are likely to be less injurious to myocardial function. Advances in understanding of the mechanisms of fibrillation and defibrillation have identified the electrophysiological events that initiate and sustain VF and the effects of defibrillation shocks on those events. Definition of the role of VEP and postshock excitation has clarified the mechanisms by which shocks can either fail or succeed. The ability of the second phase of optimal biphasic waveform shocks to exploit recruited sodium channels in negatively polarised areas and thus induce rapid propagation of postshock excitation assures uniform depolarisation and prevention of re-entry. This appears to be the major mechanism of greater efficacy of biphasic waveforms. It seems certain that continuing investigation of virtual electrodes will enhance our understanding of defibrillation and optimal waveforms. At the same time, much more needs to be known about translation of these experimental observations to mechanisms of defibrillation in human hearts with longstanding underlying structural heart disease, which often has a multifactorial aetiology. This represents a major challenge in defibrillation research.

Biphasic waveform defibrillation has replaced monophasic waveform defibrillation for transthoracic defibrillation. Various configurations of biphasic waveforms are in clinical use, including biphasic truncated exponential, rectilinear biphasic, and pulsed biphasic waveforms. All are impedance compensated. At this time both fixed and escalating energy protocols are used with the waveforms, employing low energy (90–200 J) or higher energy (300–360 J) with escalating energy protocols. There is no clinical evidence to date indicating that any one type of biphasic waveform is clearly superior to any other. While there is no definite clinical evidence of shock-induced myocardial dysfunction with higher energy shocks there does appear to be a trend towards utilisation of lower energies with biphasic waveform defibrillation, because of the very high shock success with lower energy defibrillation.

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Chapter 21

Arterial waveform analysis to determine cardiovascular parameters

S. Scolletta, B. Biagioli, P. Giomarelli

Pulsatile pressure has been recorded routinely in human cardiovascular diagnostic laboratories, operating rooms and critical care units since the present generation started work, and pulsatile flow patterns are now used increasingly both invasively and noninvasively for the quantification of a number of cardiovascular parameters. However, it is a supreme paradox that modern physicians, almost without exception, while surrounded by twenty-first century aids to diagnosis and therapy, uses the arterial pulse only to assess systolic, diastolic and mean blood pressure and heart rate and rhythm, and takes no notice of the other information that the pulse is capable of imparting [1].

The presence of the arterial pulse has been recognised as the first sign of life and its absence, as the first sign of death. The Fathers of Medicine in Greek, Egyptian, Chinese and Indian cultures recognised different forms of the pulse in health and disease. The first direct measurement of arterial blood pressure was by the Reverend Stephen Hales in 1731. He measured the blood pressure of a horse by inserting a brass tube one sixth of an inch in diameter connected to a glass tube into the crural artery. Some progress occurred over the next 100 years in developing techniques for measuring blood pressure in patients, but it was not until 1876 that Von Basch made a simple sphygmomanometer which allowed him to assess systolic pressure with a fair degree of accuracy and for the first time made it possible to collect data on blood pressure from a large number of patients. Twenty years later, Rocci developed the mercury sphygmomanometer, which has changed little in the last 100 years. Probably the most important development in the measurement of blood pressure was the recognition by Korotkoff that is was possible to define both systolic and diastolic pressure accurately by listening with a stethoscope over the brachial artery below the inflated cuff as the pressure was slowly lowered [2]. The "golden era" of the pulse was the nineteenth century. With the development of the sphygmograph by Marey [3] and its refinement over the next few years by Mahomed [4], and Broadbent [5], the art of interpreting the shape of the arterial waveform, or sphygmocardiography, began. However, when the mercury sphygmomanometer was developed, clinicians began to concentrate more on the absolute values of systolic and diastolic blood pressure than on the shape of the waveform, thereby disregarding important qualitative information in favour of information covering only the extremes of pressure. Only recently have clinicians rediscovered the importance of the arterial waveform, spawning a variety of different measurement techniques.

Applanation tonometry and arterial stiffness

The present-day interest in noninvasive analysis of the arterial pulse has grown up from the introduction of applanation tonometry and its application to the cardiovascular system [1]. Applanation tonometry is a specifically physical method, and refers to applanation (flattening) and tonometry (measurement of pressure). When a small section of a spherical structure (such as the eyeball) or a circular structure (such as an artery) is flattened, the tangential forces in the wall are eliminated and the sensor on the flattened surface measures the pressure within (Fig. 1). This is the first noninvasive method capable of accurate measurement of arterial pressure within the artery; and when a high-fidelity micromanometer is used for sensing, as in the Millar device (tonometer SPT-301, Millar Instruments Inc, Houston, Tex.),

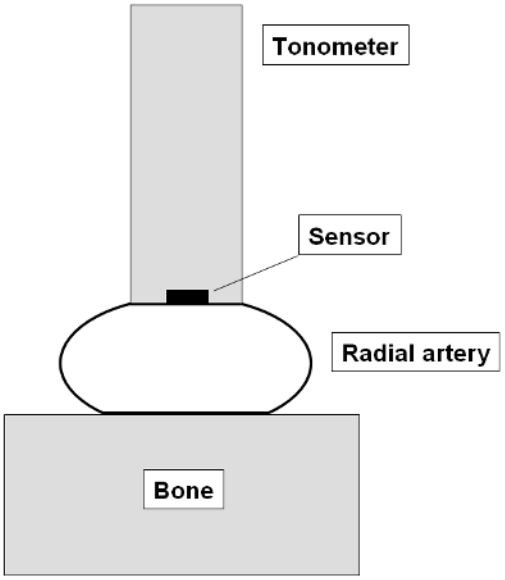

Fig. 1. Applanation tonometry. When the flat sensor of the tonometer flattens the wall of an artery, tangential pressures are eliminated and the sensor is exposed to the pressure within the artery. In these circumstances, accurate waveform recording can be expected. This of course will not apply if the sensor is not applied directly over the artery. The theory of applanation also does not apply if a large sensor is applied over the artery and adjoining structures. The sensor needs to be calibrated against intraarterial pressure to confirm accuracy. Such has been established for the Millar device in the radial and carotid sites [6, 7]. At these sites, the artery is supported by solid structures (bone, or bone plus ligaments) behind, so that applanation can be ensured; that is to say the artery does not move into soft tissue when internal pressure is applied and its surface can be flattened. Several items of information can be obtained from these arteries [1] (see text for details)

also the first method capable of recording accurate details of the waveform [6, 7].

When the tonometer is accurately applied, the following can be expected: (1) a sharp upstroke of the pulse from its diastolic nadir; (2) a steep, uninterrupted rise of pressure to a peak some 10 ms after the foot of the wave; (3) a second, late systolic shoulder between the first peak and incisura; (4) a sharp inflection to identify the incisura, which identifies aortic valve closure; (5) a second pressure rise in early diastole (only when the second systolic shoulder is close to the incisura); and (6) a near-exponential decline in pressure during the latter part of diastole before onset of the next pulse (Fig. 2A). However, in the case of stiffened arteries, the shape of pressure wave changes [1]. There has therefore been much recent interest in the relationship between arterial stiffness (AS; the rigidity of the arterial wall) and cardiovascular disease. AS increases both with age and in certain disease states that are themselves associated with increased cardiovascular risk, including hypertension, diabetes mellitus, hypercholesterolaemia, and end-stage renal failure [8]. There are several different methods of assessing AS, some of which are widely applicable in the clinical setting: (1) the pulse pressure (the difference between systolic and diastolic pressures) is a valuable surrogate marker for AS; (2) the pulse wave velocity (the speed at which the forward pressure is transmitted from the aorta through the vascular tree; (3) pulse wave analysis (PWA) and augmentation index (Aix) [1].

The arterial pressure waveform is a composite of the forward pressure wave created by ventricular contraction and the reflected wave. Waves are reflected from the periphery mainly at branch points or sites of impedance mismatch. Therefore, the arterial waveform varies throughout the arterial tree [1]. The velocity at which

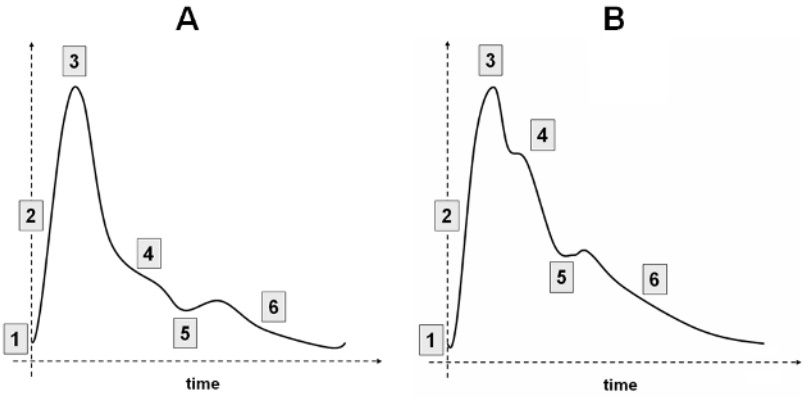

Fig. 2A, B. Radial artery pressure wave. **A** Features of a typical radial artery pressure wave noninvasively recorded by the tonometer in a healthy young subject. *Numbers* represent different points of the pressure waveform [1] (see text for details). **B** Augmentation of systolic pressure in an old patient with stiffened arteries. The augmentation index (*Aix*) is the difference between the first (*point 3*) and second (*point 4*) systolic peaks expressed as a percentage of the pulse pressure. It is a measure of systemic stiffness and is calculated by applanation tonometry [1] (see text for details)

the pressure wave travels through the vasculature is influenced by the stiffness of the vessel walls: the stiffer the walls, the higher the velocity. In elastic vessels, the reflected wave tends to arrive back at the aortic root during diastole, serving to augment diastolic pressure and hence improve coronary artery perfusion. In the case of stiff arteries, the reflected wave arrives back at the central arteries earlier, causing augmentation of the systolic pressure (generating ventricular hypertrophy) and a consequent decrease in diastolic pressure (reducing coronary artery perfusion). The Aix, which is the difference between the first and second systolic peaks expressed as a percentage of the pulse pressure and a measure of systemic stiffness, can be derived from applanation tonometry (also called the O'Rourke PWA system) (Fig. 2B) [1]. A disadvantage of using the radial site for applanation tonometry is that the pressure pulse wave is amplified in transmission from the proximal aorta and the wave contour is altered. This potential disadvantage can be overcome by exploiting the (relatively) constant arterial properties in the upper limbs; these are little affected by ageing, hypertension, drugs and disease in adults. To obviate the need for central catheterisation when measuring this central pulse contour, O'Rourke and associates developed a generalised mathematical transfer function that reconstructs central (aortic) waveforms from their corresponding peripheral (radial) waveforms [9]. With increased AS and wave reflections, more aggressive diagnostic and therapeutic strategies might be appropriate, particularly in younger patients with prematurely stiffened arteries, for prevention of cardiovascular disease.

Pulse contour methods in the intensive care unit

Continuous measurement of arterial blood pressure is an unquestioned part of the haemodynamic monitoring of critically ill patients in the intensive care unit (ICU). However, not only blood pressure but more importantly blood flow, i.e. cardiac output (CO), determines organ perfusion. This is the rationale for implementing techniques that allow measurement of CO in the ICU setting. According to the hypothesis that continuous monitoring of CO and other cardiovascular parameters could allow the detection of sudden haemodynamic changes, which may influence patients' management and outcome, different pulse contour methods (PCMs) have been utilised. The PCMs, unlike bolus thermodilution, which measure CO over a limited time-span, operates on a beat-to-beat basis, and for this reason could be suitable for the continuous monitoring of CO and other cardiovascular parameters.

PCMs and cardiac output: physiological background

PCMs are based on the main assumption, proposed by Wesseling et al. [10], that the pressure rise during systole is related to the systolic filling of the aorta and proximal large arteries [11–13]. This depends on various physical factors: (1) the force of blood ejection generated by the left ventricle, (2) the arterial impedance counteracting the pulsatile blood inflow, (3) the arterial compliance (volume

changes/pressure changes) that permits elastic storage of a portion of the kinetic energy of the cardiac upstroke, and (4) the peripheral vessels' resistance generating backward reflections of the pressure wave depending on heart rate and relative tightening, bifurcations and stiffness of downstream arterial vessels. These variables are closely interdependent and need to be evaluated simultaneously. To this end, a variable called Z_{ao} (the aortic impedance, $mmHg \times s \times cm^{-3}$), representing the relationship between changes in pressure and changes in volume with time, is taken into account for the evaluation of stroke volume (SV) in the various approaches to determining CO by PCMs [10–14]. Pulse pressure is converted to SV by calculating the area (A_{sys}) under the pulsatile portion of the pressure wave: $SV = A_{sys}/Z_{ao}$ (Fig. 3). However, (1) the compliance in the arterial tree is not a linear function, being higher for lower pressure; (2) vascular resistance is not constant over time; (3) pressure transducer systems often suffer from being either under- or over-damped, so that the signal may affect the measurement of arterial pressure; and (4) although the filling of the aorta is on an intermittent pulsatile basis, the outflow tends to be more continuous. These main confounding drawbacks put some limitations on the "ideal algorithm" for arterial pulse contour analysis [14] (Table 1).

Table 1. Characteristics of the ideal arterial pulse contour system

General requirements of a monitoring system

1 Accuracy
2 Reproducibility or precision
3 Fast response time (real time, beat-to-beat)
4 Operator independence
5 Ease of use
6 Continuous use
7 Cost effectiveness
8 Minimally invasive
9 Clear data display and interpretation
10 Real-time afterload, preload, and oxygen delivery
11 Suitability for all age groups: neonates to adults

Specific features of the algorithm

1 The system would work independently of the artery the blood pressure is monitored at
2 It would work independently of aortic nonlinearity and individual variations in aortic characteristics
3 It would be minimally affected by changes in reflected wave augmentation of the arterial pressure
4 It would not rely on identifying details of wave morphology
5 It would be only minimally affected by the damping in arterial lines

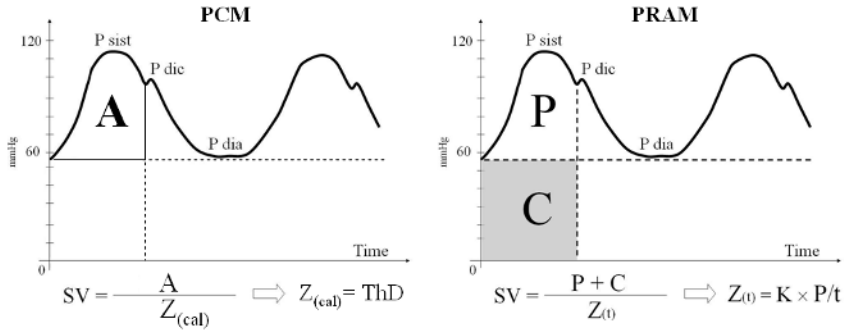

Fig. 3. Algorithms for calculating cardiac output from arterial waveforms. The figure shows the algorithm used by classical pulse contour method (*PCM*; *left*) and the new pressure recording analytical method (*PRAM*; *right*) for calculating stroke volume (*SV*). With PCM, the pulse pressure is converted to SV by calculating the area (*A*) under the pulsatile portion of the pressure wave [10–14]. With PRAM, the pulse pressure is converted to SV by calculating the whole area (*P*+*C*, pulsatile and continuous, respectively) under the systolic portion of the curve [14, 19–22]. *Psys*, *Pdic*, *Pdia* systolic, dicrotic, and diastolic pressures, *Z* aortic impedance, *cal* calibration by thermodilution (*ThD*), *p/t* description of the pressure wave profile expressed as variations in pressure (*P*) over time (*t*), *K* factor inversely related to the instantaneous acceleration of the vessel cross-sectional area (see text for details)

Available devices

There are presently four major methods with which it is possible to calculate CO and other cardiovascular parameters from the analysis of arterial pressure waveform (Table 2): (1) the PiCCO monitor, (2) the LiDCO plus system, (3) the PRAM—Pressure Recording Analytical Method—system, and (4) the Vigileo monitor.

Table 2. Main features of four different pulse contour methods

	PiCCO	LiDCO	PRAM	Vigileo
Artery used	Femoral	Radial	Radial or femoral	Radial
Dedicated catheter	Yes	No	No	Yes
External calibration	Central line	Central or peripheral line	No	No
HR, SV, CO, SVR	Yes	Yes	Yes	Yes
ITBV, EVLW, GEDV	Yes	No	No	No
SVV%	Yes	Yes	Yes	Yes
dp/dt; CCE; CFI	Yes; no; yes	No; no; no	Yes; yes; no	No; no; no
ScvO2	No	No	No	Yes

HR heart rate, *SV* stroke volume, *CO* cardiac output, *SVR* systemic vascular resistance, *ITBV* intra-thoracic blood volume, *EVLW* extravascular lung water, *GEDV* global end-diastolic volume, *SVV* stroke volume variation, *dp/dt* pressure variations over time, *CCE* cardiac cycle efficiency, *CFI* cardiac function index, $ScvO_2$ central oxygen venous saturation

PiCCO Monitor

The PiCCO monitors stroke volume and several volumes using transpulmonary thermodilution (e.g., intrathoracic blood volume [ITBV] and global end-diastolic volume [GEDV], both of which are indexes of preload and extravascular lung water [EVLW], an index of pulmonary oedema). The latest version uses an algorithm that includes analysis of arterial pressure during the diastolic phase to address issues around nonlinear compliance and flow–pressure relationships. According to PiCCO's algorithm the SV is calculated as:

$$\text{cal}\,(A\text{sys}+C(p)\times dP/dt)dt$$

where cal = calibration factor by bolus thermodilution, *A*sys = area under the systolic portion of the curve, $C(p)$ = compliance corrected for arterial pressure, P = pressure, and t = time. PiCCO needs regular recalibration in the event of major haemodynamic changes. PiCCO has been validated against the pulmonary artery catheter (PAC) in several conditions and has also proved to be a reliable tool in ICU and operating room [15, 16].

LiDCO plus system

The LiDCO system measures CO using lithium transpulmonary thermodilution. This approach is not morphology based, i.e., is not a pulse contour method. Rather it is based on the assumption that the net power change in a heartbeat is the balance between the input of a mass (stroke volume) of blood minus the blood mass lost to the periphery during the beat. It is based on the principle of conservation of mass/power and on the assumption that following correction for compliance and calibration there is a linear relationship between net power and net flow. The algorithm overcomes the problem of reflected waves by taking account of the entire beat and uses an autocorrelation to determine what proportion of the change in power is determined by the stroke volume. LiDCO has been validated in several studies and proved to be a reliable monitoring system in different conditions [14, 17, 18].

PRAM—pressure recording analytical method

The most innovative feature of this method is the lack of a requirement for calibration. The algorithm is based on the physical theory of perturbations, analysing the arterial wave using a collecting signal of 1,000 Hz. The most important points on the arterial wave for the calculation are the initial point of the pulse wave (diastolic pressure), the highest point (systolic pressure), and the point of closure of the aortic valve (dicrotic notch or incisura). PRAM uses these and other points of perturbance to take into account the interaction of left ventricle contraction, aortic impedance and compliance and peripheral resistance. With PRAM, the SV is calculated as:

$$A/(P/t\times K)$$

where A=whole area under the systolic portion of the curve, P/t=description of the pressure wave profile expressed as the variations in pressure (P) over time (t);

K=factor inversely related to the instantaneous acceleration of the vessel cross sectional area (Fig. 3). PRAM has been validated in humans and animals, and in cardiac surgery [19–22].

VIGILEO Monitor

The Vigileo system uses a dedicated transducer (FloTrac) incorporated in the monitor. As with PRAM, in this system calibration is not needed, and only an arterial line is required. The algorithm is based primarily on the standard deviation of the pulse pressure waveform:

$$CO = f(\text{compliance, resistance}) \times \sigma_p \, HR$$

where *f* (compliance, resistance) is a scale factor proportional to vasculature compliance and peripheral resistance, σ_p is the standard deviation of arterial pressure, and *HR* is the heart rate. The standard deviation of the arterial pressure is computed beat-to-beat. Compliance and resistance are derived from the analysis of the shape of the arterial pressure wave. Additional parameters, such as the pressure-dependent Windkessel compliance, C_w, based on Langwouters' study [12], and patient body surface area, are also included to take other patient-specific characteristics into account. The Vigileo system seems to be easy to use and accurate, and it provides reliable cardiac output assessment [23].

Preload monitoring and estimation of fluid responsiveness

Haemodynamic instability with low cardiac output in critically ill patients is often caused by hypovolaemia. However, determining the level of preload, and most importantly fluid responsiveness, i.e. predicting whether or not fluid loading will increase a patient's CO, is still very difficult at the patient's bedside. Several studies published within the last 15 years have clearly demonstrated that volumetric parameters such as the GEDV and the ITBV (both by PiCCO monitor) make it possible both to assess cardiac preload and to monitor changes in preload under fluid therapy in critically ill patients much more reliably than the cardiac filling pressures, central venous pressure (CVP) or pulmonary artery occlusion pressure (PAOP) [24–27]. This means that the static parameters (CVP and PAOP) do not allow prediction, prior to fluid loading, of whether or not the intervention in question will increase the patient's CO. Within the last few years, there has been renewed interest in the specific interactions of the lungs and the cardiovascular system caused by mechanical ventilation [28]. So-called dynamic parameters, such as pulse pressure variation (PPV) and stroke volume variation (SVV), all based on ventilation-induced changes in the interactions of heart and lungs, have been evaluated by different groups with a view to improving the assessment of fluid responsiveness, and by this means to optimise fluid therapy in mechanically ventilated patients [29–31]. The rationale behind the parameters SVV and PPV is similar: the alternating intrathoracic pressure during each mechanical breath induces transient but distinct changes—predominantly in cardiac preload—which, according to the Frank-

Starling mechanism, lead to undulations in left ventricular stroke volume (Fig. 4). Thus, each mechanical breath serves as a small endogenous volume loading and unloading manoeuvre. The degree of undulation depends on where on the Starling curve the patient's left ventricle is operating. The Starling (or ventricular function) curve describes the relation between preload and stroke volume [32]. A steep slope of the Starling curve is associated with a large SVV, whereas a shallow slope results in only a small SVV. Thus, high SVV indicates volume responsiveness, or in other words, shows that SV and CO can be improved by fluid loading. Conversely, a low SVV in a hypotensive patient will support the decision to use catecholamines. For example, a value under 10% for SVV implies that the patient probably does not need volume expansion, and a value over 15% implies that the patient probably does need volume expansion [33]. Arterial pulse contour analysis now seems to be a useful method for measuring, again continuously and in an automated fashion, those variations of SV that have a causative role in PPV [29–31, 33].

Finally, the early inspiration augmentation of the left ventricle (LV) stroke output is reflected as an increase in the systolic blood pressure termed delta up (dUp), while the later decrease in LV stroke output is reflected in a decrease in the systolic blood pressure termed delta down (dDown) [33]. The dUp is measured as the difference between the maximal value of the systolic blood pressure and the systolic blood pressure during a long end-expiratory pause or a short (5 s) episode of apnoea, while the dDown is measured as the difference between the reference end-expiratory systolic blood pressure and the minimal systolic blood pressure

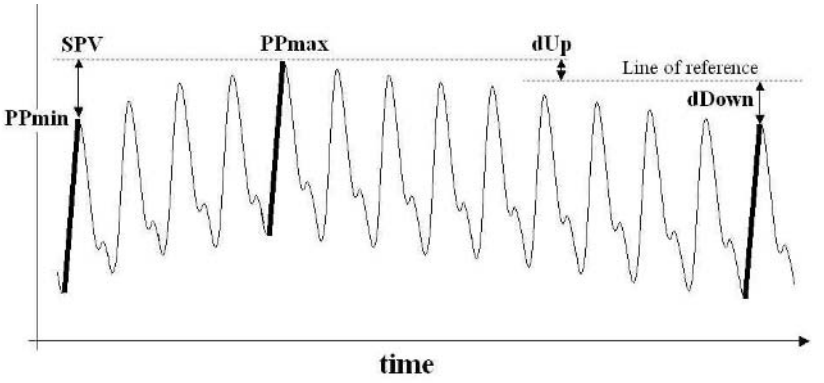

Fig. 4. Respiratory changes in arterial pressure in a mechanically ventilated patient. Pulse pressure (systolic minus diastolic pressure) is seen to be maximal (*PPmax*) at the end of the inspiratory period and minimal (*PPmin*) during the expiratory period. The respiratory changes in pulse pressure (*PPV*) can be calculated as the difference between PPmax and PPmin, divided by the mean of the two values. The delta Up (*dUp*) is the increase in systolic blood pressure, while the delta Down (*dDown*) reflects a decrease in systolic blood pressure. The systolic pressure variation (*SPV*) is the sum of dUp and dDown [25–33]. The line of reference is obtained during a long end-expiratory pause or a short (5 s) episode of apnoea (see text for details)

value. The sum of the dUp and the dDown, which is the difference between the maximal and the minimal systolic blood pressure values during one mechanical breath, is termed the 'systolic pressure variation' (SPV) (Fig. 4). It is important to note that dUp and dDown are two different haemodynamic events: dDown is due to the decrease in venous return during the mechanical breath, and its magnitude reflects fluid responsiveness [33]; dUp reflects the early inspiratory augmentation of the LV stroke output and was originally described as 'reversal pulsus paradoxus' [34]. Since the dUp can be influenced by some partial transmission of the airway pressure to the LV and aorta during the mechanical breath, it may not necessarily be representative of augmented LV stroke volume [33]. Furthermore, variations in stroke volume or pulse pressure may not be as readily attributed to hypovolaemia in the spontaneously breathing patient or in the presence of an irregular cardiac rhythm. As a result, these parameters may not be reliable in a large proportion of critical care patients [35].

Cardiac contractility assessment

Most PCMs provide an indirect measure of LV contractility. They calculate the so-called dP/dt (mmHg/s), a variable based on LV intracavitary pressure, which is generated by an active myocardial stress. Thus, a high dP/dt ratio indicates improved LV contractility, whilst conversely a low dP/dt ratio indicates reduced cardiac contractility. PiCCO also provides the cardiac function index (CFI = CO/GEDV), which represents cardiac performance independently of the preload. PRAM also provides a new parameter, the CCE (cardiac cycle efficiency), which represents the performance of the LV and the ventricular-arterial coupling. The CCE ranges from –1 to +1, with –1 being the worst and +1 the best possible cardiac cycle performance. Recently, in 70 patients who had undergone coronary operations, the CCE measured by PRAM was compared with the LV ejection fraction (EF%) by echocardiography [36]. Overall, the correlation coefficient between LVEF% and CCE values was 0.82 (r^2=0.91, p<0.001), and the correlation coefficients ranged from 0.80 to 0.84 at different points in the study (p<0.001) [36].

Conclusions

Functional haemodynamic monitoring, which allows more detailed insight into cardiovascular physiology and disease than is otherwise possible, might help to improve the detection and the understanding of pathologic cardiocirculatory situations. Theoretically, functional haemodynamic monitoring has the potential to improve the therapeutic management of critically ill patients, and thereby their outcome. Arterial pulse contour analysis is a method that can contribute to this development by (1) transferring information on CO and hence on blood flow on-line, and (2) enabling the direct interactions between the lungs and the cardiovascular system to be tracked continuously during mechanical ventilation [2, 14, 17, 24, 33].

Clinicians today are equipped with several new PCMs that provide for minimally invasive haemodynamic assessment. These monitoring systems are not mutually exclusive; each has different advantages and limitations, and each has something to offer a given patient population, health care institution budget and clinical user.

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Chapter 22

The Utstein style for the reporting of data from cardiac arrest

J.P. Nolan, C.L. Gwinnutt

Healthcare professionals who practise resuscitation come from many disciplines, organisations and backgrounds. In addition, the emergency medical service (EMS) systems in which they work differ in different parts of the world. Survival rates following out-of-hospital cardiac arrest (OHCA) vary substantially between health care systems. A review of EMS with a defibrillation capability that included 33,124 patients reported a median rate of 6.4% for survival to hospital discharge, with a range of 0–20.7% [1]. Summary data from 37 communities in Europe indicate that survival to hospital discharge after EMS-treated OHCA is 10.7% [2]. After in-hospital cardiac arrest (IHCA), the reported survival to 24 h rates range from 13% to 59% and survival to discharge rates from 0% to 42%, although major studies report a survival to discharge of approximately 20% [3–7]. The main reasons for this variation are the many confounders that influence outcome following cardiac arrest (Table 1) and the lack of uniformity in cardiac arrest reporting. This lack of uniformity in reporting pertains to both the process and the results of resuscitation attempts; for example, the definition of survival is reported variously as return of spontaneous circulation (ROSC) and as survival at 5 min, 1 h, 24 h, and discharge from hospital.

Table 1. Confounders that influence cardiac arrest. (Reproduced from Advanced Life Support, 5th edn, Resuscitation Council (UK), London, 2006)

· Differences in the type of emergency medical service system (EMS; e.g. availability of defibrillators, differences in response intervals)
· Differences in the incidence of bystander cardiopulmonary resuscitation (CPR)
· Different patient populations (e.g., a study may be confined to in-hospital cardiac arrests (IHCA) or may include pre-hospital arrests)
· Prevalence of co-morbidities
· Frequency of implementing do-not-attempt-resuscitation (DNAR) policies
· The primary arrest rhythm
· The definition of cardiac arrest used e.g. whether primary respiratory arrests are included)
· Availability of cardiac arrest and medical emergency teams

Why standardise data collection?

The lack of uniformity in cardiac arrest reporting makes it difficult to evaluate the impact of individual factors, such as new drugs or techniques on survival. Thus, if it is intended that it should be possible to generalise from the findings from research studies undertaken in one EMS system it is vitally important that the terminology and definitions used in the reporting of resuscitation events are standardised.

New interventions have been introduced that have improved survival rates only slightly; this is because cardiac arrest is common and kills thousands of people every year. Individual hospitals or healthcare systems are unlikely to have sufficient patients to allow them to identify these subtle effects or eliminate confounding factors. Adopting uniform definitions and collecting standardised data on the process and outcome of cardiopulmonary resuscitation in many patients and systems may make it possible to identify relatively small changes in outcome. Changes in the resuscitation process can then be introduced and evaluated using a reliable measure of outcome. This methodology enables drugs and techniques developed in experimental studies to be evaluated reliably in the clinical setting.

Origins of the Utstein style

In June 1990, representatives from the AHA, European Resuscitation Council (ERC), Heart and Stroke Foundation of Canada (HSFC) and the Australian Resuscitation Council (ARC) attended a meeting, hosted by the Laerdal Foundation, at Utstein Abbey on the island of Mosteroy, Norway [8]. The purpose of this meeting was to discuss problems in resuscitation nomenclature and the lack of standardised terminology in reports relating to adult out-of-hospital cardiac arrest. This was the first major collaborative venture involving resuscitation councils from around the world. A follow-up meeting was held in December 1990 in Surrey, England, where the decision was made to adopt the term 'Utstein style' for the uniform reporting of data from out-of-hospital cardiac arrests [9].

Out-of-hospital cardiac arrest

The first of the 'Utstein' papers was entitled 'Recommended guidelines for uniform reporting of data from out-of-hospital cardiac arrest (OHCR): the Utstein Style' and was published simultaneously in *Circulation*, *Resuscitation* and *Annals of Emergency Medicine* [10–12]. The Utstein meetings each took the form of a series of panel discussions to obtain consensus on definitions and terminology. The audience of experts rotated around series of panels on specific topics. Each panel session was chaired by two individuals; these co-chairmen remained in place and presented the topic to three separate audiences. The first discussion reviewed the evidence and produced a proposal. During the discussion with the second audience, reactions and comments on the draft proposal were sought, leaving the final audience to critique

and refine the final topic statement. The same format has been used in most subsequent Utstein meetings and was the style used during recent resuscitation consensus conferences [13, 14]. The 1991 Utstein paper introduced a glossary of terms used in the collection of cardiac arrest data and proposed a standard definition for each of these terms, e.g., bystander CPR was defined as an attempt to perform basic cardiopulmonary resuscitation (CPR) by someone who is not part of an organised emergency response system. Time points and event-to-event intervals were defined precisely, and a template for reporting cardiac arrest data was proposed (Fig. 1). Recommendations for the description of EMS systems were made.

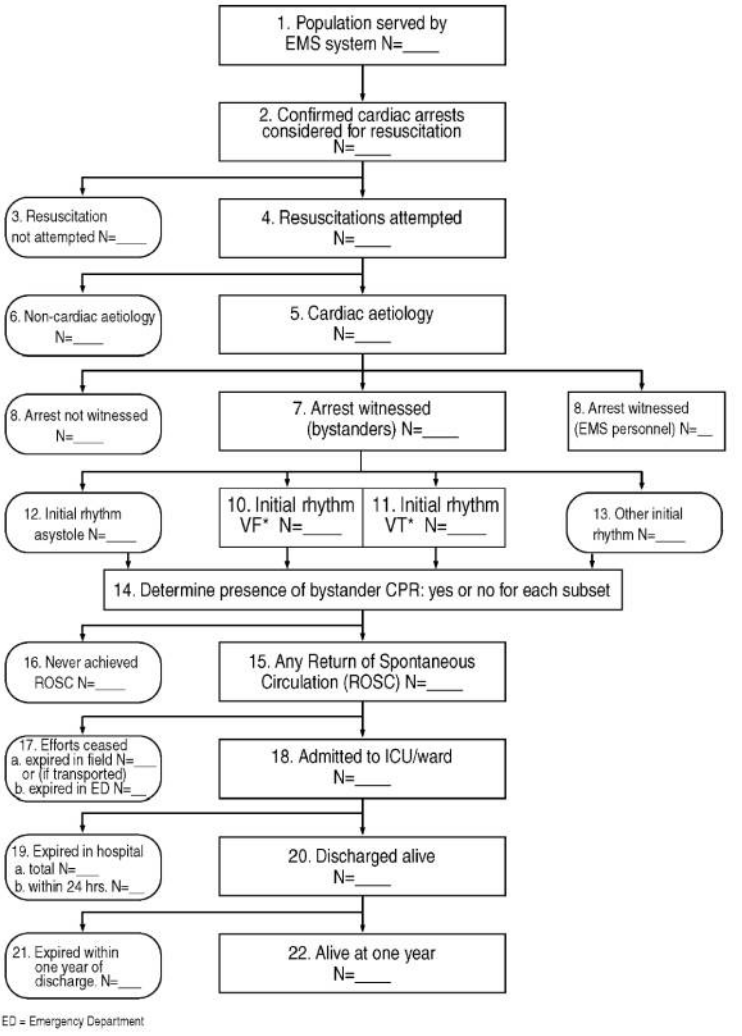

Fig. 1. The original Utstein reporting template for out-of-hospital cardiac arrest [12].

In-hospital cardiac arrest

Using the same consensus process as had generated the Utstein style for OHCA, the same organisations worked together to produce an Utstein style template for reporting IHCA [15–17]. Four major categories of variables were identified for documenting in-hospital resuscitation attempts: hospital variables; patient variables; event variables and outcome variables. The number of data items was substantial—these were classified into essential and desirable in an attempt to simplify the collection of routine audit data.

Revised Utstein template

Despite standardising resuscitation terminology successfully, the original Utstein templates for OHCA and IHCA were not widely adopted. There were several reasons for this: there were too may data items, it was difficult to capture much of the data accurately (e.g. time of collapse) and the focus was on victims of ventricular fibrillation, which accounts for only a small proportion of cardiac arrests in and out of hospital. In 2002, a task force of the International Liaison Committee on Resuscitation (ILCOR) reviewed the Utstein definitions and templates, and a revised version was published in 2004 [18, 19]. This revised version included: identification of 29 core data elements regarded as the minimum required for audit and quality improvement (Table 2); revised and updated definitions of the core data elements; identification of supplementary data required for resuscitation research; identification of core time points and intervals; a revised cardiac arrest data collection form; and a revised recording template for core data elements (Fig. 2). The revised Utstein template covers OHCA and IHCA in both adults and children.

Table 2. The 29 core data elements defined in the revised Utstein template

- Arrest, witnessed
- Assisted ventilation
- Attempted defibrillation
- Bystander CPR
- Cardiac arrest
- Cause of arrest/aetiology
- Chest compressions
- CPR
- Date of arrest
- Date of birth/age
- Date of discharge/death
- Defibrillation attempt before arrival of emergency medical services (EMS)
- Drugs
- EMS
- End of event
- First monitored rhythm
- Location of arrest
- Neurological outcome at discharge from hospital
- Patient identification
- Resuscitation
- Resuscitation attempted by EMS personnel
- Resuscitation not attempted by EMS personnel
- Return of spontaneous circulation (ROSC)
- Sex
- Shockable or nonshockable rhythm
- Successful CPR before EMS arrival
- Survived event
- Survival to hospital discharge
- Sustained ROSC

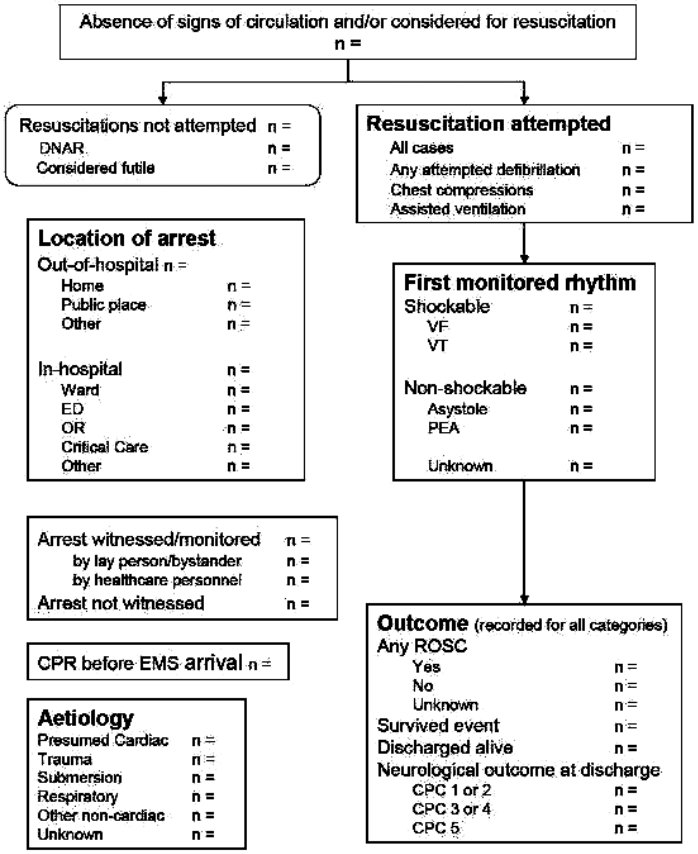

Fig. 2. The revised Utstein reporting template for reporting in- and out-of-hospital cardiac arrest (*DNAR* do not attempt resuscitation, *PEA* pulseless electrical activity) [18].

Although some time intervals are known to be key determinants of outcome (e.g. collapse to first shock in VF), collection of these data is often difficult and inaccurate, because of the urgency of the event and because unsynchronised clocks are in use. In the revised guidelines the number of core time points has been significantly reduced to highlight those that are both meaningful and reliable (Table 3).

Table 3. Core time points in the revised Utstein template

- Time of witnessed or monitored arrest
- Time call received
  - By EMS operator
  - Resuscitation team summoned
- Time of first rhythm analysis or assessment of need for CPR
- Time of first CPR attempts
- Time of first defibrillation attempt if shockable rhythm
- Date of death

Several supplementary times are defined; although they are relatively unimportant in terms of outcome, they do measure process and can therefore be used as indicators of quality assurance.

- Time first emergency vehicle is mobile
- Time vehicle stops
- Time of ROSC
- Time vascular access achieved and drugs given
- Time CPR stopped/time of death

Other Utstein consensus statements

Many other 'Utstein-style' international consensus statements have been published over the last 15 years, including those on uniform reporting of paediatric advanced life support [20], laboratory CPR research [21], in-hospital resuscitation [16], neonatal life support [22], drowning [23] and trauma [24]. It is now widely recognised that the quality of treatment in the post-resuscitation phase is a significant determinant of outcome. Many intensive care units collect comprehensive data on all admissions, including survivors of cardiac arrest. The most recent Utstein-style template standardises the way in which data are defined in the post-resuscitation phase [25]. This should enable meaningful comparison between centres and may help to determine the impact of different treatment strategies (e.g., therapeutic hypothermia) on outcome [26]. An Utstein-style template for the collection of data relating to medical emergency teams is in press.

Cardiac arrest registry

Collection of standardised resuscitation data enables large registries to be constructed. Data from multiple hospitals, from various EMS systems and from many countries can then be collected and analysed. The American Heart Association-sponsored National Registry of Cardiopulmonary Resuscitation (NRCPR) has accumulated valuable data on IHCA from 253 hospitals in the United States and Canada [4, 7]. An internet-based international registry involving several countries has recently been established [27]. The success of this registry shows that it is possible to collect data prospectively describing the structure, process and outcome associated with cardiac arrest at multiple international sites via the internet. Such a registry should make it possible to conduct large, adequately powered randomised trials of resuscitation therapies in several countries simultaneously.

Implementation of the Utstein template

The original Utstein template was undoubtedly difficult to implement because of its relative complexity, and data collection using this tool was uncommon [28]. On

the occasions when it was used, the template was generally applied retrospectively to well-established databases [29]. However, one group of investigators in Finland has applied the Utstein template prospectively over 10 years [30]. Over this period they showed improved survival after IHCA outside critical care areas—the survival-to-discharge rate increased from 6% in the first 5 years to 16% in the second 5 years.

Conclusions

The Utstein template for collecting and reporting resuscitation data has evolved into a valuable tool that enables audit of and research into resuscitation therapies and processes. The revised version is simple enough for widespread adoption.

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Chapter 23

Challenges in trauma care

P.D. Lumb

> The Sicilians never want to improve for the simple reason they think themselves perfect; their vanity is stronger than their misery.
> Giuseppe Tomasi di Lampedusa in *The Leopard*

Health care systems fail to provide treatments that are known to work, persist in using treatments that don't work, enforce delays, and tolerate high levels of error.
Smith R. Change: both desired and resisted. BMJ. 2001;322

Healthcare systems and trauma response teams should work to fulfil the following goals:

No needless deaths
No needless pain or suffering
No unwanted waits
No helplessness
No waste
For anyone

Unfortunately, practitioners find themselves in situations in which these goals are thwarted by numerous conditions, not the least important of which is the system defining their ability to practice medicine.

David Walsh, at the University of Southern California School of Business, has noted that:

Physicians are expected to work collaboratively to maximise patient care, be respectful of one another, and participate in the process of self-regulation, including remediation and discipline of members who have failed to meet professional standards. … Physicians have both individual and collective obligations to participate in these processes. *The obligations include engaging in internal assessment and external scrutiny of all aspects of their professional performance.*

All physicians are familiar with the concept of quality improvement, or as it was formerly titled, morbidity and mortality, conferences as a means of maximising patient care by studying the errors inherent in providing innovative and conscientious care. The paradoxes inherent in our practices, however, include the difficulties associated with being able to distinguish appropriate institutional practices from inherent stultifying practices that resist appropriate evaluation because they are comfortable and mask the necessity for peer review and modification in tradition. There are a number of examples of these paradoxes in trauma and

associated resuscitation paradigms, and this discussion will explore some of these questions in detail. The resource "bundles" from the Surviving Sepsis Campaign are responsible for a number of the questions, and readers are encouraged to access the following website for additional information: www.survivingsepsis.com.

Resuscitation Paradoxes
Cardiovascular
    ACLS/PALS
Trauma/haemodynamic
    ATLS protocols
    Hypotension
    Surviving sepsis guidelines
Cerebral
    Hyperventilation
    Hypothermia
    Barbiturates
End-organ
    Norepinephrine
Pulmonary
    Low (controlled) tidal volume/plateau pressure ventilation
    www.ardsnet.org

Clinicians are undoubtedly familiar with the recommendations and protocols available from each of the organisations sponsoring the protocols cited above; despite familiarity, acceptance of these protocols into routine practice is marginal at best.

At the 2006 SCCM meeting it was noted that compliance with ARDSnet recommendations for reduced tidal volume ventilation in critically ill patients was poor and that the opportunity to reduce ventilator-associated mortality was being ignored in many institutions.

New recommendations from the American Heart Association on ventilation and compression rate have changed the recommendations that should be applied when cardiac arrest victims are resuscitated; how long will it take for these to be implemented?

Data supporting hand-washing as an effective prophylaxis against infection spread has been available since the time of Semmelweiss (1847); nonetheless, central line catheter infections secondary to inadequate sterile preparation remain a significant problem.

Recommendations for brain protection following trauma concerning hyperventilation and maintenance of cerebral perfusion pressure have changed significantly; patients are still hyperventilated in ICUs despite these cautions.

Tight glycaemic control is a recognised technique to minimise morbidity and mortality; its implementation is sometimes difficult and often ignored.

The trauma team faces multiple challenges, frequently requiring rapid and concurrent interventions from a multidisciplinary team, each member of which

must understand the importance of coordinated efforts rather than the primacy of any specific task. It is only by understanding team mechanics, establishing appropriate protocols and rigorous quality improvement systems and engaging in individual patient care debriefing sessions that system improvement and better patient outcome will occur. These changes will require modification of specialist training programmes and of the undergraduate curriculum.

Current requirements in specialist education

From see one, do one, teach one to the core competencies

Specialist education has changed. Training programmes are challenged by more specific, accountable and rigorous accreditation standards than previously. The most significant change is incorporation of the Accreditation Council of Graduate Medical Education's (ACGME) six core competencies into the curricular requirements for education and evaluation of all trainees. This has all been introduced gradually, and the deadline has now arrived for incorporation of these curricular elements into training programmes: beginning in July, 2006, Residency Review Committee (RRC) site visitors will evaluate programmes of specialist training in all disciplines, with the specific intent of ascertaining compliance with the new requirements. "The accreditation focus will be on evidence that programs are making data-driven improvements, using not only resident performance data, but also external measures" [1]. This is a significant challenge for academic departments. The evaluative elements appear fair and reasonable; their execution is the problem.

The apprentice model long ago lost its relevance to medical education, amid the expanding volume and complexity of medical knowledge and technology, the growing complexity of medical and social systems, and the evolving social perceptions of the roles, responsibilities and accountabilities of physicians. From newer models, however, two paradoxes emerge. One, that it is possible for a medical resident to command a great deal of medical knowledge and still not be an effective physician, and two, that it is possible for a resident or fellow to have all the skills necessary to be an effective physician and still not be able to direct these skills towards effective patient care.

The structuring of the domains of medical education into six core competencies in part addressed the first paradox, and the notion that the most appropriate assessment of the outcomes of medical education is the demonstration of actual not potential, clinical performance addresses the second [2].

The ACGME has defined six competencies that define the educational and clinical requirements for trainees across all medical disciplines. Therefore, they define core elements in the maturation of a physician rather than concentrating on the requisite knowledge base and clinical skills of different specialties. They are:

1. Patient care
2. Medical knowledge

3. Practice-based learning and improvement
4. Professionalism
5. Interpersonal and communication skills
6. Systems-based practice

Whilst the first three are quite familiar ground for all physicians who are graduates of currently approved programmes, the rest are new and introduce significant challenges not only into the educational process but also into the manner in which medicine will be practised and taught in future. Of primary concern to programme directors are the methodologies through which the competencies will be taught and, perhaps more importantly, implemented and evaluated. All teaching requires an involved faculty, and the integration of the competencies comes at a time in which many programmes are seeing significant reductions in teaching budgets and greater competition from private sector practices for retaining gifted educators.

Traditional medical education concentrated on the independence of the physician and the priority of diagnosis and therapeutic intervention without the necessity for the intrusion of collaborative practice or recognition that outcome analysis would play a significantly greater and more accountable role with the addition of population-based statistics and process improvement methodologies. Today's physician is likely to have her or his patient care outcome statistics available on publicly accessible websites with variable attention to details of acuity correction. The public focus on "reality" television programmes creates an often difficult comparator for medical systems to meet. The recent HBO Documentary *Baghdad ER* provided a different look at medical care that for some provided a degree of insight into the lives of medical care professionals working under combat conditions. In neither case is the reality of the vast majority of healthcare portrayed, with daily frustrations associated with poor medical information systems, variable patient health maintenance habits, and an increasing volume of literature suggesting that the American healthcare system is perhaps not only overpriced but also underperforming relative to those in other countries. It is in this context that the new paradigms for medical student and resident education must be reviewed.

The involvement of third parties in decision-making may diminish the importance of physician judgment and autonomy, which may lead physicians to conclude that the technical quality of care is suffering. Technical quality was traditionally defined as care that was consistent with community norms—a definition used in malpractice litigation. The move to begin setting national standards with objective criteria based on rules of scientific evidence is quite new and for many clinicians raises the spectre of "cookbook medicine", which implies rigid insensitivity to the needs and characteristics of individual patients. However, once government, insurers, and health plans began moving aggressively towards developing practice guidelines, specialty societies also began developing their own guidelines. These national efforts have fundamentally, and for the better, changed the way quality is defined [3].

There should be little surprise about the fact that the medical educational system needs to change to incorporate new physician performance expectations

that match current physician accountability; the incorporation of Power Point presentations and electronic medical records into the curriculum was easy compared with the behavioural changes required to incorporate the six competencies into specialist training programmes. The change process begins in the undergraduate medical curriculum, and trainees are now exposed to case-based learning models from the first year of medical school. The traditional focus on acquiring rigorous basic scientific knowledge followed by a graded exposure to clinical medicine has been replaced by a less rigorous introduction to core sciences, blended with an approach to learning that parallels the mature physician's learning pattern following medical school. The concept of life-long learning is one that has gained educational traction in recent years, and medical schools have adopted the concepts through small group discussion teams that focus on a clinical problem and seek its resolution through acquiring the requisite knowledge in real time. The specificity of internet search engines and the computer sophistication of the general public has created a situation in which the physician is likely to be dealing with a patient who has detailed knowledge about his or her condition that matches or exceeds that of the provider. This is true for those physicians who do not maintain currency today; tomorrow's physicians will be even more greatly challenged as the availability, specificity and sophistication of medical information increase. The challenges will be exacerbated because of the greater scrutiny under which all physicians are evaluated in the public domain. Outcome accountability will become the norm, and physicians must learn to practise in the rapidly changing paradigm of public access to previously professionally maintained and quality-controlled information.

The educational and behavioural concepts are easy to understand. Their implementation into the curriculum and subsequent individual evaluation and/or remediation are more difficult to accommodate, which is due in large measure to the difficulty of training the trainers. This may be exacerbated in anaesthesiology, because our discipline requires the ability to interface man and machine in a manner seen in few, if any, other specialties. Gas laws, spring theory, electrical circuits and a detailed understanding of physiology are only a few of the areas that may be compromised in the current curriculum. More importantly, today's teachers are, from personal experience, unfamiliar with the teaching paradigms common to medical students, and it will take another generation of trainees to enter academic practice before current medical school disciplines are inculcated into the academic culture. The sceptic may question how academic departments are going to implement a series of training requirements formulated by educational specialists. It is important to note that development of the current requirements involved clinicians working in all specialties, and the "core competencies" must become as much a part of the academic faculty member's vocabulary as of the trainee specialist's. The benefit will be that successful faculty mentors will become better equipped to deal with medicine's future as well as his or her own.

The devil is in the detail. Despite the increasing sophistication of simulation technology, it is inappropriate for procedural skills to be relegated to the nonhuman model, and a clinical apprenticeship in one form or another will maintain its

importance in a wide variety of areas. However, not only will the procedural skills required be taught in a simulated environment, but the variability in techniques and processes in common use today will be reduced and skills relating to currently accepted and continuously evolving clinical practice guidelines will be acquired. Physicians familiar with the current attention to hospital-acquired infections will be aware of the necessity for creating and following the CDC's recommendations for practice guidelines on the insertion and maintenance of central venous catheters. Also, increasing attention is paid by medical staff credentialing committees to monitoring the clinical privileges of its members and their maintenance of certification in a number of procedural activities. The American Board of Anesthesiology has introduced time-limited certification, and today's graduates who enrol in the Board examination process are immediately enrolled in the Maintenance of Continued Accreditation (MOCA) programme, which requires demonstration not only of cognitive skills but also of practice and clinical management skills to maintain certification. This is analogous to the certification and re-certification requirements common for commercial and private pilots. Simulation has become an important tool used to teach not only procedural skills but also behaviours. This is perhaps best seen in the evolution of crisis resource management through an intermediary step of cockpit resource management to its current status as crew resource management (CRM). The fear of "cookbook medicine" could be most critically revealed in the scenarios common to the team performance requirements in many resuscitation, critical care and OR management problems. One institution utilises the Surviving Sepsis (www.survivingsepsis.com) Treatment Bundles to evaluate the success of a resuscitation scenario in its ICU simulation. Success is measured during the course of ICU instruction, and improvement is measured. Additional simulation experience can be valuable in a variety of situations, and the progression from assuming that a new anaesthesiologist is familiar with the functions of an organisation's equipment to a detailed orientation programme that includes specific simulation on all aspects of the OR environment that will be encountered by the practitioner is a likely future requirement. Locum tenens assignments provide an acute awareness of the vagaries and differences in equipment and practice parameters in different departments.

How will today's training requirements impact the future of our profession and its patient care advocacy role? It is likely that simulation will develop as one of the mainstays of medical education. This assumption derives from significant research and practical experience in the aviation industry and supports patient advocacy. The December 2005 ACGME bulletin highlights advances in simulation and provides a number of insights into the technology's increasing importance in resident education. "Understanding the characteristics of a high performing system, therefore, requires research of the context, the development and maintenance of individual skills, the role of high technology, the impact of working conditions on team performance, and the nature of high performance teams. Simulation is an essential tool in the learning and understanding of high performing systems" [4]. In the same edition, Dr. David Leach (ACGME Executive Director) speculates that "[S]imulation is a concrete expression of respect." The main reason to foster simulation

remains respect. ACGME's Committee on Innovation in the Learning Environment has said: "A high quality learning environment enables resident physicians to learn the art and science of medicine and to apply that learning in a monitored and mentored setting within an institution committed to: competency based education and practice; support for professional and personal development of learners, faculty and staff; educational and clinical excellence through continuous quality improvement and innovation. … Every patient deserves a competent physician every time. Every resident deserves competent teachers and an excellent learning environment. Simulation serves both of these core principles. … Finally a high quality learning environment is about respect. Simulation will be part of the redesign of graduate medical education (GME)" [5].

It should be noted that in all discussions involving innovation in GME, the interdigitation of environment, trainer, trainee and healthcare team becomes inextricable. In anaesthesiology and critical care medicine the distinctions become even more blurred; the disciplines require a detailed understanding of the human–machine interface from the perspectives of both practitioner and patient. The routine requirement for utilisation of machinery in patient care is ubiquitous in anaesthesia and critical care, and this makes the specialist training curriculum more challenging and less accommodating of practice-based learning than in some other disciplines. The scientific knowledge base encompasses physics, gas laws, biochemistry, physiology of the patient–machine interface, pharmacology, electrical safety and myriad other disciplines. Knowledge acquisition is rigorous, and practice is well served by use of simulated environments and practice in team skills. Not only do anaesthesia and critical care rely on appropriate application of medical and scientific knowledge, they also require close teamwork and collaboration between multi-professional and multi-specialty partners. The demanding and rigorous nature of the work environments is similar, and the personality of the practitioners concordant. In order to be successful in initiating new educational paradigms, the organisation must align the incentives of the team and its individual components; this is neither an obvious nor a simple undertaking, despite multiple publications and examples of successful innovation in multiple complementary professional environments. Perhaps the most important question remains, Why?

The current system of graduate medical education is outmoded. While many aspects are done well, remain relevant, and can and should be dragged into the world of the future, others need to be radically redesigned. The combination of changes in health care delivery, shortened hospital stays, more home and ambulatory care, variations in care not explained by science, declining reimbursements, and above all, the inexorable and visible failure of the current system to deliver safe care has been described as the "perfect storm". Safer and more predictable care is needed. Paul O'Neill has said that he knows of no other industry that accepts a 38% (or less) reimbursement on amounts billed. Beth McGlynn has said that we deliver care known to be best only 54% of the time. These numbers may be related [5].

Don Berwick reflects this perspective in his 1999 address *Escape Fire* to the 11th Annual National Forum on Quality Improvement in Health Care in the following manner.

In 1998, the American Customer Satisfaction Index rated American's satisfaction with hospitals at 70 percent, just below the U.S. Postal Service (71%) and just above the Internal Revenue Service (69%). Racial gaps in health care remain enormous; a black male born in Baltimore today will, on the average, live eight years less than an average white male. All this happens with per capita health costs 30 to 40 percent higher in the United States than in the next most expensive nation [6]. What is the relevance of these statements to the matter at hand; how do healthcare quality initiatives and recent publications highlighting error rates in medicine relate to the topic of graduate medical education and its necessary reform?

But growing evidence about the frequency of medical errors and a better understanding of how adults learn is forcing physicians to rethink the traditional approach as part of the profession's broad efforts to improve care. Teaching hospitals increasingly are requiring residents to practice their skills on mannequins and other types of simulators, in some cases before ever touching a patient [7]. The relation between education and practice performance is increasingly scrutinised, and the realisation that systems based practice requires excellent interpersonal and communication skills to be successful is now accepted. The role of the physician is becoming one of team participant as well as leader, and like the well rehearsed and coached championship sports team, all aspects of the relationships must be rehearsed and practised and deviations from anticipated behaviours must be accommodated. Despite all the new techniques, medicine remains unique; ultimately the physician accepts responsibility for individual patient care. The more invasive the specialty is, the more intimate and personal the relationship. Paradoxically, anaesthesiology and critical care medicine are some of the most personal specialties, yet they deal with patients who for the majority of the relationship are unaware of the practitioner. This relationship creates special educational challenges because the normal interpersonal feedback loops that help formulate physician behaviour are absent; residents lack a special relationship with patients, and despite the responsibilities associated with the care interface, occasionally the experience is depersonalised. It is important to recognise this situation and to create situations in which residents and other members of the healthcare team integrate more fully into the patient care paradigm. ICU rounds with residents and OR personnel with complementary visits from ICU nursing staff into the OR are ideas that help mitigate the sometimes challenging relationships occurring during patient transfer. Family conferences that include multi-disciplinary and multi-specialty team members are an important component of all ICU relationships and teaching conferences.

Despite the requirements of process and the importance of educational reform, individual physician–patient relationships will remain a critical interface for all trainees. Standardised patients and simulated environments will benefit tomorrow's students; patient care paradigms and the interdigitation of man–machine interfaces into the care of the critically ill will remain an important capability of anaesthesiologists and intensive care physicians. Ultimately, each physician must work solo, and despite the best preparation, the uncertainties of the human condition will make each one's first steps tentative. The continued maturation of the

physician is the goal of primary and continuing (life-long) learning; it remains the responsibility of academic departments to help their trainees bridge this important gap without losing the ability to innovate and create appropriate "escape fires" for their patients and colleagues.

As we review the multiple interfaces of the trauma team in its roles of resuscitation, intervention, primary patient care and maintenance, it is apparent that the foregoing discussion assumes previously unrecognised personal and professional barriers to inefficient performance and execution. The emphasis is on the team approach to management that incorporates all facets of care delivery and understands the importance of a systems-based approach to managing the patient's relationships during the continuum of illness and recovery. This requirement will challenge more traditional teaching paradigms that stress individual accountability and minimise the importance of the core competencies in the aggregate. The future of medical education is exciting; the promise of improved outcomes is great. It is up to us to deliver improvements to the patient and public in order to maximise not only individual benefit but also societal accountability.

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Chapter 24

Advances in trauma care

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The burden of trauma is increasing worldwide [1], but in a very uneven fashion [2, 3]. It is decreasing in the developed world, to the point that trauma surgery as a career is sought by very few surgical residents in the United States [4, 5], while resources are overburdened in the developing world.

Trauma is on the increase in lower income countries, but few advances can be expected where the budget is barely enough to cover day-to-day costs, let alone research into new technologies.

The overwhelming preponderance of blunt versus penetrating trauma, the mainly conservative and minimalist approach to most injuries sustained in blunt trauma and, to a lesser degree, in penetrating trauma [6–8], have blunted a lot of the excitement of trauma surgery, and most trauma surgeons and residents in the United States work mainly on non-trauma-surgical emergencies when on trauma call [9].

Many countries with limited resources, however, are aware of the savings in human lives and expenditure that can be derived from the establishment of trauma systems according to the Guidelines for Essential Trauma Care [10–14].

Indeed, one of the most meaningful advances in trauma care in countries with limited resources has been the will to establish, resource and nurture culture-appropriate trauma systems.

Trauma and war

Wars have traditionally stimulated surgical thinking and advances in trauma management, from the creation of mobile ambulances in the Napoleonic wars through the use of helicopters for evacuation in Korea and Vietnam and the development of vascular surgery for vascular injuries in Vietnam to vascular damage control in Northern Ireland.

A multitude of wars plagued the late twentieth century, but most were fought among combatants that have limited resources and are not at the forefront of surgical thinking.

Prompt evacuation of combatants and civilians and utilisation of the latest resuscitation technology was not available to populations in the middle of a genocide or working in semi-derelict hospitals under constant bombardment, as in, for example, Rwanda, Bosnia and Lebanon. Only when nations with access to expensive technologies, innovative thinking and safe hospitals have been affected

by multiple casualties have new management concepts and new products been discovered.

The lessons learned in Mogadishu and Somalia [15], and popularised in the movie Black Hawk Dawn, led to a rethink of the surgical needs of troops in urban combat, probably in the form of better body armour and immediate surgical availability. These lessons have been relearned and multiplied in the present conflicts in Iraq and Afghanistan [16].

Low-intensity warfare and suicide bombings in Israel led to large numbers of casualties, mainly victims of blast injuries to the torso and proximal limbs.

A search for better haemostasis in the face of overwhelming and complex trauma led to the utilisation of recombinant activated factor VII in situations other than haemophilia, and this has culminated in the present proliferation of studies on recombinant factor VII [17–19]. Mangled limbs from high-energy transfer gunshot and explosions are often life threatening and frequently require a long transportation time in a hostile environment: all bleeding must be stopped immediately, which has led to the re-introduction of tourniquets in the immediate management of partial amputations and severe vascular bleeding [20–24].

Haemostatic products have been tried extensively in military and civilian laboratories, as well as on the battlefield: these include chitosan, fibrin sealant dressings, QuickClot, and poly-*n*-acetyl glucosamine, with new products being developed all the time.

The use of cell-saved blood despite contamination by the GIT contents is not new, but still controversial: in the military context, however, there may be no alternative, and studies have shown it to be safe [25].

The concept of aggressive haemorrhage control extends to the operating room, where for the first time in the English literature new recommendations have lately been made for the management of pelvic fractures, with opening into the haematoma [26].

Lessons learnt from the military

Until 2000, civilian trauma surgery was leading the way in advances, thanks to exposure of the urban battlefields of inner city violence [27]. Hypotensive resuscitation, selective conservatism, damage control and the establishment of trauma systems were among the main developments in this context.

In the military, preparation for conventional warfare became largely obsolete with the end of the cold war in the early 1990s, while the first taste of things to come in a future of asymmetrical, urban warfare scenarios first hit home in Somalia in 1993.

With Operation Iraqi Freedom and, to a lesser extent, Operation Enduring Freedom in Afghanistan, military medicine and civilian trauma care started to have more in common, such as evacuations from confined and hostile spaces and injuries from small arms fire.

In view of the severity of injuries, the number of casualties involved, and the

need for standardised management protocols, military medicine has meanwhile taken the lead in most of the new trends in trauma care [28, 29].

Military research for trauma

A lot of research into how best to deal with military trauma has been carried out at the Trauma Readiness and Research Institute for Surgery (TRRI-Surg), whose motto is: "Learning to Care for Those in Harm's Way".

This Institute has been at the forefront of development of studies capable of addressing the priorities highlighted above, and of studies on the role of profound hypothermia in trauma.

Exsanguination and central nervous system injuries are the leading causes of death in both civilian and military trauma, but haemorrhage is the only one of these that can potentially be prevented in a battlefield scenario. About 20% of these deaths could be prevented if the bleeding could be controlled promptly, and most research has been aimed at reducing the chances of death from exsanguination.

Developments in massive blood transfusion

One of the aims of this research has been to limit the need for massive blood transfusions, since these lead to coagulopathy, acidosis and acute lung injury [30]. In particular, patients receiving older blood had a significantly longer ICU stay, although this did not translate into higher mortality [31]. Massive blood transfusions should therefore be avoided as far as possible; this means that the development of better haemostatic agents and devices to control blood loss must be considered a priority for major trauma.

Even when blood use is limited, however, bleeding leads to fluid resuscitation, which in turn leads to haemodilution and hypothermia, coagulopathy, and more bleeding: it is important to try to prevent hypothermia and the onset of coagulopathy.

Most patients do not need blood during resuscitation, but for those who need it, starting the resuscitation with blood delays the onset of coagulopathy. However, if a lot of blood is given, coagulopathy does nonetheless occur. This is due to the composition of the blood components in clinical use, which end up having a haematocrit of 29%, a platelet count of 88K, and clotting factor activity of only 62%. Furthermore, about 10% of the red blood cells and 30% of the platelets will not circulate and will thus not help in carrying oxygen and clotting.

The key to avoiding all of the above is therefore to minimise bleeding! The new technologies aimed at haemorrhage treatment fall into four groups:

1. Optimal resuscitation fluids
2. Alternative oxygen carrier,
3. Direct chemical haemostats
4. Activated blood coagulation factor VII

Optimal resuscitation fluids

Resuscitation fluids are not completely innocuous, and they may actually potentiate the cellular injury caused by haemorrhagic shock. "Shock lung"/"Da Nang lung", which is recognised as being one of the first descriptions of ARDS, was first described in soldiers undergoing massive crystalloid resuscitation [32].

A number of mechanisms are responsible for the deleterious effects of massive resuscitation. Resuscitation with racemic lactated Ringer's solution (DL-LR) and, even more, with artificial colloids (dextran and hespan) have a pronounced and deleterious effect on neutrophil excitation. Exposure of human blood to isotonic crystalloids and some colloids can cause up-regulated expression of adhesion molecules on the neutrophils.

Natural colloids, such as albumin, do not have this effect, while exposure to hypertonic saline (HTS) has a protective effect that comes about via the causation of suppression of neutrophil functions, even when combined with dextran (RescueFlow).

Substitution of racemic lactate (d- and l-isomer) with the l-isomer of lactate can attenuate the neutrophil activation and alter the expression of leucocyte genes known to be involved in inflammation, cell migration and apoptosis; and in particular it can decrease the extent of acute lung injury.

Fluid resuscitation for combat casualties: consensus conferences

There have been no significant changes in the methodology of fluid resuscitation since the Vietnam War era, and these protocols are adopted mostly from civilian trauma literature, in spite of obvious differences in the tactical requirements of combat care, which clearly makes them inappropriate for combat situations [32].

Prolonged isolation before casualties could be evacuated, restraints on the amount of fluids that can be carried and the need to maintain blood pressure and level of consciousness have encouraged extensive research directed at finding ideal small-volume resuscitation fluid. For this reason, Consensus Conferences have evaluated all available data and made new recommendations, mainly based on basic science findings. The resuscitation strategies currently employed by the U.S. military in Iraq and Afghanistan reflect the changing trends [33]. Modern resuscitation in the combat zones is selective, low volume, and based on colloids, and this might manifest itself in improved survival rates.

The killed-in-action (KIA) rate has dropped markedly to below the historic 20%. An analysis of 470 casualties affecting U.S. military personnel in Iraq (325 KIA, 145 killed by non-hostile action, 2,333 wounded in action, 370 wounded by non-hostile action) up to the end of 2003 reveals a KIA rate of only 12.2% [34].

There is no level I or II data supporting any treatment guidelines, which led to the organisation of three consensus conferences between 2000 and 2001. At the last of these meetings, which was held in October 2001 in Toronto, Canada and which

looked at solutions available in NATO countries even if not FDA approved, a combination fluid (7.5% saline and 6% dextran, hypertonic saline dextran, known as RescueFlow) was recommended as the initial fluid of choice.

Artificial oxygen carriers

More recently, though, exposure to clinical trials that are not yet complete, combined with the aforementioned tendency to establish protocols based on military consensus rather than level 1 studies, has triggered interest in the use of haemoglobin solutions as primary combat resuscitation fluids. Two classes of products can carry oxygen in the plasma, perfluorocarbons and haemoglobin solutions [35].

The perfluorocarbons have various adverse side effects and do not have an oxygen dissociation curve, which means that large amounts of them are needed.

Haemoglobin solutions are derived from expired human haemoglobin (Polyheme and HemoLink) or bovine haemoglobin (Hemopure) subjected to different degrees of polymerisation, such as diaspirin cross-linked haemoglobin (Hem Assist), human recombinant Hob, and maleimide-activated polyethylene glycol-modified haemoglobin [36]. Their effects have been tested mainly as in decrease of allogeneic transfusion, both in trauma and in anaemia and general surgery [37–39]. They do carry sufficient oxygen to support life, but little is known about their toxicities. What is known is that, unfortunately, they dilute coagulation factors and promote coagulopathy, while all cell-free haemoglobins have equally unavoidable toxicities in the form of neurotoxicity and potentiation of infection.

Hemopure

Bovine haemoglobin solutions, known as HBOC or Hemopure®, have been found to improve tissue oxygenation, reverse anaerobic metabolism, decrease bleeding and increase survival over that achieved with hetastarch (HEX) [40].

A more recent study [41] has shown that HBOC resuscitation of swine with severe haemorrhagic shock increases survival over that obtained with hetastarch and does not have increased oxidative potential.

If the experimental results are confirmed in clinical trials, these data suggest that Hemopure would probably be the ideal resuscitation agent, particularly for the resuscitation of combat casualties with delayed evacuation and uncontrolled haemorrhagic shock attributable to solid organ injury.

In South Africa, Hemopure has been administered officially to 336 patients, including 14 acute trauma cases, since October 2002, at an initial dose of 30 g over 1–3 h [42]. Blood was avoided in 176 of the first 200 patients who received Hemopure; the reported nitric oxide scavenging effects were easy to deal with; and recent studies suggest that vasoconstriction may even occur independently of the nitric oxide scavenging [43].

For this reason, HBOC has been proposed as a small-volume resuscitation fluid, with multiply beneficial effects for brain perfusion [44]. In view of its ability to carry

oxygen to areas with very precarious perfusion, it has been confirmed that it is more successful than treatment in the hyperbaric chamber.

There are no alternatives at present for acute reversible tissue ischaemia, and favourable reports have been posted [45, 46].

Haemostatic agents

We have already mentioned that historically about 20% of combat casualties are KIA, with the vast majority of deaths happening before casualties reach a medical facility. Although torso injuries have declined in frequency in recent years because of the use of body armour, the limbs remain a very common (the most common) site of battlefield wounds. Theoretically, haemorrhage from a limb should be considered compressible and controllable with the use of an effective dressing [47].

The ideal method for haemorrhage control should be effective and easy to apply (for a lay person), have a low complication rate and effectively work in areas that are not suitable for application of a tourniquet (e.g. groin, axilla). Although a number of promising haemostatic agents have been tested, there is no clear consensus at present on the optimal haemorrhage-control strategy for combat casualties.

Preclinical studies have been performed to compare promising haemostatic agents in clinically relevant swine models of complex groin injury (transection of soft tissues, femoral artery and vein).

The first study identified a previously unknown zeolite mineral agent (QuikClot, Z-Medica, Newington, CT) as the most effective haemostatic agent. The findings convinced the Food and Drug Administration (FDA) to approve the zeolite haemostat for clinical application in May 2002. This agent was used by the Special Operation units in Afghanistan soon afterwards, with very good results.

It causes a highly exothermic reaction in excess of 95°, causing burns to tissues and to rescuers [48]. The clotting action seems to be due to the absorption of water and gas molecules and is relative to the amount used, the quantity and quality of fluid present and the local ability to dissipate heat [49]. It is supplied in powder form, now also packaged in teabag-like sachets. It achieved 100% survival in swine with complex groin injuries [50] and also in human case reports in the civilian contest, with good results [51].

HemCon™, derived from chitosan (shrimp shells), is supplied impregnated into field dressings; these are quite rigid and unyielding, but effective [52]. Its mode of operation is totally different from that of QuickClot, as it takes effect through activation of the clotting cascade and possibly also has some antimicrobial activity. Both these agents have seen extensive combat application, being issued to every U.S. soldier in Iraq, with good results [53, 54].

More effective seems to be the "Rapid Deployment Hemostat", or Fibrin Sealant Dressing [55, 56], which has been shown in animal experiments since 1997 to improve survival after severe internal injuries and is now being used in combat situations.

Under normal circumstances, new drugs or devices are tested in multiple randomised clinical trails to gather "ideal data." However, large military conflicts create a unique challenge, where decisions have to be made based on the "best available data." Two of the haemostatic agents mentioned here (QuikClot and HemCon) have been used in the ongoing conflict in Iraq. Because neither of these agents had been tested in a large clinical trial in trauma patients, an expert panel was assembled at the Uniformed Services University (21 February 2003) to advise the U.S. Marine Corps. After reviewing all the published and unpublished data regarding QuikClot, the panel recommended its use for the control of haemorrhage that is unresponsive to standard therapy.

Following this recommendation, within a few months this agent was included in the Marine Corps individual first-aid kits, with more than 50,000 units deployed to the Iraqi War theatre, and so far there have been several reports of lives saved by the use of this agent. It has been used in the field setting (carotid injury, traumatic hemi-pelvectomy, vascular and soft tissue extremity injuries), as well as for control of life-threatening, uncontrollable bleeding in the operating room. Although the FDA had approved this agent for external application only, reports of its use in body cavities for the control of life-threatening haemorrhage are now appearing in the literature.

Injuries to the retroperitoneum and paravertebral areas, proximal rib fractures, pelvic injuries, deep injuries to the liver and trauma to the proximal limbs have traditionally been difficult to control: they are also areas that are not protected by bullet-proof vests, either because they are below it or because fragments penetrate through the side openings.

Human studies have also shown promise in the context of abdominal surgery in coagulopathic swine and human patients [57], with a modified rapid-deployment haemostat in damage control lap.

No consensus has been reached yet on the ideal haemostatic agent, since none of the top contenders, such as the dry fibrin sealant dressing, rapid Deployment haemostat, HemCon and QuickClot has yet emerged as clearly superior to any of the others; however, more specific indications for each are being finalised [58].

There is also a new type of European dressing, packaged ready to use and made of equine collagen sponge coated with human thrombin and fibrinogen [59], which seems to be equivalent to surgical suturing and has been developed specifically for major vascular injuries.

Recombinant factor VII

Recombinant factor VII (Novo Nordisk Pharmaceuticals, Princeton, NJ) has been around for almost a decade for use in haemophiliacs with inhibitors, with FDA approval [17]. Despite lack of evidence based guidelines for its use in major trauma, it has been used extensively off-label in an expanding array of conditions.

Recombinant human coagulation factor VIIa has been an exciting new agent for haemorrhage control since its use, followed by miraculous survival in an injured

soldier, was first described in 2000 by Martinowitz et al. [60].

This anecdotal case was followed by animal [61] and clinical [62] work in 2001. The following year saw a proliferation of studies all suggesting that recombinant activated factor VII could decrease bleeding and mortality [18, 19]. This in turn led to a multicentre study, conducted between 2001 and 2003, which showed a decrease in blood consumption in blunt trauma [63]. A new, worldwide, study is now under way.

Recombinant activated factor VII is now being used off label for the prevention of intraventricular haemorrhages in the premature neonate and for postpartum haemorrhage [64] and has demonstrated a significant improvement in mortality among a trauma population admitted to an ICU.

It is becoming common for it to be used in patients with acquired coagulation disorders who need to undergo major surgery [65] and for gastrointestinal bleeding [66] and intracerebral haemorrhages in adults [67], etc.

A recent study by some of the investigators engaged in the first multicentre study, however [68], has led these workers to stress the futility of administering recombinant factor VIIa to patients with a very low RTS and of giving it too late, after the onset of profound acidosis and coagulopathy, and to recommend earlier use for maximal benefit [69].

Much like the Israeli military, the U.S. military has also had a keen interest in recombinant factor VIIa, but so far only animal studies and ex vivo human blood studies have been carried out [70, 71] in the United States.

Its high cost, the limited amount of data collected in randomised controlled trials and the complexity of the clinical situations in which it is used have all combined to limit its use. New data from large clinical series and controlled trials all continue to look promising. Randomised trials of rFVIIa in prostate surgery and intracerebral haemorrhage both showed excellent efficacy and safety in clinically difficult situations.

The large series of trauma patients described by Dutton et al. shows the potential of this recombinant material to limit bleeding in massively transfused patients.

It has become clear from all the above studies that it has markedly reduced activity at low pH, so that its use can appear futile in certain massive haemorrhage situations with uncontrolled shock. It is not known whether a higher dose can compensate for reduced activity, or whether the association of other procoagulants can enhance its actions [72–74].

New devices and methodologies for use in combat

The use of vascular staples

Titanium vascular closure staples are routinely available for elective surgical procedures. They have been evaluated as an alternative to conventional methods. In large animal models of vascular injuries, their use made closure technically less challenging, improved the speed of repair and enhanced tissue healing [75]. This

approach worked very well not only for vascular injuries, but also for other repairs on difficult structures, such as the common bile duct and the ureter. Encouraged by these findings, Rhee et al. have used these clips in trauma patients, with good results [76].

Microwave detector

A portable microwave detector, which utilises electromagnetic waves in the microwave radio frequency, can identify even small pneumothoraces reliably in the field [77, 78].

In animal studies it also detected small volumes of intracranial blood [79, 80].

Developments in the use of tourniquets

Tourniquets have been used since the time of the Ancient Greeks for combat casualties. Their use has always remained part of military doctrine at all levels, but has been discouraged in civilian practice. However, reports from the military that at least 10% of combat mortality is due to vascular injuries distal to the groin and axilla and extensive research into different types of tourniquets have combined to dispel some of the myths.

A recent paper by Dorlac et al. [23] showed that of 14 patients arriving dead or in pulseless electrical activity (PEA) after peripheral penetrating trauma, in 8 (57%) it would probably have been possible to control the bleeding by the use of a tourniquet.

Tourniquets for combat troops are relatively pain free and are suitable for single-handed application (CAT); they must be kept in place until the casualty is evacuated to a safer environment [81]. The best choice seems to be simple surgical latex tubing for self-application, to be replaced by a pneumatic cuff during tactical field care by the combat medic during stage 2 or 3 of combat medical care [20].

As a consequence of the military lessons, tourniquets are being re-introduced to civilian practice.

Trauma registries

The specific contributions of Lt.-Col. Donald Jenkins and Col. J. Holcombe in creating operational theatre trauma registries from the scene of wounding onwards have led to the creation of the Joint Trauma Theater Registry (JTTR). This is the first time that detailed trauma registries have been kept, after the legendary Vascular Registry created by Dr Norman Rich in Vietnam, and for the first time trauma nurse coordinators are employed from the battlefield onwards [82].

From a civilian perspective, the importance of this type of registry is that it allows multiple entry points at different levels and thus lends itself to the management of civilians who are transferred from one hospital to another and are treated by a number of specialists during their hospital admissions [83].

Immediate surgical availability

The Forward Resuscitative Surgical System (FRSS) is a small trauma unit designed to support U.S. Marine Corps members during combat operations. It traditionally comprises one orthopaedic surgeon and two general surgeons, operating one surgical table. It can be set up in 1 hour and carry out 18 major trauma operations in 48 hours without re-supply. It has been found to work best with two FRSS working in tandem with four surgeons and two operating tables, when it produces results comparable to those achieved in a level 1 trauma unit.

It is difficult to tell to what extent this concept would be applicable in a civilian context, where hospitals already exist to serve a resident population. However, situations demanding a high level of expertise may be better served by surgical teams carrying out damage control surgery prior to evacuation, rather than by evacuation of patients still dying of their injuries.

The fact that time is vital in the presence of penetrating trauma is demonstrated by a study from Philadelphia, which demonstrated a 1% increase in mortality for every minute of delay for abdominal trauma patients who were hypotensive on presentation [84].

The walking blood bank

Blood is a very scarce commodity even in the civilian environment, where blood banks can run out of blood at busy times.

The military, with all members vaccinated against hepatitis B and frequently tested for HIV infection, can offer a pool of safe donors. Anecdotally, immediate availability of endless reserves of blood seems to make a difference [85].

Adaptation to the civilian environment might be difficult but would surely not be impossible, and it would be possible rely on patients' friends and relatives if legislation allows impromptu blood donation. High incidences of HIV and hepatitis C can render this service impractical and dangerous, however, and a more modern concept is that of frozen blood products, including packed red blood cells; this new idea in blood transfusion will be utilised more and more in the future [86].

Developments in damage control

'Damage control', a term first used by Rotondo and Schwab in 1993 [87], has usually referred to patients re-operated in the same hospital, usually by the same surgeons, after correction of some adverse factor, such as coagulopathy, hypothermia or acidosis. Patients with ongoing or reactivated bleeding can be taken back to the operating room; more senior help can be summoned without much drama.

There are still unresolved issues, 13 years after its first description: overzealous selection of patients for damage control, prolongation of life in clearly nonsalvageable situations, delays in the application of damage control in very unstable

patients, incomplete control of arterial bleeding and excessive numbers of open abdomens and reoperations, to mention but a few [88].

Almost unavoidable are the sequelae of decreased venous return with abdominal packing, fascial integrity and ventral hernias vis-à-vis the dangers of abdominal compartment syndrome [89], with recent trends encouraging aggressive, early abdominal wall closure with a need for high awareness of the dangers of abdominal compartment syndrome and of the consequences of massive crystalloid resuscitation [90].

Recent developments in damage control aim at better identification of specific categories of patients who will not benefit from damage control or anything else, through near-red spectroscopy and phosphomonoesterases [91], and of those who have not responded to early aortic cross-clamping on resuscitative thoracotomy [92].

It is important to decide early on the intention to carry out a damage control operation, and not only once the triad of coagulopathy, acidosis and hypothermia has already set in: Hirshberg and others have attempted to give some indications based on CT scan acquired bullet trajectory [93], and clearly having some idea of the expected damage to be found in advance might help with decision making.

Experiences in disasters and the rural and military settings have moved the emphasis slightly away from the concept of optimal trauma care to that of minimal acceptable care [94], in such a way that damage control can be applied to these three seemingly different situations with greater peace of mind.

In the military situation, in particular, the initial, life-saving operation will be performed close to the place of wounding and followed by tactical evacuation, the second operation at an operational area level I facility, followed by long-distance transport by ICU aircraft, and definitive or follow-up surgery in Europe and then the United States: no interventions other than supportive care are possible in between, which means damage control must be perfectly executed, without ongoing bleeding, contamination or loosening of dressings.

The lesson from the military on damage control, then, is the need for perfect results appropriate to the different stages [95].

Probably most important, however, are the efforts to decrease the need for damage control in the first place, at all levels of intervention on the injured: prehospital interventions to reduce the pro-inflammatory cascade, reversal of coagulopathy, immediate circulatory optimisation, prevention of hypovolaemic shock, understanding the genetic predisposition of individuals, energetic and controlled prevention and reversal of hypothermia while utilising hypothermia for specific situations, and so on [96].

Cell saving with contaminated blood

The first experiences with auto-transfusion on a large scale date back to World War II, when extensive reinfusion of minimally processed and contaminated blood was practised in some war theatres, with results good enough to lead to the belief that even giving contaminated blood was better than giving no blood at all [97].

More studies were carried out periodically between 1978, when the importance of giving antibiotics was demonstrated [98], and 1998, when antibiotics protected patients even against demonstrated bacterial contamination [99]. Nevertheless, the use of contaminated blood has not taken off in the civilian context or in low-intensity military situations where banked blood is not a problem.

In a prospective controlled randomised study carried out at the Johannesburg Hospital Trauma Unit in 2002, the use of intraoperative blood salvage showed a significant reduction in allogeneic blood use with no effect on infection or mortality [25].

Vascular shunts

Temporising vascular shunts were first described in 1952 [100], but were still considered somewhat experimental by 1994 [101]. In Northern Ireland temporary shunting has been the norm since the early 1980s, with dramatic improvement in survival and amputation rates [102, 103].

They have mainly been used within the same operative procedure, however, while patients are waiting for orthopaedic surgery to be completed. In 1989, the first person reported to have undertaken long-distance air travel with a shunt in a severely ischaemic leg ultimately had to undergo amputation [104].

In the current Operation Iraqi Freedom, extremity injuries predominate, representing 50–70% of all injuries [22], and on the whole result in potentially preventable exsanguination.

Transfers in the current Operation Iraqi Freedom took up to 9 hours before definitive vascular surgery could be performed, with none of the 19 temporary shunts placed in the Theatre Hospital in 6 months becoming dislodged or subject to shunt complications, and succeeded in saving 94% of limbs thus operated [29]. This is particularly impressive in view of the type of injuries seen at present. In a series of 3,057 soldiers evacuated for medical evaluation, 1,524 (50%) sustained battle injuries. Known or suspected vascular injuries occurred in 107 (7%) patients. Sixty-eight patients (64%) were wounded by explosive devices, 27 (25%) were wounded by gunshots, and 12 (11%) experienced blunt traumatic injury. The majority of injuries (59/66, or 88%) occurred in the extremities [105].

This has led to recommendations for temporary shunts to be used routinely in civilian trauma, whether blunt or penetrating, where bony and vascular injuries coexist [106].

Profound hypothermia for lethal shock

Profound shock from blood loss does not respond well to conventional methods of resuscitation. Cerebral ischaemia lasting as little as 5 minutes results in severe brain damage. At present, the modality that most reliably preserves the viability of ischaemic tissues is hypothermia, but its role in traumatic arrest is not established.

Its role after cardiac arrest is far better defined, and its use is widespread, with

temperatures of 32–34°C reached and maintained for 24–48 hours: ironically enough, the use of hypothermia after cardiac arrest was encouraged by the favourable results obtained in trauma animal studies [107].

It has recently been demonstrated in large animal studies that lethal vascular injuries, both above and below the diaphragm, can be repaired under conditions of hypothermic arrest, with >75% long-term survival. The same study also demonstrated that hypothermia could be used successfully even after 60 minutes of normothermic shock and that the surviving animals were not only neurologically intact but also had normal cognitive function. We have already determined that optimal outcome is achieved when profound hypothermia is induced rapidly (2°C/min) and reversed at a rate of 0.5°C/min [108].

Extensive human testing still needs to be done in selected patients at large trauma centres.

Retroperitoneal exploration of pelvic haematomas

Anybody dealing with trauma has to deal with pelvic fractures: they are found in about 9% of all vehicle crash victims, and of these 9% are severe. Only a small proportion; under 5%, require angiographic embolisation of arterial bleeds, and even fewer, hardly more than 1%, require surgery specifically to control pelvic bleeding, especially when there is evidence that the peritoneum has been torn.

The problem with a laparotomy is that it cannot fail to increase pelvic volume and reduce pelvic retroperitoneal pressure [109], and even external fixation probably cannot reduce the pelvic volume by much [110].

Traditionally, the teaching in the English literature has been to avoid opening any large pelvic haematomas found at any laparotomy performed, and to pack on top of the peritoneum. Conversely, liberal exploration has been advocated by many European centres for cases in which a laparotomy has become necessary [111, 112].

There is little controversy, however, about the advantage of starting with angio-embolisation for possible arterial bleeds. It is relevant to note that, whereas about 25% of severe pelvic fractures require a laparotomy, hardly more than 1% of pelvic fractures require a laparotomy to stop bleeding from the pelvis, the great majority being performed for bleeding from liver, spleen, etc. The packing is then inserted into the pelvic cavity, along the pelvic brim, and three large abdominal swabs are used [113] after mobilising the caecum or the sigmoid and the bladder, which are then temporarily re-sutured over packs. The importance of excluding iliac vein injury, either by venography or by direct vision and repair, is borne out in the literature [114]. The abdomen is then vacuum packed, in order to minimise the chance of causing abdominal compartment syndrome [115].

Recent studies from Denver and Los Angeles have introduced this technique to the English literature, although there are still some controversies [116].

Rigid pelvic fixation can be obtained with a C-clamp before or after the operative intervention, via external or internal stabilisation, or sometimes just with the aid of a pelvic binder until internal posterior fixation is possible.

Trauma and intensive care

Trauma patients who are admitted to an intensive care unit are among the most complex and labour-intensive patients, and they have prompted many of the advances in critical care [117].

The practice of performing a CT scan of the chest to map atelectatic, recruitable and nonrecruitable zones has become more widespread, although there is still no consensus on the evaluation of optimal PEEP.

The incidence and the mortality from ARDS have probably declined [118].

However, other than avoidance of barotrauma and volutrauma, and some improvement by prone positioning of gas exchange, no particular technology seems to have shown a clear decrease in mortality, which suggests that a combination of factors must be involved.

Careful attention to limiting antibiotic resistance by administering shorter and more focused courses might help with infection control. Eradication of infection and haemodynamic resuscitation has recently been flanked by new strategies on immunomodulation for better resistance to sepsis. Only activated protein C seems to have any clinical advantage at present, however, and only in patients with very severe sepsis.

The use of low doses of corticosteroid in most forms of shock seems to be replacing the initial aversion to this.

Haemodynamic monitoring has become less invasive, but probably more widespread for this very reason, and it centres around cardiac output monitoring and evaluation of the mixed venous oxygen saturation, both of which are measured by Edwards Medical Life Science Systems: the Flo Trac Vigileo measures the cardiac output through a standard arterial line, with no need for frequent intervention, and incorporates real-time cardiac output and systemic vascular resistance displays. The other measures the $ScVO_2$, a good surrogate for the SVO_2, and one of the preferred assessments of Early Goal-Directed Therapy, but its value has not been conclusively demonstrated in trauma [119, 120].

Cardiopulmonary resuscitation has recently seen some changes and improvements, such as the preference for amiodarone for treatment of ventricular arrhythmias, the use of vasopressin in combination with adrenaline during CPR, and mild hypothermia in the first 24 hours after resuscitation.

In neurosurgery, while intracranial pressure monitoring has become more widespread, more information can now be obtained through tissue oxygen monitoring or microdialysis techniques, while again some hypothermia may be protective to ischaemic brains.

Strict sugar control, steroids and vasopressin in septic shock are becoming better understood and regulated.

Leucodepleted blood, and blood components, judicious use of albumin, greater care with dialysis and diuretics, introduction of protocols and the concept of closed ICUs seem to have had an impact on mortality. Advantages may be derived from the concept of critical care without walls, and from outreach.

Large national studies have defined the roles of prone ventilation, supranormal oxygen delivery, transfusion requirements, ulcer prophylaxis and dopamine, etc.

Prone ventilation for severe lung contusion

The advantages of prone ventilation as an early, prophylactic technique in the management of severe lung contusion and consolidation have recently been widely recognised. Until recently, prone position ventilation was recognised as one mode of ventilation that could improve ventilation, but not affect mortality, in patients with early acute respiratory distress syndrome (ARDS) and acute lung injury (ALI).

Recently, studies on the distribution of ventilation in the prone and the supine position have also made it an attractive option in other conditions than ARDS. It has been used successfully in patients with severe bronchitis [121], for severe hypoxaemia in COPD patients [122] and for early acute lung contusion and aspiration [123].

Guérin [124] recently analysed the reason for the discrepancy between the beneficial effects of the prone position and proven benefits on patient outcome. He found that the prone position could do the following:

- Abolish tidal expiratory flow limitation
- Improve oxygenation of localised infiltrates
- Allow for reducing positive end-expiratory pressure level
- Reduce lung stress and strain

Experimental studies have confirmed that in the prone position there is a more homogeneous distribution of ventilation and less strain on the lungs, and that positive end-expiratory pressure affected ventilation distribution differently in the prone and the supine positions.

One recent large randomised controlled trial of systematic prone positioning of hypoxaemic patients showed less ventilator-associated pneumonia in the prone position. Mortality was not affected, however.

Voggenreiter et al. [125], in a prospective randomised trial on the effect of prone positioning on the duration of mechanical ventilation in polytrauma patients, showed that while the duration of ventilation did not differ significantly, the prevalences of ARDS and pneumonia were significantly decreased, while one patient in the prone and three patients in the supine group died of multi-organ failure.

The significance of the above studies is all the more dramatic because alveolar recruitment is not thought to be as useful in primary as in secondary ARDS, while on the other hand prone ventilation seems to be effective particularly in case of chest CT-proven direct lung injury.

Paediatric and adult ventilation are quite different, but there are studies demonstrating improved gas exchange and oxygenation, and also reduction in mean airway pressure if utilised in the first few hours of ventilation [126].

The prevention of atelectasis itself has been shown to decrease the incidence of ventilator-induced lung injury, by minimising distal airway injury away from the atelectatic regions [127].

In animal studies, Gattinoni et al. [128] have demonstrated that prone positioning delays the progression of ventilator induced lung injury through a more homogeneous distribution of strain.

The fact that prone positioning itself helps with alveolar recruitment has been

highlighted by studies showing the greatest advantage of recruitment after the patients had been prone for 6 hours [129].

Very importantly, Gattinoni et al. [130] showed that patients who responded to prone positioning by decreasing their $PaCO_2$ had better survival at 28 days.

Conclusions

War has reclaimed its supremacy over new developments in trauma care at the beginning of the twenty-first century.

While stricter policing, tougher sentencing and improved economic conditions may have turned trauma units in the United States into centres of excellence for nonoperative management of blunt trauma, for interventional radiology, and for the complex management of the ever-increasing elderly population, the management of penetrating trauma is falling back into the hands of military surgeons.

With thousands killed in action and tens of thousand of wounded in Operation Iraqi Freedom and, to a lesser extent, Operation Enduring Freedom in Afghanistan, the emphasis in the management of penetrating trauma has changed dramatically.

Cost-effectiveness, selective conservatism, best utilisation of limited resources and prospective randomised studies, seemingly suited to the inner city population served by teaching hospitals, have been replaced by practices that place the survival of our own forces' lives above the equivocal findings of controlled studies. It is therefore understandable that consensus conferences have replaced research meetings: clinical practitioners and researchers feel that troops fighting for their country deserve anything which might help them survive.

On the other hand, the useful products that have been introduced even when evidence in their favour is not yet overwhelming are applied by committed and fully trained surgeons, and not by trainees.

The outcome of this change in attitude has been overwhelmingly positive: practices such as the deployment of forward surgical teams, the extensive use of recombinant factor VII, the requirement for oxygen-carrying resuscitation fluids at the scene, the enormous amount of research on haemostatic agents, the interest in auto-transfusion and vascular shunts and the renewed interest in the use of tourniquets, among other things, would probably have taken much longer to become established in a purely civilian environment.

All of the above will in due course be recognised as academically valid after the completion of more prospective, controlled, randomised studies, and in the meantime they may have saved the lives of countless soldiers.

Other innovative ideas, such as packing the retroperitoneum in pelvic fractures and the immediate use of prone positioning in patients it has not proved possible to ventilate, both taken from established European practices, owe nothing to military surgery, but do utilise radical concepts in order to save lives in difficult circumstances.

In summary, current advances in trauma care have revolved mainly around saving valuable lives at all cost, in a scientifically valid but pragmatic fashion.

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PERIOPERATIVE MEDICINE

Chapter 25

Standards of care in operating theatres

F. Grüne, T. Ottens, M. Klimek

Most clinicians develop "routines", "protocols", "standards" or "configurations" for the evaluation and management of diseases they frequently encounter. Especially in anaesthesiology, doctors and nurses are used to working with those standards, dealing with such matters as venous access, spinal anaesthesia and airway management.

Where do these standards come from? In many cases, their first drafts were generated by postgraduate trainees and result from "updates" of the advice of their respected teachers, commands received from their consultants and information gleaned from books and congresses. Later, as these trainees gained the ability and freedom to operate in searching and appraising modes, these standards were continuously modified and developed on the basis of the highest level of evidence the operators could find. Furthermore, such evidence is modified by the values accepted by our patients and by our local hospital conditions. For years we have accepted these local routines or standards or configurations. The process of managing our standards costs us a lot of effort, but we consider the time and energy well spent.

Today we are confronted with more than local routines: We are invited to read and to follow international or national guidelines, clinical pathways, recommendations or disease management programmes—and have the feeling that if we fail to do so this might have bad consequences. Are all of them valid? And what is the role of the "good old standard operating procedure" (SOP)?

This article will give an overview of the "jungle" of phrases, definitions and terms concerning standards. In addition, we will describe how SOP can be developed and implemented.

Definitions/terminology

Every routine, protocol, standard, configuration or pathway for the evaluation and management of illness is based on three questions:

1. What is the best therapy for me (efficacy)? (patient's view)
2. Which therapy has the best evidence and efficiency for him/her? (physician's view)
3. Which therapy is most effective/efficient? (hospital economic view)

Every health care professional will consider these questions, with the aim of

developing the best medical and organisational pathways possible in the conditions pertaining locally.

Increasing shortages of resources in hospitals demand an enhanced economic performance of clinical procedures. This should be achieved by optimising all the work processes involved in the provision of healthcare. Healthcare providers are often confused by the terms used in the field of medical quality improvement. In some countries such terms as "SOP", "guidelines" and "pathways" are defined by medical societies (Table 1) [1–6].

Table 1. Definition of terms

Medical recommendations	Are descriptions of diagnostic procedures or therapeutic intervention. Adherence is not legally mandatory, but well reasonable. Are not systematically developed.
Standard operating procedures (SOP)	SOP can be seen as more specific than guidelines, defined in greater detail. Protocols provide "a comprehensive set of rigid criteria outlining the management steps for a single clinical condition or aspects of organisation".
Clinical guidelines	Are "systematically developed statements to assist practitioners and patient decisions about appropriate health care for specific circumstances" [19, 20]. They are sometimes published by international and national medical societies.
Clinical pathways	Are care paths or managed plans that display goals for patients and provide the sequence and timing of actions necessary to achieve these goals with optimal efficiency [21].

Differences between guidelines and SOPs

When we consider the definitions of SOPs and guidelines we have two distinct components (Table 2): first the evidence summary and secondly the detailed instructions for applying that evidence to our patients [6]. International or national guidelines must be rigorously developed and should pass through an appraisal process using evidence-based medicine criteria. Some authors use the terms SOP and local hospital guideline as synonyms. For the common hospital nurse or physician, nationally produced guidelines still require local adaptation to suit local circumstances and to achieve a feeling of "ownership" in local clinicians, which is a major factor in uptake and use [7].

In their local form, guidelines or SOPs should have three components: a simple algorithm that gives a practical sequence of steps to follow for each patient; an explanation of the content of the algorithm; and a detailed summary of the evidence that supports such advice (Fig. 1).

Table 2. The two distinct components of any guideline

	Evidence component	**Detailed instructional component**
Bottom line	"Here is the typical effect of this diagnostic/therapeutic/preventative intervention on the typical patient"	"Here is exactly what to do / not do with this patient!"
Underlying requirements	Validity; importance; contemporariness	Local relevance
Expertise required by those executing this component	Human biology, clinical sciences, consumerism, database searching, clinical epidemiology, biostatistics	Clinical practice; local patients' values; local current practice; local geography; local economics; local sociology; local politics; local tradition
Site where this component should be generated	Clinical guideline: national or international	Standard operating procedure: local
Form of output	Level of evidence	Grades of recommendation and detailed instructions, flowcharts

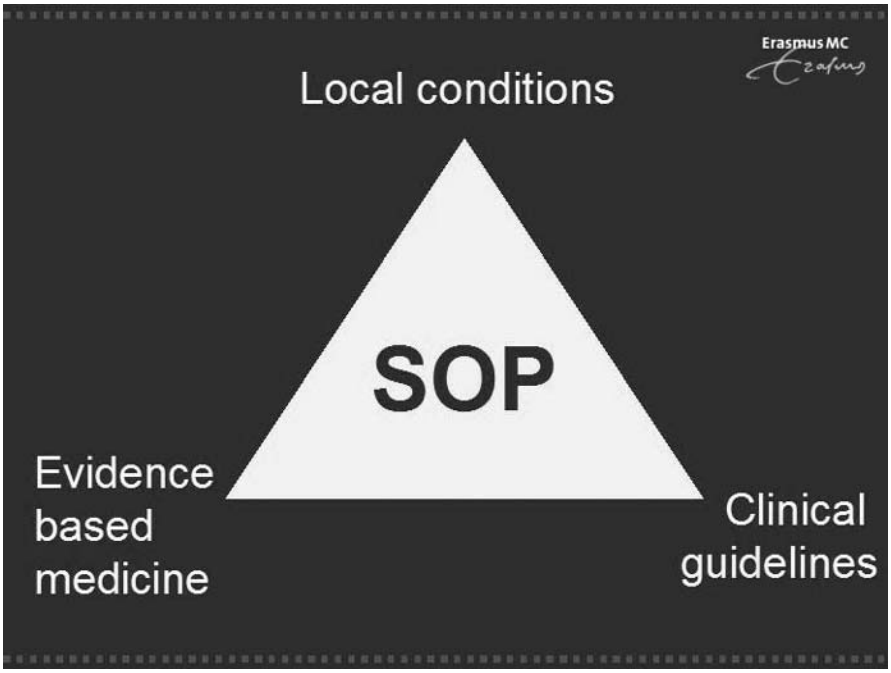

Fig. 1. What is a Standard Operation Procedure (SOP)?

SOPs are a modular instrument of clinical pathways

Clinical pathways should only be defined by departments that are responsible for organising and providing healthcare services for the patient from the point of hospital admission to discharge. They must be developed in a multidisciplinary approach and with close cooperation between the different specialties and professions involved. The SOP is an instrument that is included as one module in a clinical pathway (Fig. 2) [8, 9].

Legal and political consideration of SOPs

When they read SOPs or national guidelines, physicians and nurses are often concerned about their legal status.

1. Are guidelines advisory or mandatory?
2. Do doctors who deviate from guidelines place themselves at increased risk of being found liable for negligence if patients suffer injury as a result?
3. Can compliance with guidelines protect healthcare workers from liability in such circumstances?
4. What legal responsibility do the developers and issuers of guidelines have if their guidance is found to be faulty?

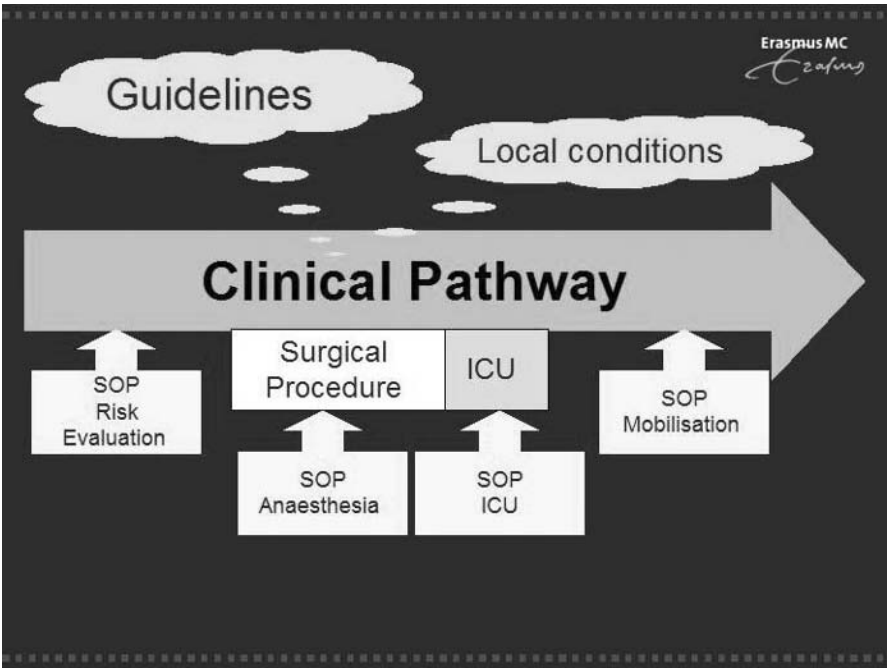

Fig. 2. SOP as a modular instrument of clinical pathways

In a case of medical malpractice, judges and lawyers are looking at medical and organisational aspects of wrong diagnostic or therapeutic procedures. Courts have to assess the applicable standard of care, the causation (the connection between the alleged wrongful conduct and the harm suffered by the plaintiff) and the damage, which often involves a medical prognosis.

Medical expert testimony helps the court to ascertain what is accepted "state of the art" and proper practice in a particular case. The definition of state of the art is based on medical textbooks, and the expert should be a graduate in a medical specialty.

International experience shows that guidelines or SOPs are regarded as "just another form of expert evidence" [10].

For consideration of the state of the art in medicine in the future, printed medical textbooks will be replaced by internet-based knowledge resources. Medical societies are asked to develop guidelines based on the best evidence. When the organisational aspects of medical malpractice are considered, hospital boards will be asked to define their clinical pathways so as to reduce the frequency of adverse events consequent on negligence.

For example: A young doctor fails in an attempt to intubate a patient. Hypoxia leads to cardiac arrest and death. In this situation the medical expert would be able to explain to the court the state of the art in difficult airway management and resuscitation, basing this explanation on the guidelines of the American Society of Anesthesiologists or the European Resuscitation Council. The defendant doctor would explain why a specific action was taken, or why one was not. If clinical guidelines are meant to enhance the quality of clinical care, then the courts might enquire why such guidelines were not followed and whether a decision not to follow them was reasonable. But the judge would also ask the hospital board about the organisation of resuscitation officers and the level of education among young doctors and the support available to them, and whether SOPs were in place in the hospital concerned.

Effectiveness of SOPs

In contrast to the relatively limited data and review of clinical pathways, there has been more careful appraisal of clinical protocols and SOPs in the medical literature. When we consider the steps in a patient's journey through the operating department, it is obvious that SOPs are aimed at improving the process quality and patient outcomes (Table 3).

The product of an operation theatre—the surgical procedure performed on a patient successfully, time-efficiently and without complications—is based on three relevant processes:

1. Technical process (instruments, equipment, rooms)
2. Organisational process (workflow, time, methods of work)
3. Social process (knowledge, skills, attitude, motivation, level of cooperation).

On the basis of these processes, the operating theatre management team can and should produce:

1. SOP for the process (steps in induction of anaesthesia, steps in surgical preparation)
2. SOP for the organisation (set of surgical instruments, operation room equipment, teamwork)
3. SOP for calculation the costs (cost of hospital staff, instruments, medicine).

This means the clinical pathway–SOP system has the following advantages in operating theatres [11]:

1. Optimised process
2. Implemented best evidence-based medicine
3. Cost-effectiveness
4. Improved education
5. Improved induction of new hospital staff
6. Integrated quality control
7. Transparency
8. Protection from malpractice

Table 3. Patient's path through a surgical department and the role of SOP

1. Risk evaluation	SOP for cardiac evaluation, preoperative beta blockade
2. Preparation prior to the surgical procedure	SOP for preoperative antibiotic prophylaxis
3. Admission to the operating theatre	SOP for preparation prior to operation
4. Induction of anaesthesia	SOP for anaesthetic technique
5. Surgical procedure	SOP for instruments, disinfection, technique
6. Postoperative care	SOP for pain therapy, PONV
7. Discharge from the operating theatre	SOP for report

Local guidelines or SOPs lead for example to a significant improvement in preoperative antibiotic prophylaxis. Wolters et al. demonstrated that the percentage of cases in which antibiotics were indicated but not administered was reduced from 15.5% to 8.4%. Compared with the result of the retrospective analysis, the prospective study showed a significantly higher percentage of adequately administered antibiotics (35.7% vs. 63.5%) [12]. Even in such difficult situations as weaning from mechanical ventilation the use of SOPs was effective [13]. Rivers et al. provided impressive evidence of the beneficial effect of early goal-directed therapy for patients in septic shock when emergency department care was carried out according to a predefined SOP or protocol. The in-hospital mortality rate was 38% in the early goal-directed protocol group and 59% in the standard care group (P=0.009) [14].

Introducing SOPs in your hospital in ten steps

Development of SOPs is a structured process [15]. The management team of an anaesthesiology department should ask questions covering matters ranging from the choice of topics through authorisation and membership to the form of reports to be submitted (Table 4).

Table 4. Developing SOPs in 10 steps

Step	Question
1. Choose your topic	Which topic is most important and most urgent? Which are our high-cost diagnoses or procedures? Are our nurses and doctors interested in a solution? Is the topic measurable?
2. Authorisation	Who will give us support? Every working group needs support an approval from the board of the anaesthesiology department (anaesthesiological topics) or from the board of hospital directors (multidisciplinary topics). This is especially needed in the phase of SOP implementation, in order to break down obstacles.
3. Team	Should we invite everybody? It is important to develop a multidisciplinary team for development of critical SOP or pathways. This means including representatives of all groups that would be affected by the pathway (house staff, physiotherapists, dietitians).
4. Moderation	Do we expect conflicts among professionals? How difficult is the topic? Moderation should be: neutral and goal orientated. For difficult topics external professional moderators are advisable.
5. The power of the first meeting	The first meeting should consider several points: Introduction to auditing Rules of communication Visions and goals (top-down) Expectations and perceptions (bottom-up)
6. Scheduling	When will we reach what? Workgroups on SOP should work in a goal-orientated manner with predefined period of times to reach their goals
7. Set standards	What is the best evidence? Do we have national guidelines? What are our local conditions? After developing SOPs the team has to define the period of validity (2 years)!

8. Evaluation	Measuring what and for how long? The SOP team has to define indicators. These could be factors of outcome, differences in time or number of personnel. They should follow R.U.M.B.A. principles: **R**elevant for the selected problem **U**nderstandable for providers and patients **M**easurable with reliability and validity **B**ehavioural, i.e. changeable by behaviour **A**chievable and feasible
9. Implementation	Which implementation techniques are suitable for my hospital? Systematic reviews of rigorous studies provide the best evidence on the effectiveness of different strategies to promote the implementation of research findings Consistently effective interventions are [22]: Educational outreach visits Reminders (manual or computerised) Multifaceted interventions (a combination that includes two or more of the following: audit and feedback, reminders, local consensus processes, or marketing) Interactive educational meetings (participation of healthcare providers in workshops that include discussion or practice)
10. Reports	What, when and how? SOPs could be published on paper or on internet/intranet. It depends on the level of implementation All SOP must be coded. The code should include: SOP number, version and period of validity!

The most urgent and important topics for SOP development can be found in risk factor studies relating to anaesthesia management. Arbous et al., in a case-control study, described an incidence of 24-h postoperative death of 8.8 (95% confidence interval 8.2–9.5) per 10,000 anaesthetics. After multivariate analysis they identified equipment check, direct availability of an anaesthesiologist, presence of an anaesthetic nurse and no intraoperative changeover of anaesthesiologist as factors associated with a decreased risk of death [16]. Kendall et al. showed that 60–82.5% of machines checked had at least one fault, and 11–18% of these were deemed serious [17]. Montasser cited another example of identified malpractice. Based on the standards of the American Society of Anesthesiologists (ASA), a spreadsheet was developed for documenting features of pre-, intra- and postanaesthetic care. The spreadsheet enabled the researcher to document all equipment, supplies and personnel involved from the preanaesthetic evaluation to discharge. Even in developing nations this evaluation of structure, processes and outcome of anaesthetic practice has improved the identification of risk factors leading to perioperative death [18]. All these findings support the need for SOPs used as modules in clinical pathways.

Conclusions

1. Standard operating procedures (SOPs) are a vital component in any quality management system. Written instructions on standardised processes provide guidance to ensure that activities are conducted in a consistent way, leading to reliable product and service quality. SOPs should be prepared in full compliance with guidelines and regulations and must mirror current organisational practices.
2. SOPs can and should be used to decrease variation in care, improve guideline compliance, and potentially improve overall quality of care.
3. Development of SOPs should follow a structured and transparent process.
4. Implementation of SOPs should be backed up by a mixture of dissemination techniques (manuals, intranet, interactive educational meetings).

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Chapter 26

Audit

M. Klimek, F. Grüne

In 1993 the United Kingdom's National Health Service (NHS) formally introduced "Clinical Audit" as a quality improvement process. The idea was to improve patient care and outcomes by reviewing (i.e. auditing) current performance of, for example, a department against explicit criteria and implementing changes where necessary. In simple words, the key component of audit is to ensure that what *should* be done *is being* done; and if not it provides a framework to enable improvements to be made.

During the Crimean War of 1853–1855 Florence Nightingale performed one of the first clinical audits ever, when—shocked by the high mortality among the young soldiers—she applied strict sanitary routines and standards of hygiene to the equipment, leading to a decrease in mortality from 40% to 2% among her patients, which she carefully documented. Based on these numbers, she finally succeeded in convincing the British government to make sanitary routines mandatory for the care of the wounded patient.

In the paper "Principles for Best Practice in Clinical Audit" the National Institute for Health and Clinical Excellence (NICE) defines clinical audit as "a quality improvement process that seeks to improve patient care and outcomes through systematic review of care against explicit criteria and the implementation of change. Aspects of the structure, processes, and outcomes of care are selected and systematically evaluated against explicit criteria. Where indicated, changes are implemented at an individual, team, or service level and further monitoring is used to confirm improvement in healthcare delivery" [1].

In the United Kingdom's healthcare system, clinical audit is one part of the "Clinical Governance" project, a project intended to improve the standards of clinical practice in all fields of care. Other aspects of Clinical Governance are clinical effectiveness, research and development, openness, risk management and education and training.

Audit and research—what audit is, and what it isn't

- Clinical audit is all about the quality of care given to patients [2]. It involves asking questions such as:
- Did we give the best available treatment? What are we trying to achieve?
- Did we deliver that treatment in the best possible way? Are we achieving it? Why are we not achieving it?

– Did our treatment benefit or harm patients? Did we make things better?

Clinical audit is not the same as research; neither is it just about counting things. Clinical audit and research are closely related but distinct disciplines. Research is about creating new knowledge about whether treatments work or whether one treatment works better than another. Clinical audit is about making sure that this knowledge is being used to best effect. Clinical audit and research can both look at the outcomes of treatment, but for different reasons: Research might observe outcomes to find out whether a treatment works whereas clinical audit might monitor outcomes to ensure that best practice is producing the results we know (from research) that it should. The process of conducting clinical audit sometimes identifies areas where new research is needed. It may be expected for the future that multi-professional team-working between researchers and health care practitioners undertaking audit will represent an important step in establishing the necessary synergy needed between audit and research [3]. In short: "Research is concerned with discovering the right thing to do; audit with ensuring that it is done right [4]" (Table 1).

Table 1. Differences between clinical audit and research [5]

Clinical audit	Research
Based on facts (standards)	Based on hypotheses; creates new knowledge
Each patient receives the same care	May involve randomisation into different treatment groups, including placebo group/s
Informed consent might be required	Informed consent always required
Results usually apply to the local population	Results are often generalisable, that is, they may influence widespread clinical practice
Methodology is less stringent than in research	Rigorous methodology and extensive statistical analysis
Typically do not require ethics approval, but should abide by an ethical framework	Always require ethical approval from the local or national ethics committee

Auditing structure, processes and outcomes

When auditing, say, an anaesthesia department, we can look at different aspects of care:

Structure is defined as the resources that are available. Examples of these are the ventilators and monitors in the operating room (OR), but also the staff members working in the department, their level of training and experience, the existence of a recovery room and its staffing and much more.

Processes are the pathways followed, the procedures performed, such as the way epidural catheters are inserted, the level of supervision of the residents (which can be limited by a structural shortage of staff members) or the use of a checklist for discharge from the recovery room.

Results can be measured in different ways, such as by the number of procedures performed, the amount of resources used to perform this number, the frequency of dental damage during intubation, the percentage of failing brachial plexus blocks or the percentage of central venous catheter infections on day 3 after insertion.

All these examples (and many more!) can be addressed by an audit, which—if performed in different hospitals and departments—makes benchmarking between the departments possible, which might be threatening to some. However, benchmarking is considered to be one of the most important criteria used by healthcare insurances (which want their members to be treated in the best possible way) and the government (which has national responsibility for the quality of healthcare) when deciding about investing in a certain department or hospital.

The effects of auditing

Auditing is one possible starting point for a change-management process: a problem is addressed and identified, and the people who have to deal with this problem get concerned about it. This will result in the intention to solve this problem by means of intervention. This intervention will influence daily routines, which finally will have a great influence on behaviour, attitude and culture in hospital staff. A diagnostic treatment or an operation can been done on the basis of the highest evidence level and without complications but not be effective. Disturbed relationships are common between doctors and nurses or surgeons and anaesthesiologists. Auditing in a multiprofessional setting can improve the culture of communication [6, 7]. However, one should be aware that creating a change in culture takes much longer than making a change in daily routines (Table 2).

Table 2. Audits improve changes in daily routine and in hospital culture

Changes in daily routine	Changes in hospital culture
Improvement of care	Improvement of multiprofessional acceptance
More effective and more efficient production	Definition of work and workflow for each professional
Development of standards or guidelines	Working for multiprofessional aims
Increasing responsibility for quality and cost of care	Changes of attitude towards colleagues
	Reduction of interpersonal conflicts
	Improved rules of communication

Clinical audit - the process

Clinical audit is a kind of cyclic process, which can be described in six steps [8]:

1. Identify the problem/issue to be audited
2. Define the criteria and standards
3. Observe the practice and collect data
4. Compare the performance measured with the given standards and criteria
5. Implement a change
6. Do a re-audit after an agreed period

These six steps need some more highlighting to be well understood:

Identify the problem/issue to be audited

The selection of an audit topic will be influenced by earlier studies that have been shown to produce best outcomes for patients. In this case, measuring of adherence to recommended procedures/protocols will be one issue of the audit. When looking at recent studies dealing with improvement in perioperative care, this can be in the field of structure (e.g. is every OR equipped with pulse-oximetry? Is there a recovery room available 24/7?), in the field of processes (e.g. how many patients with known risk factors receive beta blockers perioperatively? How many patients are seen by an acute pain team postoperatively?) and in the fields of results (e.g. is the length of hospital stay after hemicolectomy comparable to that in other hospitals? Is the success of in-hospital reanimation comparable to that in other hospitals?). Of course, the findings in any of these fields can lead to the implementation of a change-project in another field, too: for example, bad results might be influenced by better structures and better processes.

Besides the comparison of daily practice with current standards and practice guidelines, the selection of an audit topic can also be influenced by other factors, including recommendations from the government or other authorities, acute problems encountered in clinical practice and areas of high volume, high risk or high cost in which improvements are possible (Table 3).

Table 3. Points to consider when formulating audit objectives

Effectiveness	Is the treatment being administered correctly and does it have the desired effect?
Efficiency	Is this approach achieving the desired outcome with minimum effort, expense, and wastage?
Equity	Do all patients have equal access to care?
Accessibility	Is it easy for patients to get appointments with general practitioners?
Appropriateness	Is this the right management strategy?
Acceptability	Is the treatment acceptable to patients?
Timeliness	Is the care provided at the correct time?

Define the criteria and standard

Criteria are defined as a measurable outcome of care, aspect of practice or capacity, whilst the standard is defined as the threshold of compliance for each criterion. In intensive care medicine, for example, a *criterion* might be: tight glycaemic control of the patients and the *standard* might be set at: more than 90% of the patients with blood glucose no higher than 8 mmol/l during their stay in the ICU. The leading questions when defining the criteria and standards are: What should happen as a result of the audit? And: What question do you want the audit to answer?

Remember that standards have to be SMART! This means Specific, Measurable Achievable and Agreed, Relevant and Theoretically sound.

Observe the practice and collect data

To avoid unnecessary data collection and to gain high data precision, the details of the data collected must be defined before starting the audit process. This definition should include: The population observed, the period observed, the care providers involved and all possible exceptions. Also confidentiality and privacy (of the patient *and* the health care practitioner!) issues should be addressed; in case of doubt a consultation of the local ethics committee is strongly recommended. Some data are available in hospital information systems, while others need to be collected manually using special registration forms.

Compare the performance measured with the given standard and criteria

This step can be summarised as analysis, finally resulting in the conclusion on how well standards were met and, if possible and applicable, identifying reasons why the standards were not met in all cases. There are two options in looking for such reasons: the reason might be considered acceptable, in which case this will form another exception criterion for definition of the standard in future, or it will suggest a possible improvement project. If the standard is not met 100% in all cases, results close to 100% suggest that further improvement will be difficult to obtain, but—depending of the topic (think of a "life-and-death" question)—it might nevertheless be important to make the effort it will require. In general, results further away from 100% must be considered to be the main target points for improvement projects.

Implement a change and do a re-audit after an agreed period

The results of an audit must be discussed and (at least inside the organisation audited) published. Based on these findings a change plan must be implemented, and recommendations for change should be made. It is important to record who has agreed to do what and by when. Individual responsibilities and an agreed timescale are mandatory parts of such a change project. Sometimes the results

make refinement of the audit tool necessary, for example, if the audit results in criticism of other departments or individuals not involved in the actual audit process, a new joint audit has been shown to be more profitable. For this important organisational issues the implementation of a clinical audit lead and manager must be strongly recommended (as it is in the UK) [9].

After an agreed period the effects of the change-project should be re-evaluated by a re-audit. The same steps must be taken again, resulting in a re-audit that demonstrates successful implementation of the changes and improved adherence to protocol. This step is considered to be critical for successful outcome of an audit process, giving direct feedback to all care-providers and finally resulting in a cultural change, which means deep implementation of a new/different way of working inside a department/hospital/organisation. It should not remain unmentioned that sometimes second and third re-audits are necessary for optimal performance to be reached.

Clinical audit in anaesthesiology

There are some small examples showing the use of audit in anaesthesiology: Recently the first national audit conducted by the Royal College of Anaesthetists was published. The anaesthetic audit coordinators had chosen the topic "supervision and responsibility" and analysed the availability of a consultant in different settings in UK hospitals [10]. The results show many interesting aspects: many consultants find the conflicting demands of service and supervision difficult. Many of them work in systems that do not permit direct, immediate support to those supervised. However, whilst most anaesthetists think supervision is very important, around half of them disagree with the national guideline stating that every NHS patient should have a named consultant. These few, summarised results give a great example of the possible impact of an audit: you might think about the structure, the amount of staffing needed to work in accordance with the national guidelines. You might think about the processes, how the staff organise their supervision and their daily workload, and you might think about a new research project and whether the outcomes in the badly organised hospitals are really worse than elsewhere. This might be interesting, because low adherence to and disagreement with the guideline was observed.

Another study has demonstrated the value of clinical audit in the establishment of acute pain services [11]: the authors performed a survey of current practice in different hospitals, implemented an educational programme for staff and patients on pain and its management combined with formal assessment of pain and an algorithm to allow more flexible, yet safe, intramuscular opioid analgesia and, after that, a repeat survey of clinical practice. They found a marked reduction in the proportions of patients experiencing severe pain at rest and on movement: from 32% to 12% and from 37% to 13%, respectively.

A third published audit deals with the successful implementation of measures to prevent perioperative hypothermia [12]: in this study the authors demonstrated

that the more frequent use of intraoperative measures to prevent hypothermia (heat and moisture exchanger, circle breathing system, foil hat, forced air warmer) led to a highly significant ($P<0.0001$) increase in core temperature on arrival in the recovery room from 35.5°C to 36.6°C, although on average the procedures lasted about 20 min longer (154.7 vs 133.5 min) in the second audit.

These three examples show different aspects of the (possible) impact of audits in anaesthesiology on structures, processes and outcomes. There are many unsolved problems in daily anaesthesiological patient care, which should also be addressed!

Clinical audit in intensive care medicine

Whilst the aspects of structures, processes and outcomes can also easily be transferred to innumerable topics in the ICU setting, too, there is one recent paper describing a different methodological approach to auditing in the setting of an ICU, a technique called a "real-time patient safety audit", which is derived from industrial methods providing timely error detection, including feedback to the responsible person in the frontline [13]. It is obviously not always necessary to perform long-lasting studies with complex observations, but even the use of a brief checklist reminding the members of the care staff of the existing standards can improve healthcare outcomes and avoid disasters: in one study of ICU a 36-item checklist was used, which focused on errors associated with delays in care, equipment failure, diagnostic studies, information transfer and noncompliance with hospital policy. This checklist revealed a lot of errors in a short period of time; for example, unlabelled medication was used at the bedsides, some of the patients had no ID bands and the alarm settings of the pulse oximeter were inappropriate. Based on these findings many policies were changed and many educational initiatives were launched, with the intention of making patient care in this ICU setting much safer.

Auditing the audit—where are the limitations?

It must be stressed that auditing is a cyclic business and part of a continuous improvement and educational programme which ultimately will lead to a cultural change in a hospital or department. Therefore, it is mandatory not only to detect the "weak points" of a process, but also to try to improve them by education and training and later to check whether this training has been successful by re-auditing. Gnalalingham et al. evaluated the standard of 213 clinical audits performed in a teaching hospital and found disappointing results [14]: only 14% of the audits satisfied the fifth step, and only 24% of the audits were followed by a re-audit during the subsequent 3 years. When discussing the reasons for this poor performance, they see structural problems (audits are frequently performed by the junior medical staff, and the rotational nature of their posts hinders completion of the cycle) and problems in the processes (e.g. lack of interest on the part of some care providers,

the time-consuming work of data collection), leading to incomplete audits that will not really contribute to health care improvement.

The value of an audit

The value of audit and feedback, with reference to their effects on professional practice and health care outcomes, was recently the topic of a Cochrane Review [15]: Providing healthcare professionals with data about their performance (audit and feedback) may help improve their practice. Audit and feedback can improve professional practice, but the effects are variable. When it is effective, the effects are generally small to moderate. The relative effectiveness of audit and feedback is likely to be greater when baseline adherence to recommended practice is low and when feedback is delivered more intensively. The results of this review do not support mandatory or unevaluated use of audit and feedback as an intervention directed at changing practice. However, it must be stressed that only 118 studies have been considered for this review and that many of these had some methodological weakness. Therefore, the conclusion must tend more towards: "There must be more and better audit-research performed!" than towards "Forget it, it is worthless."

What can I do?

Whoever is thinking critically about structures, processes and outcomes in his or her personal working environment will identify some problems. Addressing these problems, creating alertness, building a base on which a change-process can be started, developing oneself and one's co-workers, getting a more precise picture of the structure, the processes and the outcomes—an audit can be recommended for any and all of these. There are many supportive textbooks and web resources available, which enable almost anyone to perform an audit. The results gained should be interpreted carefully and widely discussed before a change-process is started. When the need for a change-process is agreed the goal is announced and the way in which a successful change-process might be started is described. However, this must include a re-audit, to evaluate whether the goal is reached and patient care is improved. The results of audit processes should be published, to encourage a culture of blame-free risk management. Auditing demands staying power!

Nine steps to starting a first audit

For those who want to start an audit cycle in their own department / hospital, the following checklist summarises the questions it is most important to answer before the process is started.

1. Choice of topic — Which topic is most important and most urgent?

2.	Authorisation	Approval! Are we talking about a department or a hospital audit?
3.	Workgroup	Should we invite everybody?
4.	Moderation	Internal or external?
5.	Power of the first meeting	Introduction to auditing Rules of communication Visions and/or aims
6.	Scheduling an audit	When will we reach what?
7.	Evaluation	Measuring what and how long?
8.	Implementation	Possible techniques in my hospital?
9.	Reports!	What, when and how?

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Chapter 27

Focus on entropy and surgical stress index

M. Sorbello, S. Mangiameli, A. Gullo

Monument to Morton, Mt Auburn Cemetery, Boston
Inventor and Revealer of Anaesthetic Inhalation
Born August 9, 1819; died July 15, 1868

BEFORE WHOM in all time Surgery was agony.
BY WHOM Pain in surgery was averted and annulled.
SINCE WHOM Science has control of pain.
H.G. Bigelow, Surgeon

Few words for a great discovery

According to the words of Dr Bigelow, one of the most important goals achieved by Dr Morton's discovery of anaesthesia was, as is obvious from the point of view of a surgeon, that pain was abolished from surgery. This is quite true when anaesthesia is in the skilled hands of an able anaesthetist; the same cannot be said of the idea that science has control of pain.

In effect, more than 160 years later, we really have very few certainties about our anaesthetised patients. What we can be sure of is muscular paralysis, as on one hand we are able to measure all parameters of neuromuscular block and, on the other, pharmacokinetics, sites of action and pharmacodynamics of neuromuscular blocking agents (NMBAs) are fully understood; besides we can also objectively assess the degree of muscular paralysis, simply by the surgeon's complaint (more often than necessary, indeed) or by the awakening patient respiratory difficulty. Finally, we must not forget the valuable possibility of pharmacological block reversal.

What, then, about unconsciousness? First of all let us decide to consider it as "hypnosis", to clearly identify it as one of the three components of general anaesthesia (GA). And, so on, what about analgesia/nociception imbalance? Few data, many hypotheses, and a huge amount of uncertainties; that could be a good answer; but what is the question?

If we explore other aspects of anaesthesia we have few or no answers at all. We are discussing anaesthetic depth (AD) or antinociception monitors, but we had better discuss what it is we want to measure! It has been claimed that we will not understand GA and its effects on consciousness until we understand what consciousness itself is [1].

"Gentlemen, this is no humbug." A few words from Dr Warren, also a surgeon, to announce the wonder of something that would change medicine for ever. It was 16 October 1846, in Massachusetts General Hospital, Boston (see a wonderful online slideshow at http://www.etherdome.org/Humbug.html) when Thomas Morton officially discovered anaesthesia and started the "ether era" [2]; ironically, some time before, a similar demonstration attempted by Horace Wells in the same hospital but using nitrous oxide had failed through technical problems with the animal bladder used as reservoir for anaesthetic gas delivery. Probably he would have succeeded, anticipating the birth of anaesthesia, if he could have used an AD monitor (the patient awoke, experiencing pain, less than usual, but nonetheless pain).

Even nearer the present, up to the early 1990s, Dr Wells would not have found such a monitor. And if, as a curious scientist, he could have jumped forward to yesterday, he still would not have found anyone able to explain him exactly how, when and where old and modern anaesthetic agents act.

Let us try to help him imagine…

Anatomy and physiology of hypnosis

What is hypnosis?

An excellent review recently provided by John et al. [3] provides "theories" and "proposed mechanisms" referring to the anaesthetic cascade, while Lydic et al. [4], in their recent review considering 40 years of research into the cellular and molecular mechanisms contributing to arousal state control, conclude that a large body of data is available but still not enough to enable us to understand the underlying mechanisms or to attempt any comparison with GA.

For the first 100 years of anaesthetic practice the basic principles were to suspend conscious awareness and produce a deep stage of anaesthesia to facilitate surgery by profound relaxation of skeletal muscles. This deep stage could be achieved only with high concentrations of general anaesthetic agents, and it was difficult to avoid the risk of "too-deep anaesthesia" with consequent cardiorespiratory depression. The introduction of NMBAs in the 1940s produced neuromuscular paralysis without the need for a high concentration of anaesthetic; the risk of too-deep anaesthesia then gave way to the potential condition of "too-light anaesthesia", making anaesthetists aware of patients' conscious awareness [5].

Let us make a break. Anaesthesia can be considered as the condition achieved by administration of different molecules aimed at allowing patients to tolerate otherwise painful or unpleasant procedures; all pharmacodynamic effects elicited by anaesthetics can be typically classified as modification or loss of consciousness, amnesia, analgesia, muscle relaxation and control or suppression of autonomic responses.

In the modern anaesthetic era every single effect is generally and ideally achieved by a single molecular mechanism occurring in a certain anatomical site,

which is now largely, but not yet completely, identified. There is an important limitation, indeed, for this schematic vision: it might let us underestimate the large number of molecular, anatomical, functional and pharmacological interactions and pharmacodynamic interindividual variability in drug responses [6].

AD is hence a general "multimodal concept", which can be variously defined according to the specific component of anaesthesia we are investigating, and it must definitely be emphasised that most of the currently available AD monitors have been designed to explore only a single pharmacodynamic aspect of GA, i.e. alteration of consciousness: even the best of them, then, is still exploring only one part of a process and will not consider other factors (such as muscular responses) unless perhaps as artefacts, when they might sometimes indicate incoming variations of GA depth or imminent arousal or awareness phenomena.

From the pharmacokinetic point of view, AD is easily achieved (just think of the stabilised end-tidal concentration of inhalatory anaesthetic agents, which is assumed to be equal to the concentration at the site of action [1] or the calculated concentration at the site of action for intravenous anaesthetics according to widely demonstrated pharmacodynamic models); but from the pharmacodynamic point of view, AD is different and more complex, as we still do not know exactly how and where the anaesthetic effect is exerted, whilst we do know that all aspects of GA are strictly interrelated and influence each other: it is well known that surgical noxious stimuli tend to lighten the depth of hypnosis [7], or, in other words, that strong nociception causes arousal or strong hypnosis causes antinociception [8].

Is it possible to assess AD?

This is also a good question; but first of all we should ask why we need AD assessment. The principal risk in this era of too-light anaesthesia is undoubtedly awareness.

A large number of studies [9] have demonstrated that patients can remember events that have occurred during GA and that conscious retrieval of information can occur during GA (explicit memory or awareness): patients report having heard conversations or noises or having felt discomfort, such as being operated on or paralysed [10]. This phenomenon is rare (0.1–0.2%) [11, 12], but its psychological consequences can be dramatic. Other studies suggest that automatic or unconscious retrieval of information presented during GA is also possible (implicit or automatic memory) [13], with the evidence of an immediate postanaesthetic change in behaviour or in performance on a memory test without conscious recall of the information presented during GA.

This phenomenon could have far-reaching implications for anaesthesiologist activity, including legal implications [14], so that according to the results of the most important studies on awareness [15], which show that the use of AD monitors reduces its incidence, AD should be monitored [16] in high-risk patients such as trauma patients, those undergoing caesarean section, cardiac surgery, rigid bronchoscopy and emergency surgery, TIVA patients; patients with previous episodes of awareness; patients with increased tolerance to anaesthetic drugs because of

previous treatments or substance abuse; and in all cases in which heavy neuromuscular blockade is required.

AD monitoring seems important for different reasons in addition to awareness prevention: optimising AD would mean patient-tailored anaesthesia, with optimal, reduced drug consumption, shortening of length of stay in the PACU, and, in all probability, as a result of a more stable intraoperative course (including haemodynamic changes and autonomic responses), a better patient outcome. The last objective seems intuitively hard to demonstrate, but we should not forget the studies on the use of pulse oximetry in operating rooms, which never demonstrated the technique's impact on outcome [17]. Last but not least, AD monitoring would allow two important steps forward: the possible development of *closed-loop* anaesthesia delivery systems and the possibility of further understanding anaesthesia itself [18].

It is clear, then, that assessment of patients' AD is not merely a desirable goal in modern anaesthesia, but a real need; unfortunately the real depth of hypnosis is a theoretical concept and as such cannot be measured directly, but only estimated.

This concept was already familiar to Guedel or Lundy, who proposed their widely known scales for anaesthesia progression and AD assessment [19]: but it was still the ether era, and with the introduction of NMBAs the usefulness, not the value, of these scales was severely restricted.

Not surprisingly, 70 years later, the first subjective way of estimating AD remains the anaesthetist's skill, experience and clinical judgement; this "method" has the great limitation of being influenced by drugs (e.g. heart rate is affected by beta blockers) and dependent on the operator's experience, making comparison and reproducibility difficult; besides recent studies [20] suggest that one important error in such a setting could be underestimation of AD by experienced anaesthetists, resulting in a concrete awareness risk. Scales such as the Observers Assessment of Alertness and Sedation (OAAS) [21] and the blood pressure–heart rate–sweating–tear scale (PRST) [22] represent an attempt to convert promptly a subjective observation into an objective scale.

The first attempt to make AD an objective measurement is due to Tunstall [23] and his *isolated forearm technique*, which, despite its limitations (arm immobility and tourniquet-induced ischaemia), represented the first conceptual step towards modern AD monitors.

The next step forward in AD monitoring was the application of electroencephalography (EEG) to anaesthesia; Caton reported its application during chloroform anaesthesia in 1875 [24], and Gibbs was the first to postulate its usefulness as an AD monitor in 1937 [25]; later on, new analysis techniques to improve signal capture and data manipulation were applied to EEG processing, such as spectral edge frequencies (SEF) analysis [26]; this approach to EEG processing allowed the development of modern EEG-based AD monitors such as the BIS™ [27], Narcotrend™ [28], Cerebral State Index™ [29] and PSA4000™ [30] monitors, and more recently the Entropy™ [31] monitor.

All these monitors simplify the technical approach to the patient (limited number of cranial/frontal/forehead electrodes) and allow some numerical indexes

on proprietary scales designed to assess AD and some related parameters. Almost all of them use frequency analysis to obtain simple numbers rather than complicated waveforms or voltages, to allow quick and comparable interpretation of the hypnotic state; the common pitfalls of almost all these monitors are essentially represented by:

1. Reference scale: in the BIS monitor, which is one of the most widely studied, the analytical algorithm is not available, and displayed values are yielded by a comparison with a pre-existing database recorded in a large number of patients [14, 15, 17]. The objection has been raised that this approach might not reflect the anaesthetic state and takes little account of patients' individual variability. Narcotrend was considered not to admit of direct interpretation; here too, the patient database was a pre-existing one and there are too few published studies to support its reliability [32]. The Entropy monitor is currently the only one providing a "pure" single-patient value on a scale of 0–100 with no comparison against pre-existing databases or hypnosis scales.
2. Anaesthetic agent "blindness": all the EEG-based monitors result differently blind to nitrous oxide, xenon and ketamine administration, while showing further differences depending on the inhaled anaesthetic used. Similar differences have been recorded within a single and between different monitors, depending on anaesthesia regimen, including intravenous anaesthesia [33]. Opioid administration has also been reported to be responsible for misleading data when certain AD monitors are used [34].
3. Muscular artefacts: it has been demonstrated that movement depends on subcortical structures [35]: this observation implicates that it cannot be used as a correct index to assess AD or central antinociception. On the other hand, muscular activity may contaminate any cerebral activity recordings "electrically", because both EEG and recordings of evoked potentials are normally carried out by surface electrodes attached to the scalp of the patient. Whatever the monitor, the resulting signal consists of three components: EEG, electromyography (EMG) and artefacts. The last are noises coming from movements, electrical devices, electrodes and errors in the analogue-to-digital conversion, and they are usually eliminated with different filters. The EMG component is more difficult to eliminate because the frequency content of the EMG has a last overlap with that of the EEG, the former being typically of greater intensity than the latter. Therefore, it is difficult to know how much of the recorded signal is represented by the EMG, with obvious consequences for the reliability of the AD index [36]. Certainly, if the patient receives NMBAs the percentage of the signal accounted for by the EMG will be close to zero, but, on the other hand, in a nonparalysed subject the EMG percentage might play a considerable part in the AD index. A recent study [37] has demonstrated that an important part of the BIS signal is derived from the EMG and that the monitor itself is provided by a signal quality index informing the operator of the degree of EMG contamination and, consequently, of the loss of reliability of the BIS index.

Attempts to overcome the aforementioned problems have resulted in the e-

voked potentials-based monitors, such as the Auditory Evoked Potentials (AEP) monitor A-line(ARX Index)^{TM} [38] and the AEPex^{TM} [39]. All these monitors show good sensitivity independently of the anaesthetic drug or regimen used, allowing a precise definition of brainstem (directly) and brain (indirectly) function during anaesthesia [40] while affected by muscular signal contamination in a similar way to other monitors; finally, their use is strictly related to the integrity of the auditory pathways. Further studies are needed to attain better definition of their role in AD monitoring and to find answers to some questions.

What makes the Entropy monitor different? In a nutshell, we might say it is the only one that has solved some of the above problems with the unique conceptual approach, "If you can't defeat it, search for an alliance". Entropy, as a physical concept, expresses the amount of disorder in a thermodynamic system, its value being proportional to the logarithm of the number of microstates available in that system. Applied to the information theory, entropy was first defined by Shannon and Weaver in 1948 [41], and it was further applied to power spectrum signal analysis by Johnson in 1984; consequently, entropy describes the irregularity, complexity or unpredictability characteristics of a signal. A signal in which sequential values are generated by a random number of generators has high entropy; conversely, a regular and well-ordered signal has an entropy value of zero. The Datex-Ohmeda Entropy Module provides two indices: state entropy (SE) and response entropy (RE). SE is computed over the frequency range of 0.8–32 Hz; consequently, it includes the EEG part of the spectrum and therefore primarily reflects the cortical state of the patient. RE is computed over a frequency range of 0.8–47 Hz and thus includes both the EEG and the EMG parts of the spectrum. As a result, SE can be considered as a stable indicator of hypnotics cortical effect, while RE accounts for the same information plus EMG activity. This is how Entropy overcomes EMG contamination; it just accounts for it as part of the signal itself rather than as something to be eliminated. Important implications derive from such an approach: first of all window lengths for data analysis are chosen so that each frequency component is obtained from a time window optimal for that particular frequency, so as to extract information from the signal as fast as possible. Compared with SE, RE thus reacts faster to changes because of higher frequency sources (meaning higher sampling frequencies): 15-s vs 2-s time windows are needed, respectively, for SE and RE values to be refreshed. Another important result is that RE, including EMG activity information on the face muscles, might open a window on prediction of variations in AD: in effect SE (range 91–0) and the RE (range 100–0) are normalised in such a way that RE becomes equal to SE when there is no EMG activity at all [42].

Conversely, a typical situation in which the RE–SE gradient rises quickly is seen in arousal reactions, when RE first rises simultaneously with muscle activation and is then followed some seconds later by SE. It seems that a sudden increase in EMG signal might indicate that the patient is responding to some external stimulus (such as a surgical one), especially if the analgesia plan is insufficient. If stimulation continues and no additional analgesic drugs are administered it is highly likely that the level of hypnosis will eventually start to lighten (bearing in mind that strong

nociception might cause arousal [7, 8, 43–45]. As we shall see later, this is not enough; but it might be a good starting point. Similarly to other monitors, Entropy is "blind" to some anaesthetic agents, seeming more reliable when halogenated rather than intravenous anaesthetics are used for GA maintenance [46]; it differs from other AD monitors in that the Entropy algorithm is based on physical principles, so that output data are referring to the patient concerned in isolation, without any reference to prior values scales, accounting for really patient-tailored AD monitoring [42]. Interestingly, Entropy is one of the few monitors that has been demonstrated to bring about optimisation of anaesthetics delivery, with potential implications for patient outcome and discharge from hospital [47].

The dark side of AD: nociception

What is nociception?

The trachea is intubated, parameters are stabilised; one quick look at the vaporiser: it is full, it is working, the monitor showing stabilised end-tidal concentrations; Entropy value is fixed at 50, no twitch in response to Train of Four (TOF) stimulation. The surgeon is ready: "May I cut?". "Of course", is the proud answer.

As soon as the scalpel's tip depresses the patient's tissues, the heart rate rises, sweating appears, tears start to fall, sighing starts and the patient moves; what has gone wrong? Obvious! A strong nociceptive stimulus caused arousal. And until the patient awakes we cannot be sure whether it will also have caused recall or, even worse, awareness. This hypothetical (but not completely so) scenario is itself the answer to the introductory question. We know how and where pain perception starts; we can almost see it travelling along amyelinated fibres, firing interneurons, running fast along ascending pathways towards the thalamus up to its projection on the cortex, a lot of automated responses being evoked in both motoneurons and neurovegetative and emotional circuits. We imagine neurons sparking, delivery of P-substance, gene activation [48]. Is this all? Confirmation is immediate from an awake "ouching" patient; what about an anaesthetised patient? Pain is a conscious description, and in an anaesthetised unconscious patient the response to stressful stimuli (a better term than 'painful' in this context) is called nociception [49], which activates sympathetic pathways and increases the secretion of pituitary hormones exactly as pain does [50, 51]. It is no longer pain, then, but nociception, and per se it cannot be referred. One of the first anaesthetists, John Snow, wrote that "Ether contributes other benefits besides preventing pain. It keeps patients still who otherwise would not be" [52]. This is what we do actually know of nociception during GA, and it is a kind of bet: maybe analgesics are working properly, and no autonomic responses are triggered, resulting in a stable anaesthesia course. Or maybe anaesthesia is so deep as to blunt any kind of perceived reaction, while silent mechanisms are triggered in the patients' brain, including genetic and neurobehavioural responses to unperceived but existing nociception.

Consciousness might be considered as a quantal phenomenon of the "ON/OFF"

type with three or four intermediate steps indicating deepening of unconsciousness; analgesia, or better antinociception, is more of a continuum-type phenomenon, with infinite intermediate degrees of both stimulus and perception. That is why it is so difficult to measure, and why we can only refer to such surrogates as movement or autonomic responses. Unfortunately, these surrogates coincide with effects, undesirable side-effects whose occurrence marks the difference between general and generic anaesthesia.

This is sad, if we think that the most important reward to Morton's anaesthesia discovery was centred on the defeat of pain: "BEFORE WHOM in all time Surgery was agony. BY WHOM Pain in surgery was averted and annulled. SINCE WHOM Science has control of pain". To date, nociception is what we know less about, and what we encounter more difficulty in measuring!

Nociception depth monitors: what we have and what is missing

Monitoring of analgesia remains the final challenge during GA [49]. We cannot count on nociception effects to measure it; not only because we need to avoid them, but also because of their deleterious effects on the intraoperative course and on the postoperative outcome, including pain sensitisation (think of pre-emptive analgesia on one side and of wind-up like phenomena on the other [53–54]), and undesirable haemodynamic effects, especially in compromised patients.

Furthermore, there is growing evidence of an association between the attenuated surgical stress response and improved overall postoperative recovery [55–61], including the possibility that intraoperative nociception could somehow be predicted [62–65] with all sorts of implications for individual titration of analgesics. Therefore, monitoring of analgesia may turn out to be important in evaluating different strategies for control of the intraoperative stress response and their association with patient outcome.

Movement itself cannot be a good nociception indicator: first of all because of the effects of NMBAs and then because it has been demonstrated that motor responses to nociception depend on subcortical structures [35]. Another option might be evaluation of autonomic responses; though it must be interpreted as an a posteriori intervention, early detection of such responses is the most powerful tool anaesthetists have ever had for detecting nociception and driving analgesic administration.

In recent decades it was supposed that the available AD monitors could be extended to nociception monitoring [66], with particular reference to muscular activity. While especially active during the awake state, the frontal EMG (fEMG) may also be active during surgery. On the basis of this consideration, activation of RE may give an early indication of incoming arousal response to some painful stimuli, and it has also been suggested that it might represent a sign of inadequate analgesia [31].

Several studies explored this possibility, with both positive and negative results [67-71]. To date we cannot consider RE activation a reliable marker of nociception, and we can generally affirm that EEG-derived parameters of hypnosis are not able

to predict any changes in the level of surgical stress [72-74]. This affirmation is supported, interestingly, by Segawa et al.'s observations [75]: in a study measuring plasma norepinephrine as a measure of stress response during sevoflurane anaesthesia it was found that high sevoflurane concentrations could not suppress the adrenergic nervous system responses to surgical stimulation while suppressing motor responses. As high doses of hypnotics might suppress motor response (and not nociception or stress response), using fEMG as a measure of antinociception will be anything but helpful and, conversely, the absence of fEMG activation after noxious stimulation will not always indicate adequate analgesia. It is time to move on, so let us summarise: movement is not a good indicator of nociception; and the currently available AD monitors cannot reliably be used for nociception assessment, though they can be useful to detect the arousal reaction following nociception. The only thing we can use is the autonomic response [76].

Which parameters could then be used as potential inputs for nociception assessment? Clinical signs represent the state of the art, but they are difficult to monitor objectively, especially in the anaesthetised patient. Blood pressure per se is a good parameter: often continuously measured via intravascular catheters, its usefulness limited by too many confounding factors, such as prior hypertension or pharmacological interferences, including anaesthetic drugs. Heart rate (HR) is subject to similar limitations, though tachycardia should always be considered the first sign of inadequate antinociception; a beta blocker, unfortunately, will stop tachycardia with no effects on nociception. Spectral analysis criteria have been applied to HR variability to obtain a more reliable assessment of autonomic system activation, but with poor results when HR alone is considered [77]. The ANSiscope™ is a recently developed monitor that analyses autonomic activation via fractal analysis of R–R intervals on the ECG, and in a recent paper it showed a very good correlation with plasmatic catecholamine concentrations in a nociception swine model [78]. Respiratory sinus arrhythmia has also been used for nociception assessment [79], with poor results because of very (unacceptably) large inter- and intraindividual variability; similar results were found with automated systems for ocular microtremor detection, assuming its correlation with AD [80]. Skin vasomotor response (SVmR) measured by laser Doppler was considered useful as an expression of sympathetic-mediated vasoconstriction elicited by nociception [81, 82]. Pulse plethysmography (PPG) has also been widely considered, as PPG variability, as pulse transit time (PTT) and as PPG amplitude; results have been controversial owing to lacking specificity and to interference from pharmacological, technical and physical (temperature) factors. Up to this point, although commonly used by clinicians to titrate hypnotics administration, haemodynamic changes to surgical stimulation are neither sensitive nor specific for awareness or recall during general anaesthesia and are poor predictors of both voluntary and involuntary reflexes. It seems probable that it will be difficult to base the measurement of analgesia on a single physiological parameter [83]: the only possible approach is multiparametric, in order to minimise interferences and synergise advantages.

This was the aim that led the General Electric Healthcare Research Team to develop a novel multiparametric approach, including advanced analysis of HR

variability and PPG characteristics and dedicated Entropy measurements for intraoperative nociception monitoring: the Surgical Stress Index™ (SSI) [84]. Using data coming from conventional operating room monitoring, a three-lead ECG and conventional PPG, a dedicated software provides advanced analysis of both ECG variability (through beat-to-beat R–R analysis) and PPG signal (PPG amplitude and area analysis + PPG dicrotic notch location); the latest release of the SSI software also includes analysis of the Entropy data (RE+SE).

These continuously monitored signals are collected via the S/5 Anaesthesia Monitor (GE Healthcare; Central and Wincollect software) and submitted to real-time analysis with a dedicated Matlab software application (Matlab, version 6.5, release 13, The Mathworks Inc., Mass., USA) [85].

The rationale for such an approach lies in the combination of various signs of autonomic activation (modulation of HR variability, PPG morphology and dynamics variations because of vascular tone) in order to minimise contamination and increase reliability in nociception monitoring. Preliminary data reports [84, 85] and our group's unpublished data [86] suggest a good relationship between SSI and intraoperative nociception assessed during several anaesthetic regimens (sevoflurane, desflurane/fentanil; propofol/remifentanil; combined anaesthesia), different types of surgery and heterogeneous patient populations.

This kind of multiparametric approach overcomes the limitations of single

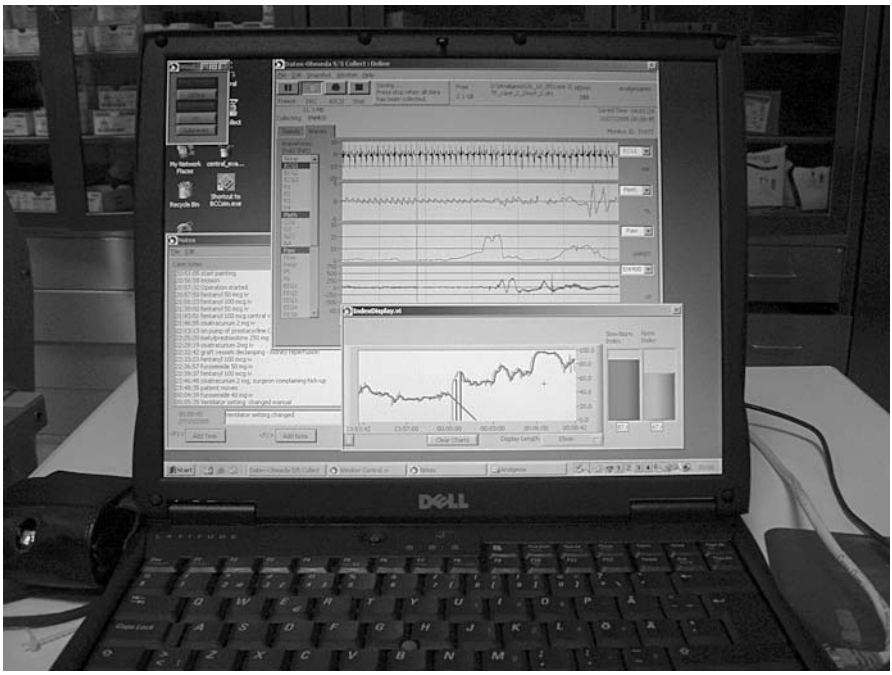

Fig 1. Laptop equipped with SSI™ software during clinical trial. Azienda Ospedaliero Universitaria Policlinico Catania

parameters: interestingly, a recent paper by Luginbuhl et al. [87] showed the lack of correlation between stimulation-induced variability of PPG and responsiveness to intubation, even though vasoconstriction mediated by nervous system activation exerts pronounced effects on PPG morphology and dynamics (lowering of PPG amplitude and proximal shift of the dicrotic notch of the pulse wave towards the systolic peak). The key is a true multiparametric approach: in our experience, in standardised operating conditions laryngoscopy was one of the noxious events best detected by SSI, and there were close correlations with duration and difficulty of the laryngoscopy and even with the operator's experience [86].

Limitations of SSI are currently represented by particular conditions that deserve further study: local temperature [88], vascular repletion state or vasoactive drugs such as amines [89-90], systemic and local diseases affecting peripheral vascular tone and response to autonomic activation [91], all of which result in interference with detection by SSI, must be better studied.

They might mimic nociceptive responses although no stimulation is applied or, conversely, make the vascular musculature refractory to constricting stimuli, yielding false-negative data. Sevoflurane, isoflurane [92] and desflurane [86], or powerful opioids [93-95] might have these effects, so that further studies are needed to asses SSI's reliability and to exclude the possibility that the absence of any increase in SSI increasing really depends on an adequate antinociceptive plan rather than on nociception masked by opioid-mediated inhibition of a vascular response. The type of surgery might also have a role in SSI response contamination: one interesting example we have experienced is that of thyroid surgery, during which manipulation of the gland or the nearest vascular reflexogen sites [96] might trigger reflexes mimicking nociception responses according to SSI detections [86]. Last but not least, it will be important to exclude the possibility that a lacking autonomic response resulting in a missed SSI increase is not dependent on a too-deep hypnotic state [97] that can blunt an autonomic response despite active nociception, or on a really adequate antinociception plan providing effective blocking of incoming noxious stimuli.

To date, finally, many candidate signs are available for analgesia monitoring, and technical research is moving faster and faster; according to our present knowledge, at least, whatever the latest monitors are like, they will never be able to predict whether the depth of analgesia is sufficient for the next painful surgical stimulus: they can only monitor the anaesthetic state at the time of measurement and the existing balance between excitation and responsiveness. The anaesthetists' role is still pivotal, their experience being ahead of any technique for monitoring analgesia depth, and better than any monitor despite their lower capacities in terms of number of operations per second.

But this is a different challenge.

Role and future of AD and nociception monitors

Proper use of AD monitors improves the quality and safety of GA, while the availability of a nociception monitor will allow really "protective" anaesthesia with

possible effects on perioperative course and outcome. For such a purpose, wide knowledge of consciousness/awareness and nociception/antinociception imbalance and anaesthetic pharmacology, clinical experience and a technical background are mandatory: otherwise there will be constant errors and pitfalls, even in the presence of redundant monitoring [44, 98]. Anaesthesia will then be tailored to individuals, to surgical procedures and to pharmacological agents, with potentially enormous effects on length of stay, costs and outcome.

Last but not least, we might envision a near future in which a fast and logical neural network taking account of all possible data, interactions and consequences will allow error-proof closed-loop anaesthesia [99] or a fully programmable analgesic protocol developed on the basis of preoperative estimation of nociception integrated with intraoperative need and consumption of analgesics.

A setting in which, if Thomas Morton could travel into his future, standing in front of an incomprehensible array of screens, cables, computers and closed-loop systems covering the anaesthetised patient and substituting the anaesthetist, he would probably say: "Gentlemen, this must be humbug!". And even then, the futuristic anaesthetist staring at him should not forget that the eyes see what the mind knows.

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Chapter 28

Neuraxial anaesthesia and anticoagulation

D.J. Wedel

Neurological complications associated with spinal or epidural anaesthesia can be due to toxic effects of the injected agent, incorrect placement of a needle or catheter causing direct neural tissue damage, infectious agents or spinal cord compromise due in turn to ischaemia or mass effect. Adverse events related to the surgical procedure, positioning or a patient's underlying medical condition can also present as "complications" of regional anaesthesia. Anticipation and prevention of complications, along with their early diagnosis and treatment, are the most important factors in dealing with regional anaesthetic risks. Several large studies have confirmed the rarity of permanent neurological injury associated with this type of anaesthesia [1, 2].

Intraoperative technical problems

Direct nerve trauma with a large-gauge, sharp bevel needle, injection of local anaesthetic solutions intraneurally and injection of an inappropriate agent are avoidable causes of nerve injury. Large studies have documented the risk of peripheral nerve injury associated with surgery under general anaesthesia. Scrupulous documentation of paraesthesias elicited during the block and of the presence or absence of pain during injection of local anaesthetic can be helpful in determining the aetiology of postoperative neurological complaints. Tourniquet duration and pressure, a description of the patient's position on the operating table, including documentation of efforts to pad vulnerable anatomical sites, and a record of local anaesthetic injections given by the surgeon should also be part of the permanent anaesthesia record.

Faulty equipment and technique can cause complications during performance of a block. Attempted withdrawal of an epidural or intrathecal catheter through the needle can result in shearing of the catheter, leaving a portion of it in the epidural or intrathecal space. Surgical exploration is not recommended for pieces of catheter that are left in the epidural space, though the patient should be informed of the presence of the remnant. When the catheter breaks off at or just beneath the surface of the skin during removal the remnant may serve as a theoretical conduit for bacteria from the surface of the skin into the epidural space; in such cases efforts to retrieve the catheter are recommended. Inserting the catheter beyond the recommended 2–4 cm may result in coiling and subsequent knotting of the catheter

in the epidural space. This problem will usually present as difficulty in removing the catheter; radicular pain during attempted removal may indicate a knot around a nerve root. Epidural catheters have a high tensile strength, so that it is sometimes possible to apply gentle, continuous traction on the catheter until the knot becomes sufficiently attenuated to allow it to be removed intact.

Neuraxial haematoma

Epidural haematomas present as neurological deficits in the postoperative period due to cord compression. Epidural needles and catheters frequently (2.8–11.5%) cause vascular trauma associated with minimal bleeding, which usually resolves without sequelae. Patients with abnormal coagulation are at increased risk, although coincidental haematoma development is also possible. In a review of the literature published between 1906 and 1994, Vandermeulen et al. [3] reported 61 cases of spinal haematoma associated with epidural or spinal anaesthesia. In 42 of the 61 patients (68%) the spinal haematomas occurred in association with haemostatic abnormality. Twenty-five of the patients had received IV or subcutaneous heparin, while an additional 5 patients were assumed to have received heparin, as they were undergoing vascular surgery. In addition, 12 patients had evidence of coagulopathy or thrombocytopenia or were treated with antiplatelet medications, oral anticoagulants, thrombolytics or dextran 70 immediately before or after administration of the spinal or epidural anaesthetic. Needle and catheter placement were reported to be difficult in 15 (25%) and to cause bleeding in 15 (25%) patients. Thus, in 53 of the 61 cases (87%), either a clotting abnormality or a problem with needle placement was present.

Recommendations—specific anticoagulants

Fully anticoagulated patients are usually not candidates for central neural blockade, but antiplatelet drugs are often self-administered for pain relief or prescribed for a wide variety of preventative or therapeutic reasons. While the effects of most NSAIDs are measured in days, the antiplatelet effects of aspirin may last for a week or longer. A large retrospective study suggesting that central neural blockade is safe in patients taking these medications has been confirmed prospectively [4]. Bleeding time is not a good predictor of the risk of bleeding. Newer antiplatelet agents, such as ticlopidine and clopidogrel, have not been extensively studied. The relative risk of bleeding with these drugs is unknown, but case reports of bleeding following these agents suggest that a waiting period of 5–10 days after discontinuation of these drugs would be prudent [5]. COX-2 inhibitors do not have antiplatelet effects and therefore should not increase the risk of spinal haematoma.

Coumadin has a good safety profile when used postoperatively in orthopaedic patients for anti-thrombosis [6]. A small dose is usually given the day before

surgery and its use is then continued in the postoperative period. A neuraxial technique can be used, but the catheter should be discontinued before an international normalised ratio (INR) of 1.5 is reached. Patients on long-term coumadin therapy should have a normalised INR prior to needle placement. The INR is a measure of factor VII activity, which is the factor with the shortest half-life. Therefore, low levels of factors II, IX and X may persist when the INR is only slightly prolonged (representing normalisation of factor VII) when discontinuing coumadin therapy. Conversely, early prolongation of INR in a patient beginning coumadin therapy can be associated with adequate levels of other factors. Individual factor levels may be helpful.

The safety of continuous epidural techniques in the presence of *standard heparinisation* during major vascular surgery has been well documented [7]. The recommendations for neuraxial blockade in the presence of unfractionated heparin include: (1) wait 1 h after needle/catheter placement before administering heparin; (2) wait 4–6 h after stopping heparin and check PTT prior to needle placement; (3) follow PTT or ACT to avoid excessive heparin effect; and (4) manage catheter removal with the same safety precautions as used for placement. The use of neuraxial techniques in the presence of full heparinisation during cardio-pulmonary bypass has been studied and according to the limited data available has not been associated with a high risk of complications. However, this technique must be considered controversial; important clinical outcome advantages have not yet been demonstrated [8, 9].

Several cases of spinal haematoma have been reported in patients receiving *fractionated low-molecular weight heparin* (LMWH) after undergoing epidural or spinal anaesthesia [10]. A total of 60 cases are in the Medwatch series as of 2002 [11]. Enoxaparin is the most commonly prescribed LMWH in the U.S.; the recommended dosage is larger than that used in Europe, and a regimen of two doses per day is recommended. The first dose of LMWH is given 10–12 h after surgery; however, a shorter time interval may be recommended later as anti-thrombotic efficacy studies are completed. If LMWH has been administered, a waiting period of 10–12 h is recommended prior to block placement, and single-shot spinal is considered the safest alternative. Catheters should be removed before the first postoperative dosing. The risk of bleeding has been shown to be lower with a single-shot small needle (i.e. spinal). These recommendations are evolving as the use of these drugs expands and new agents are released. Addition of other anticoagulants, such as NSAIDS, increases the risk. Measurement of Xa activity has not been helpful in determining an appropriate course of action.

Spinal haematomas associated with in-dwelling epidural catheters and intrathecal bleeding with continuous spinal anaesthesia in patients receiving *thrombolytic agents* (streptokinase, urokinase, t-PA) have been reported in the literature [12]. Spinal and epidural anaesthesia should be avoided in these patients. If a catheter is in place and these agents are given, the safest course is to allow the effects of the thrombolytic agent to dissipate (at least 24 h) before removing the catheter.

Newer anticoagulants, such as *hirudin* and the pentasaccharide *fondaparinux*, involve serious risks of bleeding. Hirudin is used primarily in patients with heparin

allergy and induces irreversible antithrombin activity. Fondaparinux is currently under review by the FDA and will be recommended for perioperative anti-thrombosis. This highly effective anti-Xa drug is the active portion of the heparin molecule. The present recommendation, based on the pharmacological profile of this drug, is that no neuraxial technique be performed in its presence. Clinical experience may modify this recommendation.

Herbal medications enjoy widespread use in the surgical population [13]. Three commonly used herbals are associated with anticoagulation activity: ginseng, garlic and ginkgo. Both garlic and ginkgo have antiplatelet effects; ginseng has been shown to increase PT/PTT in animals [14]. These herbals should be discontinued preoperatively (garlic 7 days, ginkgo 36 h, ginseng 24 h before surgery).

Allowing the local anaesthetic to wear off before instituting continuous postoperative infusions and using low dose local anaesthetic and/or narcotic infusions when appropriate permits ongoing evaluation of the patient's neurological status during the postoperative period. The patient should be monitored closely for early signs of cord compression, such as complaints of back pain or an increase in the intensity of motor or sensory blockade, and particularly the development of new paresis. If a spinal haematoma is suspected, the treatment of choice is immediate decompressive laminectomy. Recovery is unlikely if surgery is postponed for more than 8–12 h. Recommendations for neuraxial blockade in the presence of anticoagulant therapy are presented on the American Society of Regional Anesthesia (ASRA) website (www.asra.com).

Postoperative neurological complications

Persisting sensory blockade renders affected anatomical sites vulnerable to injury and interferes with the patient's ability to feel painful responses to such surgically induced problems as ischaemia or compression of tissues due to too- tight casts or surgical dressings. Neurological complications of regional anaesthetics are usually discovered after the patient has left the recovery room. Persistent motor blockade during recovery from sensory anaesthesia may indicate anterior spinal artery occlusion or spasm. Lack of recovery from spinal or epidural blockade in the expected time interval may indicate spinal cord compression due to epidural haematoma or abscess (Table 1). Since early intervention, preferably after less than 12 h, is the key to success in managing these potentially devastating complications, prompt diagnosis (MRI) and early surgical management are indicated.

Table 1. Differential diagnosis of epidural abscess, epidural haemorrhage and anterior spinal artery syndrome

	Epidural abscess	*Epidural haemorrhage*	*Anterior spinal artery syndrome*
Age of patient	Any age	50% over 50 years	Elderly
Previous history	Infection[a]	Anticoagulants	Arteriosclerosis /hypotension
Onset	1–3 days	Sudden	Sudden
Generalised symptoms	Fever, malaise, back pain	Sharp, transient back and leg pain	None
Sensory involvement	None or paraesthesias	Variable, late	Minor, patchy
Motor involvement	Flaccid paralysis, later spastic	Flaccid paralysis	Flaccid paralysis
Segmental reflexes	Exacerbated[a]—later obtunded	Abolished	Abolished
MRI/CT/myelogram	Signs of extradural compression	Signs of extradural compression	Normal
Cerebrospinal fluid	Increased cell count	Normal	Normal
Blood data	Rise in sedimentation rate	Abnormal coagulation studies	Normal

[a]Infrequent findings

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Chapter 29

Regional anaesthesia in the patient with pre-existing neurological dysfunction

T.T. Horlocker

Patients with pre-existing neurological disease present a unique challenge to the anaesthesiologist. The cause of postoperative neurological deficits is difficult to evaluate, because neural injury may occur as a result of surgical trauma, tourniquet pressure, prolonged labour, or improper patient positioning or anaesthetic technique. Progressive neurological diseases such as multiple sclerosis may coincidentally worsen perioperatively, independently of the anaesthetic method. The most conservative legal approach is to avoid regional anaesthesia in these patients. However, high-risk patients, including those with significant cardiopulmonary disease, may benefit medically from regional anaesthesia and analgesia. The decision to proceed with regional anaesthesia in these patients should be made on a case-by-case basis. Meticulous regional anaesthetic technique should be observed to minimise further neurological injury.

Intracranial tumours, aneurysms and arteriovenous malformations

Patients with pre-existing intracranial masses and vascular lesions, such as primary or metastatic brain tumours, saccular aneurysms or arteriovenous malformations, are at increased risk of neurological compromise during spinal or epidural anaesthesia. Alterations in intracranial pressure and mean arterial pressure associated with neuraxial block may result in subarachnoid haemorrhage, cerebral infarction or cerebral herniation. Dural puncture is not recommended in patients with evidence of increased intracranial pressure, such as cerebral oedema, lateral shift of the midline structures and obliteration of the fourth ventricle, since the associated leakage of cerebrospinal fluid (CSF) decreases CSF pressure and may produce cerebellar herniation [1]. In patients with uncorrected vascular malformations the decreased CSF pressure increases the aneurysmal transmural pressure (mean arterial pressure–intracranial pressure) gradient and may result in subarachnoid haemorrhage.

Rupture of an occult arteriovenous malformation coincident with dural puncture during attempted epidural anaesthesia has been reported [2]. Epidural and caudal anaesthesia are also contraindicated in patients with increased intracranial pressure, because of the risk of accidental dural puncture and because the intracranial pressure may be further increased by injection of local anaesthetic solution

into the epidural space. Patients with surgically repaired vascular malformations may undergo spinal or epidural anaesthesia without an increased risk of neurological complications (Fig. 1).

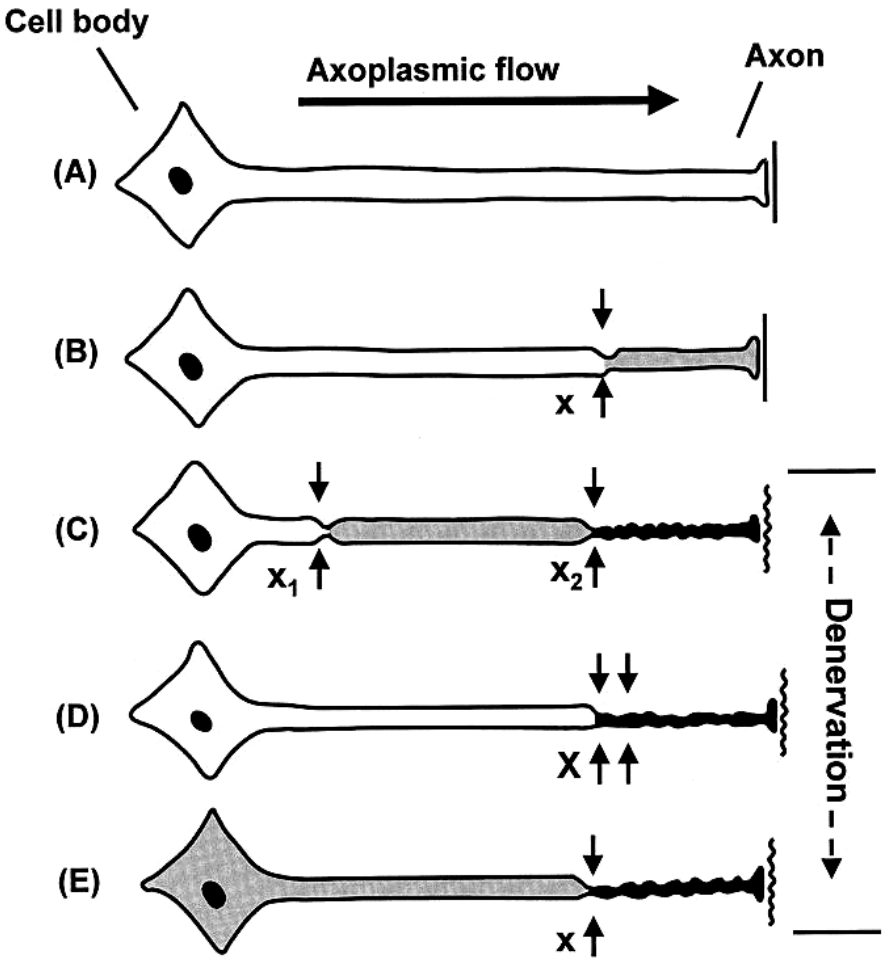

Fig. 1 **A–E.** Neural lesions resulting in denervation. Axoplasmic flow is indicated by the density of shading. Complete loss of axoplasmic flow results in denervation (**C–E**). **A** Normal neuron. **B** Mild neuronal injury at a single site (×) is insufficient to cause denervation. **C** Mild neuronal injury at two separate sites ($\times_1$ and $\times_2$) may cause distal denervation. **D** Severe neuronal injury at a single site (X) may also cause distal denervation. **E** Diffuse underlying disease processes (toxic, metabolic, or ischaemic) impair axonal flow throughout the neuron, and this predisposes the axon to distal denervation after a single minor neural insult at ×. From [19]

Epilepsy

Epilepsy is a recurrent seizure disorder that affects 0.5–1% of the population. Idiopathic epilepsy typically begins in childhood, but adult-onset seizure disorders represent pathologic intracranial conditions such as neoplasm, trauma, infection or stroke. Seizure activity results from synchronous discharge of a group of neurons in the cerebral cortex. The neuronal hyperactivity may remain localised or may propagate to the thalamus and across to the contralateral hemisphere, resulting in generalised seizures. Epilepsy is treated with anticonvulsant medications; the choice of drug is determined primarily by the classification of the seizure disorder.

Central nervous system (CNS) toxicity is a known complication of regional anaesthesia. Most local anaesthetic effects are believed to be dose-related, but a dichotomy of these effects on the brain is well documented. At low blood levels, local anaesthetics are potent anticonvulsants, but at high levels they act as convulsants [3, 4]. Intravenous infusion of lidocaine at 4–6 mg/kg in human volunteers produced initial depression of the electroencephalogram, with a slowing down or a decrease in the amplitude of the alpha waves. Higher doses of lidocaine (7–9 mg/kg) induced tonic–clonic convulsions and spike waves. After convulsions ceased, no electrical activity was found for 10–20 s, raising the possibility of neuronal hypoxia secondary to convulsive activity [4]. However, results of a subsequent study indicate that lidocaine-induced seizures result in only small increases in cerebral blood flow and metabolism, unlike the seizures associated with epilepsy [3].

The initial state of CNS excitation elicited by local anaesthetic agents is produced by a selective block of the inhibitory pathways in the cerebral cortex. Activity of the unopposed excitatory neurons leads to convulsions. Eventually, the inhibitory and excitatory pathways are blocked, resulting in generalised nervous system depression. The CNS toxicity of specific local anaesthetic solutions is primarily related to anaesthetic potency, but it is also affected by rate of biotransformation and penetrability through the blood–brain barrier. The acid–base status of the patient also profoundly affects the CNS toxicity of local anaesthetics. Hypercapnia and acidosis may decrease the convulsive threshold by 50%.

Many regional anaesthetic techniques may be safely performed in patients with seizure disorders. Anaesthetic management in the patient with epilepsy includes consideration of the cause and treatment of the seizure disorder and also of physiological factors affecting local anaesthetic CNS toxicity. Anticonvulsant medications should be identified. Measurement of serum anticonvulsant levels is useful to assess the adequacy of treatment. Selection of a less potent and therefore less toxic local anaesthetic is recommended. Local anaesthetic blood levels should be minimised through the use of an appropriate dose and concentration of the local anaesthetic, addition of vasoconstrictors, and slow and incremental injection (with frequent aspiration) through a short-bevel needle. A continuous catheter may be used if the regional anaesthetic technique is associated with rapid uptake of local anaesthetic solution, as in the case of epidural or brachial plexus block.

The patient should be continuously monitored for early warning signs of local

anaesthetic systemic toxicity until the peak plasma concentration is achieved. Even small amounts of local anaesthetics injected into the carotid, subclavian or axillary arteries can result in seizures [5]. Administration of a benzodiazepine, thiopental or propofol raises the seizure threshold. However, if hypoventilation occurs from oversedation and results in hypercapnia and acidosis it increases the likelihood of CNS side-effects. Postoperative infusions must be carefully managed to avoid accumulation of local anaesthetic. An opioid rather than a local anaesthetic infusion may be a more prudent choice in these patients.

Chronic disorders of central and peripheral nerves

Patients with pre-existing neurological disorders of the CNS, such as multiple sclerosis or amyotrophic lateral sclerosis, and those with disorders of the peripheral nerves, such as lumbar radiculopathy, history of poliomyelitis, and sensorimotor peripheral neuropathy, present potential management dilemmas for anaesthesiologists. The presence of pre-existing deficits, signifying chronic neural compromise, theoretically puts these patients at an increased risk of further neurological injury. It is difficult to define the actual risk of neurological complications in patients with pre-existing neurological disorders who receive regional anaesthesia; no controlled studies have been performed, and accounts of complications have appeared in the literature as individual case reports. The decision to use regional anaesthesia in these patients is determined on a case-by-case basis and involves understanding the pathophysiology of neurological disorders, the mechanisms of neural injury associated with regional anaesthesia and the overall incidence of neurological complications after regional techniques.

Risk factors for regional anaesthesia-related nerve injury

Neurological injury directly related to regional anaesthesia may be caused by trauma, neurotoxicity and ischaemia. Direct needle- or catheter-induced trauma rarely results in permanent neurological injury. The overall incidence of persistent paraesthesias has been estimated at 0.08% after spinal anaesthesia and at 2% after brachial plexus block [6, 7]. It has been suggested that paraesthesia techniques may be associated with a higher incidence of neurological injury after brachial plexus block, but there are no conclusive data supporting that claim [7].

The needle-bevel configuration may influence the frequency and severity of peripheral nerve damage during regional anaesthesia. In an in vitro study, Selander et al. [8] demonstrated an increased frequency of perineural injury when a long-bevelled need was used instead of a short-bevelled needle. Rice and McMahon [9] assessed frequency and severity of neural trauma after nerve impalement by histological and clinical methods and reported that injury produced by short-bevelled needles was more severe and more frequent, and that recovery from it was slower than in the case of injury produced by long-bevelled needles. Although no human studies have been performed to determine which of these in vitro studies

accurately predicts clinical outcome, these studies illustrate the importance of minimising direct needle trauma during regional techniques, especially in patients at increased risk of neurological complications.

Neurological deficits after regional anaesthesia may be a direct result of local anaesthetic toxicity. Clinical and laboratory findings indicate that anaesthetic solutions are potentially neurotoxic [10–14]. It is generally agreed that local anaesthetics administered in clinically appropriate doses and concentrations do not cause nerve damage [15]. However, prolonged exposure to high concentrations of local anaesthetic solutions may result in permanent neurological deficits. Patients with underlying nerve dysfunction may have a decreased requirement for local anaesthetic and a decreased threshold for neurotoxicity [12]. Indeed, Yee et al. [16] have demonstrated that the dose requirement for local anaesthetics is decreased and potency increased in aged animals. This may have implications for the use of local anaesthetics in an ageing patient population.

Neural ischaemia may occur as a result of systemic or local vascular insufficiency. Systemic hypotension with or without a spinal anaesthetic may produce spinal cord ischaemia in the watershed areas between radicular vessels, resulting in flaccid paralysis of the lower extremities (anterior spinal artery syndrome). The use of local anaesthetic solutions containing epinephrine or phenylephrine may theoretically result in local ischaemia, especially in patients with microvascular disease, but clinical data are lacking [11, 17]. Furthermore, large clinical studies have failed to identify the use of vasopressors as a risk factor for neurological injury. Most cases of presumed vasopressor-induced neurological deficits after spinal anaesthesia have been single case reports, often with several other risk factors involved [18].

The neural double crush

Patients with a pre-existing neurological condition may be at increased risk for regional-anaesthesia-related nerve injury on the basis of the "double crush", which hypothesises that nerve fibres that are already compromised are also more vulnerable to injury at another site (Fig. 1).

All patients (N=360) who underwent ulnar nerve transposition at the Mayo Clinic from 1985 to 1999 were retrospectively studied to evaluate whether the performance of an axillary block in the presence of a pre-existing (ulnar) neuropathy [19]. A general anaesthetic was performed in 260 (72%) patients. The remaining 100 (28%) patients each received an axillary block, including 64 patients in whom an ulnar paraesthesia or nerve stimulator motor response was elicited at the time of block placement. Patient characteristics, the severity of preoperative ulnar nerve dysfunction and surgical variables were similar in the two groups. Anaesthetic technique did not affect neurological outcome (new or worsening pain, paraesthesias, numbness or motor weakness) immediately after surgery or at 2 or 6 weeks after surgery. All 6 patients in the axillary group who reported new or worsening neurological symptoms after surgery had received bupivacaine in combination with either an ulnar paraesthesia or motor response.

Although laboratory studies have identified multiple risk factors for the deve-

lopment of neurological injury after regional anaesthesia, clinical studies have not been performed to verify the results. Even less information is available for the variables affecting neurological damage in patients with pre-existing neurological disease. However, several disorders of the central and peripheral nerves require further mention.

Multiple sclerosis

Multiple sclerosis is a degenerative disease of the CNS and is characterised by multiple sites of demyelination in the brain and spinal cord. The peripheral nerves are not involved. The course of the disease consists in exacerbations and remissions of symptoms, and the unpredictability in the patient's changing neurological status must be appreciated when an anaesthetic technique has to be selected. Stress, surgery and fatigue have been implicated in the exacerbation of multiple sclerosis. Epidural and, more often, spinal anaesthesia have been implicated in the relapse of multiple sclerosis, although the evidence is not strong [20]. The mechanism by which spinal anaesthesia may exacerbate multiple sclerosis is presumed to be direct local anaesthetic toxicity. Epidural anaesthesia has been recommended in preference to spinal anaesthesia, because the concentration of local anaesthetic in the white matter of the spinal cord is one-fourth that after epidural administration [21]. A dilute solution of local anaesthetic with spinal or epidural anaesthesia is also advised. Because multiple sclerosis is a disorder of the CNS, peripheral nerve blocks do not affect neurological function and are considered appropriate anaesthetic techniques.

The largest series of neuraxial anaesthesia in patients with pre-existing CNS conditions involved 139 patients [22]. Post-polio syndrome and multiple sclerosis were the most common CNS disorders (Table 1).

Table 1. Central nervous system diagnoses

Neurological diagnosis	Number of patients (*N*)[a]	Percentage (%)
Post-poliomyelitis	79	56.4
Multiple sclerosis	35	25
Traumatic spinal cord injury	13	9.3
Amyotrophic lateral sclerosis	5	3.6
Guillain–Barré syndrome	3	2.1
Meningomyelocele	2	1.5
Cauda equina syndrome	1	0.7
Huntington's chorea	1	0.7
Neurosyphilis with paraplegia	1	0.7

[a]One patient had a diagnosis of both multiple sclerosis and prior poliomyelitis.
From [22].

Twenty-five (18%) patients had a co-existing radiculopathy, peripheral sensorimotor neuropathy or spinal stenosis. Gender distribution was 86 (62%) male and 53 (38%) female. The mean age of these patients was 60±17 years. CNS diagnoses had been known for a mean of 23±23 years. The majority of patients had sensori-

motor deficits at the time of block placement. There were no patients with new or worsening postoperative neurological deficits compared with preoperative findings (0.0%; 95%CI 0.0–0.3%).

Diabetes mellitus

A substantial proportion of diabetic patients report clinical symptoms of a peripheral neuropathy. However, a subclinical peripheral neuropathy may be present before the onset of pain, paraesthesia or sensory loss and may remain undetected without electrophysiological testing for slowing of nerve conduction velocity. The presence of underlying nerve dysfunction suggests that patients with diabetes may have a decreased requirement for local anaesthetic. The diabetes-associated microangiopathy of nerve blood vessels decreases the rate at which local anaesthetic uptake occurs from the site of administration, resulting in prolonged exposure to local anaesthetic solutions. The combination of these two mechanisms may cause nerve injury with an otherwise safe dose of local anaesthetic in diabetic patients.

In a study examining the effect of local anaesthetics on nerve conduction block and injury in diabetic rats, Kalichman and Calcutt [12] reported that the local anaesthetic requirement is decreased and the risk of local anaesthetic-induced nerve injury is increased in diabetics. These findings support the suggestions that diabetic patients may require less local anaesthetic to produce anaesthesia and that a reduction in dose may be necessary to prevent neural injury by doses considered safe in nondiabetic patients. Similarly, Singelyn et al. [23] reviewed block difficulty, success rate and neurological complications in a series of 1,342 patients undergoing popliteal fossa block using a nerve stimulator approach. The 371 patients with a diagnosis of diabetes mellitus required more needle passes to obtain a satisfactory motor response, but also noted a higher success rate. There were no neurological complications in any patient.

A recent retrospective review of 567 patients with a sensorimotor neuropathy or diabetic polyneuropathy who underwent neuraxial block evaluated the risk of neurological complications. All patients had a single neurological diagnosis; there were no co-existing spinal canal or CNS disorders [22]. The majority of patients had sensorimotor deficits at the time of surgery. Two (0.4%; 95%CI 0.1–1.3%) patients experienced new or worsening postoperative neurological deficits compared with preoperative findings. This frequency is consistent with previous investigations examining nondiabetic patients. The investigators concluded that neuraxial blockade does not appear to increase the risk of neurological complications among patients with diabetic sensorimotor or polyneuropathy.

Epidural and spinal anaesthesia after major spinal surgery

Previous spinal surgery has been considered to represent a relative contraindication to the use of regional anaesthesia. Many of these patients experience chronic back pain and are reluctant to undergo epidural or spinal anaesthesia, fearing

exacerbation of their pre-existing back complaints. Several postoperative anatomical changes make needle or catheter placement more difficult and complicated after major spinal surgery. In a study 105 of 48 patients with chronic low back pain after spinal fusion, 8 showed significant spinal stenosis on computed tomographic scans and required surgical decompression [24]. The ligamentum flava may be injured during surgery, resulting in adhesions within or obliteration of the epidural space. The spread of epidural local anaesthetic may be affected by adhesions, producing an incomplete or 'patchy' block. Obliteration of the epidural space may increase the incidence of dural puncture and make subsequent placement of an epidural blood patch difficult. Needle placement in an area of the spine that has undergone bone grafting and posterior fusion is not possible with midline or lateral approaches; needle insertion can be accomplished at unfused segments only.

The guidelines for epidural anaesthesia after spinal surgery are unclear. Daley et al. [25] reviewed the charts of 18 patients with previous Harrington rod instrumentation who underwent 21 attempts at epidural anaesthesia for obstetric analgesia. Continuous lumbar epidural anaesthesia was successfully established in 20 of 21 attempts, but only 10 procedures were performed easily at the first attempt. The remaining 11 patients required larger amounts of local anaesthetics or complained of a patchy block or both. There was no correlation between the level of surgery and the easy of insertion or the quality of epidural anaesthesia. There were no side-effects except for low back pain in two patients in whom multiple attempts at catheter placement had been necessary.

Crosby and Halpern [26] studied nine parturients with previous Harrington rod instrumentation who underwent epidural anaesthesia for analgesia during labour and delivery. Five of the nine catheters were successfully placed at the first attempt. Four of the nine procedures were complicated and involved multiple attempts before successful insertion, traumatic catheter placement requiring a second insertion, inadequate epidural analgesia with subsequent dural puncture on a repeated attempt or inability to locate the epidural space despite attempts at two levels. Seven of the nine patients obtained satisfactory analgesia. There were no adverse sequelae related to the epidural insertion.

Hubbert [27] described attempted epidural anaesthesia in 17 patients with Harrington rod instrumentation. Four of five patients with fusions terminating above the interspace between L-3 and L-4 had successful epidural placement. However, in 12 patients with fusions extending to the interspace between L-5 and S-1, 6 attempts were unsuccessful, 5 patients required multiple attempts, and 1 patient had a dural puncture after multiple attempts at epidural placement before it was successfully achieved. A false loss of resistance was reported to have occurred frequently.

Thus, historically it was concluded that epidural anaesthesia may be successfully performed in patients who have had previous spinal surgery, but successful catheter placement may be possible on the first attempt in only 50% of patients, even by an experienced anaesthesiologist. Although adequate epidural anaesthesia is eventually produced in 40–95% of patients, there appears to be a higher incidence of traumatic needle placement, unintentional dural puncture and unsuccessful

epidural needle or catheter placement, especially if spinal fusion extends to between L-5 and S-1.

A more recent investigation examined the overall success and neurological complication rates among 937 patients with spinal stenosis or lumbar disc disease undergoing neuraxial block between 1988 and 2000 [22]. Of these, 210 (22%) patients had a co-existing peripheral neuropathy in addition to their spinal cord pathology. Gender distribution was 619 (66%) male and 318 (34%) female. The mean age of these patients was 67±14 years. Neurological diagnoses had been known for a mean of 5±6 years; 335 (51%) patients had active symptoms at the time of the block. In addition, 207 (22%) patients had a history of prior spinal surgery before undergoing neuraxial block, although the majority were simple laminectomies or discectomies (Table 2).

Table 2. Outcomes of neuraxial blockade in patients with spinal stenosis of lumbar disc disease. From [22]

	Patients without prior spine surgery (N=730)		Patients with prior spine surgery (N=207)	
Block efficacy	**N**	**(%)**	**N**	**(%)**
Satisfactory	709	(97.1)	202	(97.6)
Unilateral	0	(0.0)	1	(0.5)
Segmental	9	(1.2)	0	(0.0)
No block	12	(1.6)	4	(1.9)
Technical complications				
Unable to locate epidural or intrathecal space	6	(0.8)	0	(0.0)
Traumatic (bloody)	19	(2.6)	8	(3.9)
Paraesthesia	37	(5.1)	9	(4.4)
"High" spinal	1	(0.1)	0	(0.0)
Unable to advance catheter (epidural)	14	(4.9)	3	(4.1)
Accidental dural puncture (epidural)	8	(2.8)	2	(2.7)
Neurological complications	7	(1.0)	3	(1.4)

Success rates did not differ between patients who had previous surgery and those who had undergone a spinal procedure. Ten (1.1%; 95%CI 0.5–2.0%) patients experienced new or progressive neurological deficits compared with preoperative findings. Although the majority of the deficits were related to surgical trauma or tourniquet ischaemia, the neuraxial block was the primary aetiology in 4 patients.

The preliminary nature of these data warrants care in their interpretation. However, overall, patients with spinal stenosis or lumbar disc disease may undergo successful neuraxial block without a significant increase in neurological complications. Importantly, this includes patients who have undergone prior (minor) spinal surgery.

Anaesthetic management of neurological disease

Progressive neurological disease is considered by some to be a relative contraindication to regional anaesthesia, because of the difficulty in determining the cause of new neurological deficits that appear perioperatively. There are no controlled clinical studies identifying regional anaesthesia as a significant factor in increased risk of neurological injury; only anecdotal reports are available. The medicolegal issue, however, remains, and if regional anaesthesia is indicated for other pre-existing medical conditions or by patient request, the patient should be informed of the risk of neurological complications, including coincidental progression of preoperative deficits, associated with anaesthesia and surgery. This discussion, along with preoperative neurological status, should be fully documented in the patient's record.

Patients with preoperative neurological deficits may undergo further nerve damage more readily from needle or catheter placement, local anaesthetic systemic toxicity, and vasopressor-induced neural ischaemia. Although the use of paraesthesia techniques is not contraindicated, care should be taken to minimise needle trauma and intraneuronal injection. Dilute local anaesthetic solutions should be used whenever feasible to decrease the risk of local anaesthetic systemic toxicity.

The use of epinephrine-containing solutions is controversial. The potential risk of vasopressor-induced nerve ischaemia must be weighed against the advantages of predicting local anaesthetic intravascular injections, improved quality of block, and decreased blood levels of local anaesthetics. Because epinephrine also prolongs and block and therefore neural exposure to local anaesthetics, the appropriate concentration and dose of local anaesthetic solutions must be considered. Patients with microvascular disease in combination with an underlying peripheral neuropathy, such as those with diabetes, may be most sensitive to the vasoconstrictive effects of epinephrine.

Efforts should also be made to decrease neural injury in the operating room through careful patient positioning. Postoperatively, these patients must be followed closely to detect potentially treatable sources of neurological injury, including constrictive dressings, improperly applied casts and increased pressure on neurologically vulnerable sites. New neurological deficits should be evaluated promptly by a neurologist for formal documentation of the patient's evolving neurological status and the arrangement of further testing and long-term follow-up.

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Chapter 30

Infectious complications of regional anaesthesia

D.J. Wedel

Infectious complications may occur after any regional anaesthetic technique, but are of greatest concern if the infection occurs near or within the central neuraxis. Possible risk factors include underlying sepsis, diabetes, depressed immune status, steroid therapy, localised bacterial colonisation or infection, and chronic catheter maintenance. Bacterial infection of the central neuraxis may present as meningitis or cord compression secondary to abscess formation. The infectious source may be exogenous (e.g. contaminated equipment or medication), or endogenous (a bacterial source in the patient seeding to the needle or catheter site). Microorganisms can also be transmitted via a break in aseptic technique, and indwelling catheters may be colonised from a superficial site (skin) and subsequently serve as a wick for spread of infection from the skin to the epidural or intrathecal space.

Although individual cases have been reported in the literature, serious central neuraxial infections such as arachnoiditis, meningitis, and abscess are rare following spinal or epidural anaesthesia. In a combined series of more than 65,000 spinal anaesthetics, there were only 3 cases of meningitis. A similar review of approximately 50,000 epidural anaesthetics failed to disclose a single epidural or intrathecal infection [1]. A more recent multicentre, prospective study including 40,640 spinal and 30,413 epidural anaesthetics reported no infectious complications [2]. Few data suggest that spinal or epidural anaesthesia during bacteraemia is a risk factor for infection of the central neuraxis. Although the authors of the large studies cited did not report how many patients were febrile during administration of the spinal or epidural anaesthetic, a significant number of the patients included in these studies underwent obstetric or urological procedures, and it is likely that some patients were bacteraemic after (and perhaps during) needle or catheter placement. In a recent retrospective review of 4,767 consecutive spinal anaesthetics by Horlocker et al. [3], two infectious complications were noted. One patient, who developed a disc space infection following spinal anaesthesia, was noted to have had a recent untreated episode of urosepsis. The second patient developed a paraspinal abscess 11 days after spinal anaesthesia performed after unsuccessful attempts at caudal blockade for treatment of a suspected rectal fistula. Despite the apparently low risk of central nervous system infection following regional anaesthesia, anaesthesiologists have long considered sepsis to be a relative contraindication to the administration of spinal or epidural anaesthesia. This impression is based largely on anecdotal reports and conflicting laboratory and clinical investigations.

The clinical presentation of infections of the central nervous system, the laboratory and clinical studies evaluating the association between meningitis and dural puncture in bacteraemic subjects, the risk of central neuraxial blockade in patients with herpes simplex and human immunodeficiency virus (HIV) and the clinical studies investigating the risk of infection during chronic epidural catheterisation in febrile and immunocompromised patients will be discussed. An understanding of these concerns will assist clinicians in evaluation of the febrile patient for central neuraxial blockade.

Neuraxial anaesthesia and infection

Dural puncture has been cited as a risk factor for meningitis in the septic patient. The presumed mechanisms include introduction of blood into the intrathecal space during needle placement and disruption of the normal protective mechanisms provided by the blood–brain barrier but these have not been confirmed. In 1919 Weed et al. [4] demonstrated that dural puncture performed in septicaemic rats invariably resulted in fatal meningitis. In the same year Wegeforth and Latham [5] described 93 patients suspected of having meningitis, all of whom underwent diagnostic lumbar puncture (LP) and blood cultures. It was found that 38 patients had proven meningitis, while the other 55 (6 were bacteraemic at the time of LP) had normal CSF. Of the 6 patients with bacteraemia, 5 subsequently developed meningitis. These findings suggest that patients with bacteraemia are at risk. The LPs in this study were performed during two epidemics of meningitis occurring at a military installation. These two historical studies provided support for the claim that LP during bacteraemia was a risk factor for meningitis. Subsequent clinical studies yielded conflicting results. Pray [6] reported that the incidence of meningitis in children who underwent diagnostic LP during pneumococcal sepsis was no higher among patients who had normal CSF results than among those who did not undergo diagnostic LP. Eng and Seligman [7] retrospectively reviewed the records of 1,089 bacteraemic patients, 200 of whom underwent LP. There was no difference between the incidence of spontaneous and "LP-induced" meningitis. Teele et al. [8] reviewed the records of 277 children with bacteraemia from 1971 to 1980. Meningitis occurred in 7 (15%) of 46 children in whom LP revealed normal CSF, but in only 2 (1%) of 231 children who did not undergo LP. This difference was statistically significant. In addition, children receiving antibiotics at the time of LP were less likely to develop meningitis.

Carp and Bailey [9] supported the finding that treatment with antibiotics may prevent LP-induced meningitis. Twelve of 40 bacteraemic rats subjected to cisternal puncture with a 26-G needle developed meningitis. Neither bacteraemic animals not subjected to dural puncture nor animals undergoing dural puncture in the absence of bacteraemia developed meningitis. In humans, antibiotic therapy is often deferred until after cultures are obtained. There are several other limitations to this study. While *E. coli* is a common cause of bacteraemia, it is an uncommon cause of meningitis. In addition, the authors knew of sensitivity to the bacteria

injected, allowing for appropriate antibiotic coverage. The authors also performed a cisternal puncture (rather than LP) and utilised a 26-G needle, producing a relatively large dural defect in the rats in proportion to the corresponding puncture site in humans. Finally, no local anaesthetics, which are typically bacteriostatic, were injected. Human data are scarce, although epidural anaesthesia has been extensively used in febrile pregnant patients with rare adverse infectious complications. The importance of a localised infection at a site distant from the site of needle insertion in the aetiology of epidural or intrathecal infectious complications is unknown, but such an association is at best highly theoretical.

Epidural abscess formation following epidural or spinal anaesthesia can be superficial, requiring limited surgical drainage and IV antibiotics, or occur deep in the epidural space with associated cord compression. Superficial infections present with local tissue swelling, erythema and drainage, often associated with fever, but rarely cause neurological problems unless untreated. Epidural abscess formation usually presents several days after neural blockade with clinical signs of severe back pain, local tenderness, and fever associated with leucocytosis. MRI is advocated as the most sensitive modality for evaluation of the spine when infection is suspected [10]. Du Pen et al. [11] reported a 5.4% incidence (1:1,700 catheter-days) of infection during chronic epidural catheterisation, which compared favourably with infection rates associated with other "chronic" catheters (e.g. Hickman).

Factors affecting bacterial colonisation during epidural catheterisation

Although the epidural catheter tip is frequently colonised, progression to epidural space infection is rare [11, 12]. The low frequency of significant epidural infection (1–2 cases per 10,000 hospital admissions [13]) associated with epidural catheter placement is especially notable when compared to the frequency of intravenous catheter-related septicaemia, which is approaching 1%, or more than 50,000 cases annually. Several factors may contribute to the low incidence of epidural space infections, including meticulous attention to aseptic technique, careful monitoring of catheter insertion site, antibiotic prophylaxis, and use of bacterial filters. However, since these interventions are commonly initiated in patients with indwelling central venous catheters, additional factors unique to epidural anaesthesia and analgesia, such as the bactericidal effect of local anaesthetic solutions, may also contribute significantly.

Bupivacaine and lidocaine have been shown to inhibit the growth of a variety of microorganisms in culture [14]. Unfortunately, the bactericidal effect declines significantly with the concentrations of local anaesthetic typically used to provide analgesia, while opioid solutions do not exhibit any ability to inhibit bacterial growth. In addition, growth of *S. aureus,* and of coagulase-negative staphylococci, the most commonly identified pathogens in epidural infections, is inhibited only at higher concentrations of local anaesthetic, such as solutions of 2% lidocaine and 0.5% bupivacaine. Therefore, although it appears that local anaesthetic solutions are unlikely to prevent epidural infections in most patients receiving epidural

analgesia, it is possible that in immunocompromised patients, local anaesthetics may inhibit the growth of more fastidious organisms even at low concentrations. Further clinical studies are needed to investigate the in vivo bactericidal effects of dilute local anaesthetic solutions.

The catheter hub, the catheter insertion site, and haematogenous spread are three major routes of entry for microorganisms into the epidural space, with the catheter hub accounting for nearly half the sources [11, 15, 16]. A bacterial filter placed at the catheter hub acts as a physical barrier for bacteria present in the infusing solution, and should theoretically reduce the incidence of epidural colonisation. However, studies of epidural catheter tip cultures have yielded mixed results, and cases of epidural infection following hub colonisation despite the use of filters have been reported [11, 16, 17]. Possible explanations for hub-related epidural infections in patients with bacterial filters in place include a reduced antimicrobial effectiveness with prolonged use and direct contamination of the hub during filter-changing techniques. De Cicco et al. [18] reported a trend toward a positive association between the number of filter changes and the rate of positive hub cultures. These data suggest that continued attention to aseptic technique is warranted throughout the period of epidural catheterisation and that the use of bacteriological filters alone is unlikely to be efficacious in preventing epidural colonisation and infection [19].

Aseptic technique

Although previous publications have repeatedly recommended meticulous aseptic technique, there are no defined standards for asepsis during the performance of regional anaesthetic procedures [20]. Hand-washing remains the most crucial component of asepsis; gloves should be regarded as a supplement to, and not a replacement for, hand-washing [21]. Conversely, the use of gowns and gloves does not further reduce the likelihood of cross-contamination. Surgical masks, initially considered a barrier to protect the *proceduralist* from patient secretions and blood, may be appropriate owing to the increasing number of cases of postspinal meningitis, many of which result from contamination of the epidural or intrathecal space with pathogens from the operator's buccal mucosa [22–25]. Schneeberger et al. [23] reported four cases of iatrogenic meningitis following spinal anaesthesia occurring over a 4-year period. The patients typically presented with a severe headaches 24 h postoperatively (2 received an epidural blood patch). All these cases involved the same anaesthesiologist, who had a history of recurrent pharyngitis and did not wear a mask during the procedure. Interestingly, similar reports have been noted among patients undergoing pain procedures [26].

Infectious complications of peripheral regional techniques

Although meningitis and epidural abscess are the most significant infectious complications of regional anaesthesia, the associated risk following plexus and peripheral techniques remains undefined. Auroy et al. [2] reported no infectious complications in 21,278 single-injection peripheral nerve blocks. This low incidence is supported by Borgeat et al.'s [27] report of no complications in 521 patients undergoing interscalene nerve blockade.

The more frequent placement of catheters for peripheral nerve blockade, often for prolonged periods, might be expected to increase the risk of infectious complications; however, few data are available to support this theoretical assumption. Two studies look more specifically at the risk of infection in continuous peripheral nerve blocks. Capdevila et al. [28] prospectively studied 1,416 patients in ten centres who were undergoing continuous peripheral nerve blocks for orthopaedic procedures. A total of 969 (68%) catheters were cultured when removed, and patients were actively monitored for signs of localised infection or sepsis. Positive bacterial colonisation was found in 278 (29%) catheters, most commonly with *S. epidermidis*. The incidence of local inflammation was present in 3% of patients. In these patients 44% of the catheters were colonised, whereas in patients without inflammatory signs only 19% of the catheters were colonised. There was no correlation between colonisation and the presence of fever. Risk factors for local infection/inflammation were admission to an intensive care unit, male gender, catheterisation for over 48 h and lack of antibiotic prophylaxis. A study by Cuvillon et al. [29] investigated the incidence of infectious complications in patients with a total of 211 continuous femoral catheters. Colonisation of the 208 catheters examined after 48 h showed a rate of 57%, with the most common organism (71%) again being *Staphylococcus epidermidis*. Echography was performed in each instance of positive catheter colonisation. No cellulitis or abscess was noted, but three cases of transitory bacteraemia were attributed to the presence of the femoral catheters. There were no long-term sequelae with infectious causes. Although the necessity of antibiotic prophylaxis during placement of permanent epidural catheters and implantable devices to treat chronic pain is well defined [30, 31], the importance of antibiotic prophylaxis during placement and maintenance of neuraxial or peripheral catheters is less clear. In a series of 405 axillary catheters, the single infectious complication occurred in a nonsurgical patient who did not receive the "usual" perioperative antibiotic prophylaxis [32].

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Chapter 31

The Mayo Clinic total joint analgesic pathway

T.T. Horlocker

Peripheral nerve blocks are well described, but not universally accepted or utilised. In a national survey of 409 anaesthesiologists evaluating the use of peripheral nerve blocks, Hadzic et al. [1] reported that while nearly all respondents perform regional techniques, less that half performed more than five peripheral nerve blocks per month. Importantly, lower extremity blocks other than ankle blocks were seldom used. This is unfortunate, since lower extremity blocks have many advantages over neuraxial techniques and represent alternatives for both intraoperative anaesthesia and postoperative analgesia. Anaesthesiologists in Europe have already shifted their practice towards peripheral blocks. A prospective study of 103,730 regional anaesthetics performed in France over a 5-month period included 21,278 peripheral blocks.

Lower extremity blocks may be accomplished when neuraxial blockade is contraindicated. Spinal and epidural anaesthesia are often avoided in the anticoagulated or febrile patient, because of the catastrophic consequences of bleeding or infection in the central nervous system. Although it is difficult to quantitate the incidence of haemorrhagic or infectious complications of peripheral nerve blocks, the lack of case reports suggests that the risk of serious morbidity is minimal.

Despite these many advantages, peripheral nerve blocks have not been widely used in the United States of America. Peripheral blocks are more technically demanding than neuraxial techniques, often requiring multiple injections, longer onset time, and larger volumes of local anaesthetic. Advances in needle and catheter technology, refinement of devices to localise neural structures, and the introduction of longer lasting encapsulated local anaesthetics will improve the acceptance and popularity of peripheral techniques.

Lower extremity techniques

Lower extremity peripheral techniques, which allow complete unilateral blockade, have traditionally been underutilised [2]. In part, this is due to the widespread acceptance and safety of spinal and epidural anaesthesia. Furthermore, unlike the brachial plexus, the nerves supplying the lower extremity are not anatomically clustered where they can be easily blocked with a relatively superficial injection of local anaesthetic. Because of the anatomical considerations, lower extremity blocks are technically more difficult and require more training and practice before exper-

tise is acquired. Many of these blocks were classically performed using paraesthesia, loss of resistance or field block techniques, with variable success.

Advanced needles, catheters and nerve stimulator technology have facilitated the localisation of neural structures and improved success rates. These blocks are safe, and their unilateral nature makes them ideal for the patient undergoing total hip or knee arthroplasty, as the contralateral limb is immediately available to assist with early ambulation. Although single-injection techniques have been utilised, the duration of effect after a single injection is not sufficient to result in major improvements in analgesia or outcome [3–5]. Recent applications of peripheral nerve block techniques have allowed prolonged postoperative analgesia (with an indwelling catheter) to assist rehabilitation and facilitate hospital discharge [6–14].

The lumbar plexus can be blocked by three distinct approaches. Block of the full lumbar plexus (femoral, lateral femoral cutaneous, obturator) is accomplished with the psoas block [2, 5, 15, 16]. In comparison, the fascia iliaca and femoral approaches will reliably block the femoral but not the lateral femoral, cutaneous and obturator nerves [5, 16, 17]. Complete unilateral lower extremity blockade is achieved by combining a lumbar plexus technique with a proximal sciatic block [2]. The selection of the regional analgesic technique is dependent on the surgical site. For example, the psoas compartment approach to the lumbar plexus is preferable for surgery to the hip, because it is the farthest proximal lumbar plexus technique. Conversely, for surgery to the knee, the more distal femoral and fascia iliaca approaches are sufficient (Fig. 1).

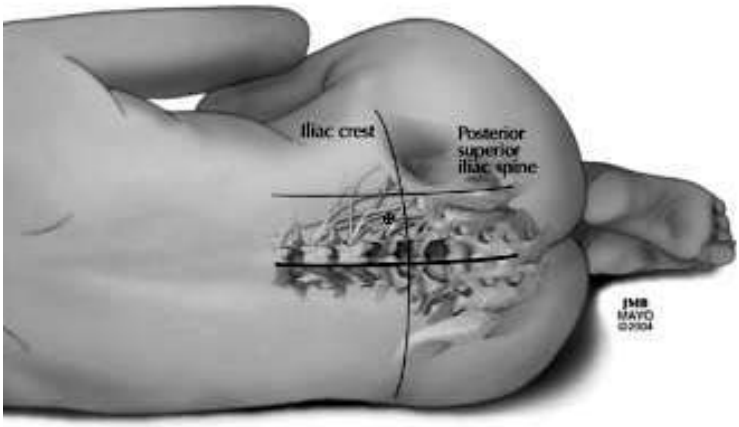

Fig. 1. Psoas compartment block. A horizontal line is drawn parallel to the posterior superior iliac spine (PSIS), while a vertical line is drawn at the L4–5 level. The distance from midline to the PSIS horizontal is divided into thirds, and the junction of the lateral third and medial two-thirds is identified. Needle insertion is 1 cm cephalad to this point. A 10-cm (4-in.) stimulating needle is advanced until the transverse process of L4 is contacted. The needle is redirected caudad and advanced behind the transverse process. Approximately 2 cm deep to the transverse process, the lumbar plexus is identified (through elicitation of a quadriceps motor response) and 25 ml of local anaesthetic is incrementally injected.

Hip fracture

Femoral neck fracture occurs in elderly patients, who often have multiple medical co-morbidities. Complications include thromboembolic events, confusion and pulmonary infections. In addition, quadriceps spasm contributes to perioperative pain and the need for opioid analgesia. Several studies have evaluated the use of continuous lumbar plexus block (psoas approach) in the pre-, intra-, and postoperative management of hip fracture.

An early study performed in 1978 included 21 patients with femoral neck fracture. Continuous psoas catheters were placed, using a loss-of-resistance technique, upon patients' arrival on the ward. The catheters were used intraoperatively combined with a general anaesthetic, and were removed 48 h postoperatively. During this time, the catheters were intermittently bolused with 15–20 ml of 0.5% bupivacaine. Eighty percent of patients had adequate analgesia and did not require supplementation [18]. Similar results were reported in a more recent study by Chudinov et al. [19]. Forty patients undergoing stabilisation of femoral fractures were randomised to receive a continuous psoas block (implemented 16–48 h preoperatively and continued 72 h postoperatively) or meperidine. The lumbar plexus block was inadequate for surgical anaesthesia in 85% of patients. VAS scores were lower and patient satisfaction was higher in the psoas group. These studies suggest that continuous psoas block is an effective perioperative analgesic technique, but that supplementation is required during surgical repair. In addition, possible improvement in patient outcomes has not been formally investigated.

Total hip arthroplasty

The usefulness of peripheral nerve blocks for total hip arthroplasty (THA) has not been clearly established. Innervation to the joint involves both the lumbar and the sacral plexuses. Therefore, while a lumbar plexus block may reduce pain postoperatively, it would not be sufficient as surgical anaesthesia. A study in the orthopaedic literature [20] demonstrated reduced intraoperative blood loss (310±81 ml vs 617±230 ml) in THA patients who received a single-shot psoas block (0.42 ml/kg of 0.375% bupivacaine). No other outcomes were monitored.

Stevens et al. [4] prospectively studied 60 patients undergoing THA who were randomised to receive general anaesthesia with or without a psoas block. Blocks were performed using a nerve stimulator, and 0.4 ml/kg of 0.5% bupivacaine with epinephrine was injected. Intraoperative supplemental fentanyl was needed three times as often in the control group. Pain scores and morphine consumption remained lower in the psoas group 6 h postoperatively. Perioperative blood loss was also modestly decreased in the psoas group. There was epidural spread in 3 of 28 patients, but no other side-effects were noted. A single study suggests that continuous psoas technique would further facilitate the rehabilitation of patients undergoing THA [12].

Total knee arthroplasty

Patients undergoing total knee arthroplasty (TKA) experience significant postoperative pain. Failure to provide adequate analgesia impedes aggressive physical therapy and rehabilitation, which are critical to maintaining the joint's range of motion and potentially delays hospital discharge.

Although numerous methods of providing postoperative analgesia after TKA have been reported, the optimal technique from the aspects of efficacy, number/type of side-effects, surgical outcome and resource utilisation is unknown. Several European studies have suggested that aggressive postoperative analgesic techniques maintained for 48–72 h result in a shorter rehabilitation period and increased joint mobility. Singelyn et al. [7] assessed the influence of three analgesic techniques (patient-controlled analgesia, continuous femoral 3-in-1 block, and epidural analgesia) on postoperative knee rehabilitation after TKA. Patients in whom regional analgesic techniques had been applied reported significantly lower pain scores, better knee flexion (until 6 weeks after surgery), faster ambulation, and shorter hospital stay than patients who received intravenous morphine. However, these benefits did not affect the outcome at 3 months (Fig. 2).

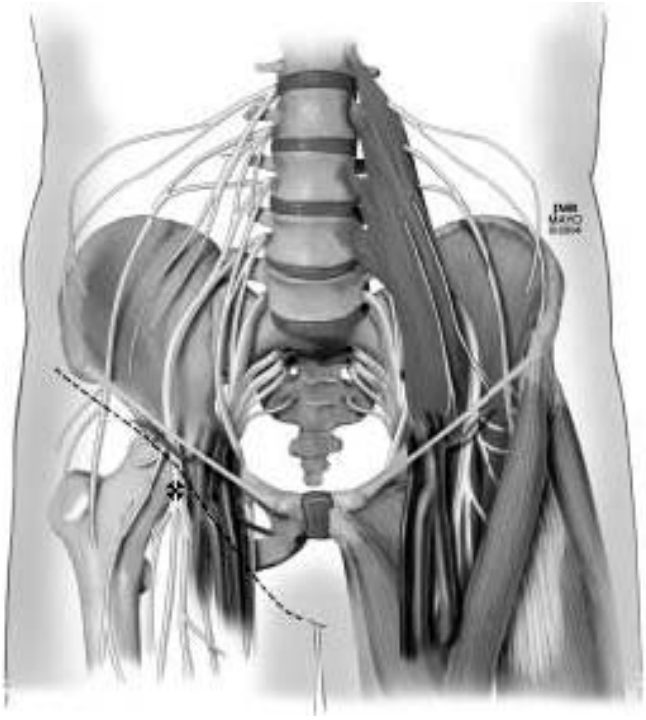

Fig. 2. Femoral block. The *dotted line* corresponds to the inguinal crease. Needle insertion site is 1–2 cm lateral to the femoral arterial pulsation at this level. A 5-cm (2-in.) needle is advanced until a quadriceps response is noted, and 25 ml of local anesthetic is incrementally injected.

Capdevila et al. [6] also evaluated the effect of postoperative analgesia on surgical outcome and rehabilitation following TKA. Patients were randomised to receive one of three postoperative analgesia techniques for 72 h: continuous epidural infusion, continuous femoral block or intravenous patient-controlled morphine. Pain was assessed at rest and during continuous passive movement using a visual analogue scale. To evaluate functional outcome, the maximal amplitudes were measured again on postoperative day 5, at hospital discharge (day 7), and at 1- and 3-month follow-up examinations. When the patients left the surgical ward they were admitted to a rehabilitation centre, where their length of stay depended on prospectively determined discharge criteria. The continuous epidural infusion and continuous femoral block groups showed significantly lower visual analogue scale scores at rest and during continuous passive motion than did the patient-controlled morphine group. The early postoperative knee mobilisation levels in both the continuous epidural infusion and the continuous femoral block groups were significantly closer to the target levels prescribed by the surgeon than those in the patient-controlled morphine group. The durations of stay in the rehabilitation centre were significantly shorter in the regional analgesic groups than in the patient-controlled morphine group. Side-effects were encountered more frequently in the continuous epidural infusion group (Table 1).

Table 1. Knee flexion and duration of stay during rehabilitation after total knee arthroplasty

	Patient-controlled analgesia (PCA) *N*=19	Continuous femoral block (CFB) *N*=20	Continuous epidural analgesia (CEA) *N*=17
Knee mobility in degrees median (25^{th}–75^{th} percentiles)			
Day 5	60 (50–70)*	80 (65–85)	85 (75–100)
Day 7	80 (65–90)*	90 (70–95)	90 (78–100)
1 month	90 (85–100)	95 (95–100)	105 (100–120)
3 months	125 (100–125)	125 (105–125)	130 (115–130)
Days of rehabilitation, median (range)	50 (30–80)*	40 (31–60)	37 (30–45)

*$P<0.05$ vs CFB and CEA. Adapted from [6]

These landmark studies demonstrate the long-term effects of an aggressive postoperative analgesic technique following orthopaedic surgery—continuous femoral and epidural analgesia hastened rehabilitation and improved joint mobility [21]. Additional studies are required to assess these outcomes in a managed care environment with shorter hospital stays of approximately 5 days and discharge home, rather than to a rehabilitation centre for an extended period, as is the standard in parts of Europe. For example, the median duration of hospital stay (including rehabilitation unit) in the study by Singelyn et al. was 19 days, while the patients in the investigation by Capdevila et al. were hospitalised for as long as 80 days postoperatively. An additional relevant result of these investigations is the finding that continuous femoral block provides a quality of analgesia and surgical outcomes similar to that of continuous epidural analgesia, but is associated with

fewer side-effects. This suggests that continuous peripheral techniques may be the optimal analgesic method following TKA (Fig. 3).

More recent investigations suggest that supplemental sciatic [13, 14] or obturator [22] nerve blockade is required to obtain adequate analgesia following total knee (but not hip) arthroplasty. The sciatic nerve can also be blocked at several sites in the hip and thigh. However, the more proximal approaches are necessary to achieve blockade of the posterior femoral cutaneous nerve, which is important in decreasing the posterior knee pain that knee replacement patients often experience in the early postoperative period.

Current innovations emphasise continuous peripheral nerve blocks combined with multiple scheduled analgesics (OxyContin®, acetaminophen), and *prn* (oxycodone) analgesics; no intravenous opioids are administered. Using strict criteria, 90% of patients undergoing minimally invasive primary hip or knee replacement achieved readiness for hospital discharge within 48 h [23]. These studies support the movement towards the continuous peripheral technique as the optimal analgesic method following total knee and hip arthroplasty. Additional information is

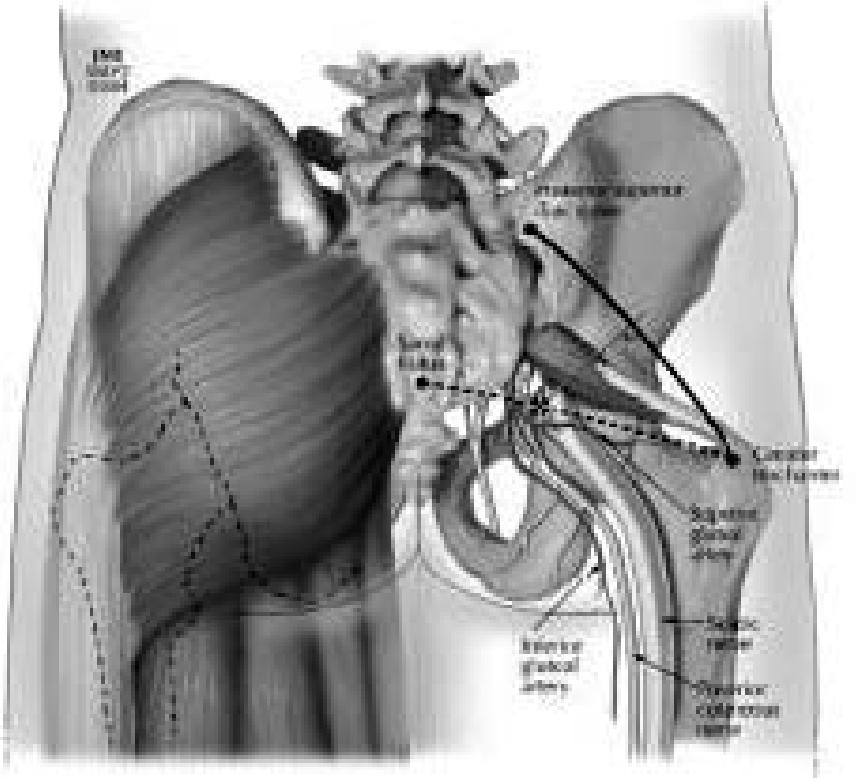

Fig. 3. Classic (posterior) approach to sciatic nerve block. Needle insertion is 5 cm along the perpendicular that bisects a line connecting the greater trochanter and posterior superior iliac spine. A 10-cm (4-in.) stimulating needle is advanced until either a tibial or a peroneal motor response is elicited; then 20–30 ml of local anesthetic is incrementally injected.

needed to determine the effectiveness of these techniques in conventional primary and revision joint arthroplasty.

Conclusions

In summary, peripheral nerve blocks are valuable regional anaesthetic techniques. Additional outcome studies are required to define their role in ambulatory and inpatient procedures. It is also imperative that before attempting the new approaches and applying continuous catheters, anaesthesiologists thoroughly review neural anatomy and practise meticulous regional anaesthetic technique, to improve success rates and avoid neurological complications.

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Chapter 32

Acute therapy in patients with wide-QRS complex tachyarrhythmias

R.D. White

Treatment of patients with wide-QRS-complex tachyarrhythmias mandates knowledge of both pharmacological and electrical interventions. In haemodynamically unstable patients emergency cardioversion always takes therapeutic precedence over drug therapy.

In stable patients correct drug therapy can safely and effectively terminate the majority of such tachyarrhythmias. This chapter discusses both pharmacological and electrical therapies. Correct diagnosis and immediate and appropriate therapy can often prevent degeneration of wide-complex tachyarrhythmias into potentially lethal events.

This discussion is based upon the 2005 Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care and the European Resuscitation Council Guidelines for Resuscitation 2005 [1, 2]. These documents should be consulted for detailed information on the management of patients with all forms of cardiovascular emergencies. The following tachyarrhythmias will be discussed and illustrated in this chapter: monomorphic and polymorphic ventricular tachycardia, the latter including torsades de pointes; wide-QRS-complex tachycardias of uncertain origin, wide-complex tachycardias in patients with Wolff-Parkinson-White syndrome and ventricular fibrillation and pulseless ventricular tachycardia.

Ventricular tachyarrhythmias

Monomorphic ventricular tachycardia

In the intensive care and perioperative settings, ventricular tachycardia (VT) can occur as a consequence of a variety of disorders, including acute myocardial ischaemia or myocardial infarction (MI); hypoxaemia; electrolyte derangements, especially hypokalaemia and/or hypomagnesaemia; and congestive heart failure (CHF). Although it is true that VT can result in rapid cardiovascular collapse or degenerate into ventricular fibrillation (VF), it is often not appreciated that VF can be accompanied by haemodynamic stability, which is rate related, as well as a consequence of compensatory sympathetic stimulation. The urgency of therapy is therefore dependent on the haemodynamic status of the patient, and it is not the fact that the tachycardia is ventricular in origin that makes it urgent.

Monomorphic ventricular tachycardia (MVT) is characterised on the ECG by the presence of QRS complexes that are wide and of uniform morphology (Fig. 1). ECG evidence that the wide-complex tachycardia is ventricular in origin includes the presence of intermittent P-waves unrelated to the QRS complexes (AV dissociation) and fusion/capture complexes (Figs. 2, 3). Other helpful evidence is a QRS complex width greater than 140 ms and negative concordance of the QRS complexes across the precordium on a 12-lead ECG (Fig. 4) [3]. Although these types of ECG evidence should be sought, they may not be present. It is important to recognise that clinical clues can provide strong support for a suspicion that the tachycardia is ventricular in origin: a clinical history of previous MI or signs and symptoms of acute myocardial ischaemia are strongly indicative that the wide-complex tachycardia is ventricular in origin. In fact, any wide-QRS complex tachycardia should initially be considered to be ventricular in origin until proven otherwise, and therapy should be directed with this consideration in mind.

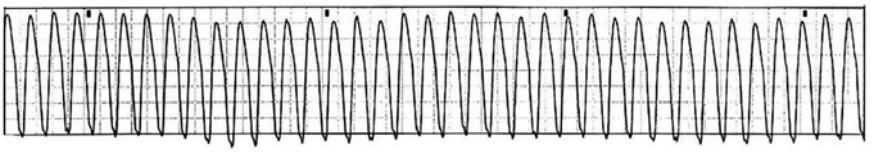

Fig. 1. Monomorphic ventricular tachycardia. The rate is 200/min, the rhythm is regular and all the QRS complexes have the same morphology

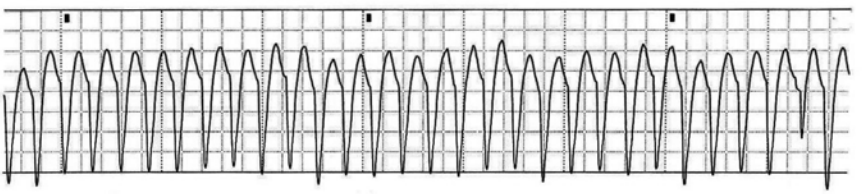

Fig. 2. Monomorphic ventricular tachycardia. A capture complex is seen (*second complex* from the *right*). The P-wave is seen in the preceding T-wave

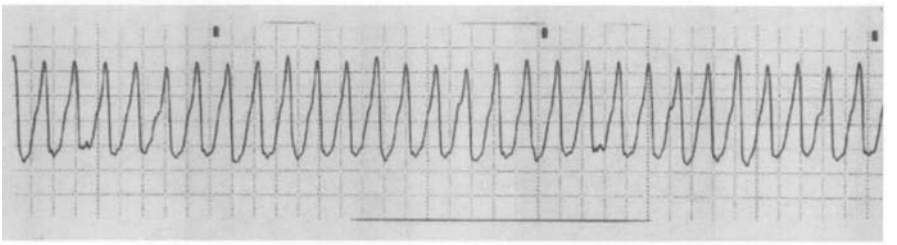

Fig. 3. Monomorphic ventricular tachycardia with AV dissociation. Two dissociated P-waves are clearly visible

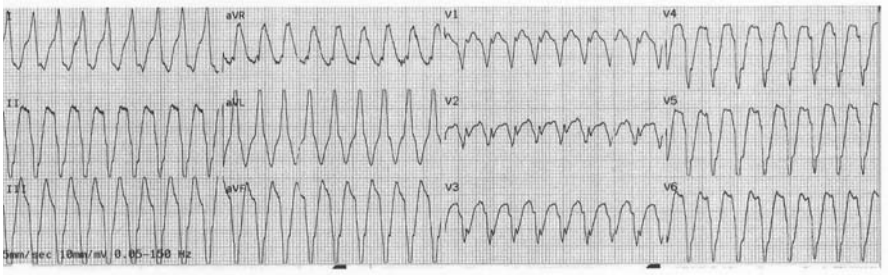

Fig. 4. Monomorphic ventricular tachycardia with negative concordance across the precordium

In patients who are haemodynamically unstable following the onset of MVT or any other wide-QRS tachycardia, emergency synchronised cardioversion is the intervention of choice. With monophasic waveform defibrillators an initial energy dose of 100 J (joules) can be used, with escalation if needed. If a biphasic waveform shock is being delivered the initial dose can be 100-120 J; if additional shocks are needed either the same energy dose or an escalating dose can be used [4]. Sedation and analgesia can be achieved with several different drug choices, including midazolam, fentanyl and etomidate. Alternatively a general anaesthetic can be administered with a thiobarbiturate, with rapid recovery.

In haemodynamically stable patients with MVT amiodarone is considered the drug of choice. It is given in a dose of 150 mg over 8–10 min and repeated if needed. An infusion of 1 mg/min can be started after the loading dose. The maximum dose is 2.2 g/24 h. Procainamide also is a useful drug for termination of MVT. It is administered in a dose of 20–50 mg/min up to a total dose of 17 mg/kg. An infusion of 1–4 mg/min can follow the loading dose. The patient must be observed closely for hypotension or widening of the QRS complex. If cardiac or renal dysfunction is present the total dose should be reduced to 12 mg/kg and the infusion dose to 1–2 mg/min.

Cardioversion should always be considered an appropriate intervention for MVT, either initially or after failure to control the arrhythmia with drug therapy. In fact, when drug therapy with a single drug is ineffective it is best to proceed directly to cardioversion rather than to introduce another antiarrhythmic drug, because of the proarrhythmic potential of mixing these drugs.

Polymorphic ventricular tachycardia

Polymorphic ventricular tachycardia (PVT) is characterised by irregular and wide QRS complexes that vary in amplitude and twist around the isoelectric baseline (Fig. 5). PVT can occur in a variety of settings, such as acute MI, in which case therapy is as described above for MVT. If cardioversion is needed for haemodynamic or drug failure reasons the energy doses are those recommended for VF, e.g., 360 J with monophasic waveforms and 120–200 J for biphasic waveforms.

When accompanied by QT-interval prolongation the PVT is defined as torsades

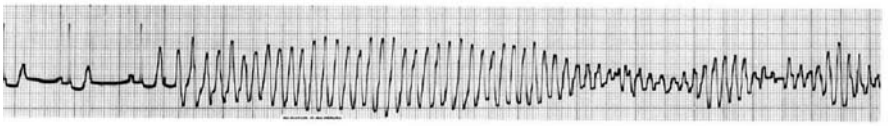

Fig. 5. Polymorphic ventricular tachycardia emerging from normal sinus rhythm with normal QT interval

de pointes ("twisting of the points"). Torsades de pointes is a specific form of PVT with distinct diagnostic and therapeutic considerations [5–7]. In addition to the QRS morphological features, the ECG shows evidence of prolonged repolarisation, which is evident as lengthening of the QT interval preceding and/or following the torsades episodes (Fig. 6). Clinical associations must be sought because correction of the underlying cause is essential for ultimate control of the arrhythmia. Magnesium may be useful in the treatment of torsades; the usual dose is 1–2 g of magnesium sulphate given over 1–2 min. If this drug does not control the arrhythmia overdrive ventricular pacing or isoproterenol infusion can be used to suppress the prolonged repolarisation giving rise to the torsades. It is critical, if treatment is to be successful, to identify the underlying cause of the repolarisation abnormality while suppression of the arrhythmia is undertaken. Traditional antiarrhythmic drug therapy is not likely to control this form of PVT, and thus recognition is essential. A variety of drugs and electrolyte disorders can prolong the QT interval and provoke torsades de pointes tachycardia. Awareness that class IA antiarrhythmic drugs such as procainamide can cause torsades can lead to rapid diagnosis and ultimate control of the arrhythmia.

Ventricular tachycardia accompanying acute hyperkalaemia may manifest as a sine-wave QRS pattern (Fig. 7). Again, clinical suspicion or documentation of hyperkalaemia can lead to prompt corrective therapy with sodium bicarbonate,

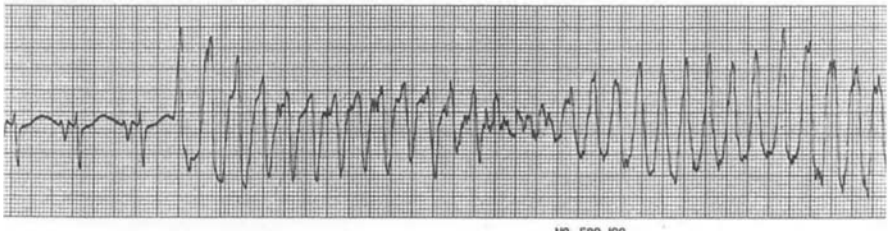

Fig. 6. Torsades de pointes tachycardia. The QT interval in the sinus beats preceding the paroxysm of torsades is very prolonged

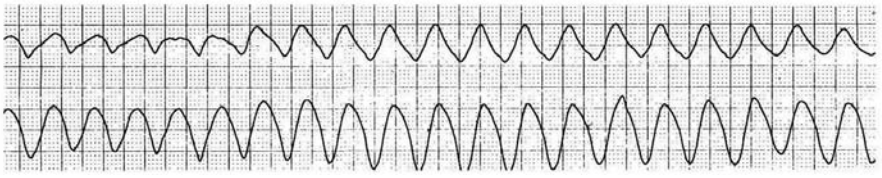

Fig. 7. Hyperkalaemic sine wave ventricular tachycardia. The serum potassium was 7.2 mEq/l

calcium chloride and sympathomimetic agents such as albuterol. Diuresis should be promoted if needed with frusemide or other rapid-acting diuretics. In some cases it may be necessary to use glucose and insulin to promote intracellular movement of potassium. A therapeutic approach might then include sodium bicarbonate 1–2 mEq/kg; calcium chloride 1 g, inhaled albuterol, and glucose 1 g/kg with regular insulin 0.3 U/g glucose, given over 1 h [8].

Wide-complex tachyarrhythmias of uncertain origin

When a wide-complex tachycardia is observed a concerted effort should be made to identify the specific origin. This should include acquisition of a 12-lead ECG and a search for the evidence of a ventricular origin discussed above under MVT. The clinical circumstances should also be considered, given that a history of prior MI or the presence of signs and symptoms of acute ischaemia are strongly indicative of a ventricular origin. Table 1 lists the electrocardiographic signs that are useful in making a diagnosis of ventricular tachycardia.

Table 1. ECG Signs supporting a diagnosis of ventricular tachycardia

•	AV dissociation
•	Fusion/capture complexes
•	Precordial concordance
•	QRS width >140 ms
•	"No man's land" QRS axis
•	More than one of these

If despite an attempt to define the mechanism of the tachycardia one cannot be certain of its origin, intervention will be dictated by the patient's haemodynamic state (Fig. 8). In unstable patients emergency cardioversion should be undertaken promptly. Otherwise drug therapy can be used. Previously lidocaine and adenosine were considered therapeutically or diagnostically useful. In fact lidocaine has no diagnostic or therapeutic utility in this situation. Adenosine is not effective for the most common forms of VT and can be accompanied by side-effects, the most serious being acceleration of the ventricular rate if atrial fibrillation is the arrhythmia in the presence of an accessory pathway. Amiodarone is the drug of choice, with procainamide an acceptable alternative, in the doses discussed above.

Wide-complex tachyarrhythmias in the presence of accessory pathways

Accessory conducting pathways can be located in several atrioventricular areas of the heart. Pathways bridging the AV annulus are present in patients with the Wolff-Parkinson-White (WPW) syndrome. In patients with this syndrome who have tachycardias the most common form is orthodromic AV reciprocating tachy-

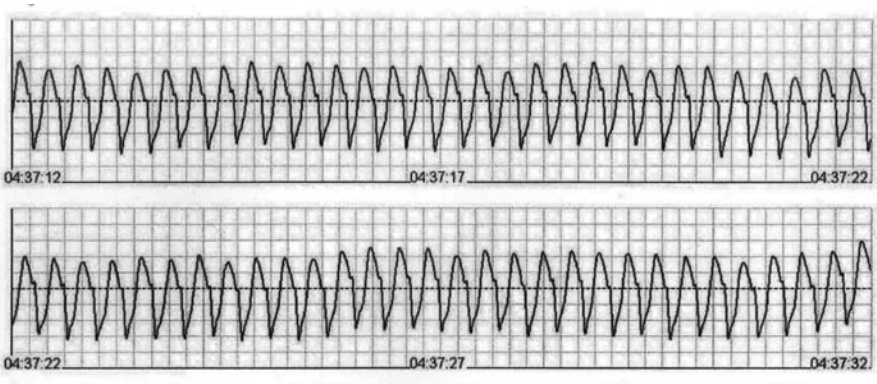

Fig. 8. Wide-QRS complex tachycardia of uncertain origin. Ventricular tachycardia should be considered first and the condition treated as such if a diagnosis cannot be secured

cardia, and unless aberration or a pre-existing bundle branch block is present the QRS complexes are narrow, confirming their antegrade conduction through the AV node. Antidromic AV reciprocating tachycardia occurs much less frequently and is characterised by a wide-complex regular tachycardia caused by antegrade conduction into the ventricles over the accessory pathway. On the ECG this tachycardia is very difficult to differentiate from VT, and the clinical history is very important in diagnosis. If the diagnosis is uncertain amiodarone or procainamide should be used.

Atrial fibrillation or atrial flutter is the tachyarrhythmia of greatest concern in patients with WPW syndrome. When either of these is present the wavefronts from the atria are conducted very rapidly into the ventricles, most of them over the accessory pathway, resulting in a wide-complex tachycardia with very rapid ventricular rates (Fig. 9).

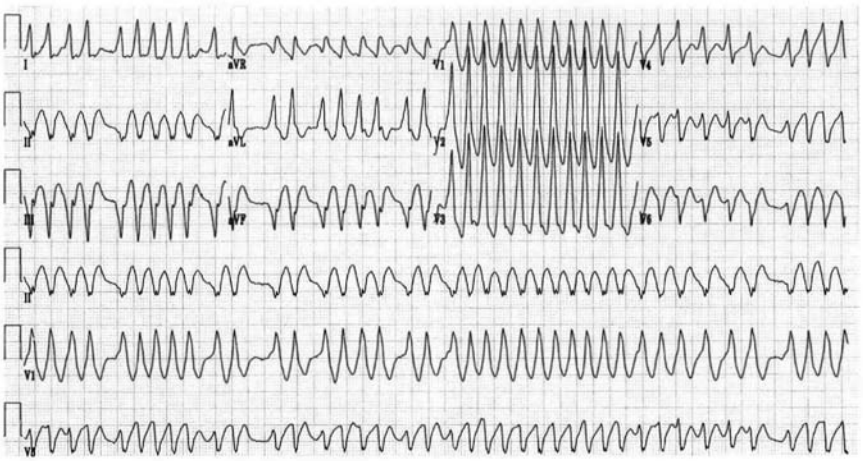

Fig. 9. Atrial fibrillation with rapid ventricular response in a patient with an accessory pathway (WPW syndrome). The rhythm is irregularly irregular and the QRS complexes are wide but of varying width

On the ECG the tachycardia may strikingly resemble VT, especially if occasional narrow QRS complexes are present, because of antegrade AV nodal conduction. These complexes resemble fusion/capture complexes diagnostic of VT (Fig. 10). Characteristics that help to make the diagnosis from the ECG are the irregular irregularity of the tachycardia and the varying QRS width, indicating intermittent simultaneous ventricular activation over both the AV node and the accessory pathway. Again, the clinical history can be very helpful in making the diagnosis. In rare instances of sudden death in patients with WPW syndrome VF results from very rapid activation of the ventricles, resulting in dispersion of recovery of ventricular excitability. Cardioversion is the treatment of choice when haemodynamic instability is present, though this is infrequent because the tachycardia typically occurs in young persons with preserved ventricular function. Procainamide in the doses described above is a safe and effective drug; amiodarone is an alternative, although its safety has been challenged [9]. Most importantly, all AV-nodal-blocking drugs must be avoided, including beta blockers, calcium-channel blockers and digoxin. Although the AV-nodal action of adenosine is short-lived it should also be avoided [10, 11]. Drugs that block AV-nodal conduction with little or no block of conduction in the accessory pathway can produce alarming acceleration of the ventricular rate, risking precipitation of VF.

The role of lidocaine in the treatment of wide-complex tachyarrhythmias

Lidocaine is no longer considered to be of significant therapeutic benefit in the treatment of these tachyarrhythmias. Both amiodarone and procainamide have been shown to be superior to lidocaine in the treatment of VT [12–15]. Other studies have shown a low rate of termination of VT with lidocaine in patients with and without acute MI [16–18]. Though not available for intravenous use in the United States sotalol, available in Europe, has been demonstrated to be more effective than lidocaine in terminating VT [19].

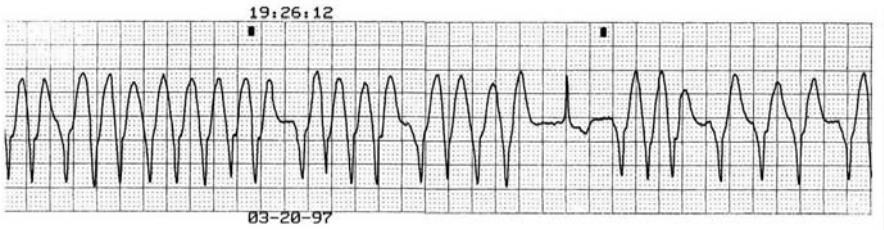

Fig. 10. Atrial fibrillation with rapid ventricular response in a patient with WPW syndrome. The one narrow QRS complex representing normal conduction through the AV node can be confused with a capture beat such as seen in ventricular tachycardia

Electrical and drug therapy in cardiac arrest

VF and pulseless VT are best managed with prompt defibrillation, though in unwitnessed arrest or arrest that may have been present for several minutes before commencement of treatment a 90- to 120-s period of CPR may make the heart more amenable to defibrillation shocks [20, 21] (Fig. 11). If a monophasic waveform defibrillator is used the initial and subsequent shocks, if needed, should be at a 360-J energy setting. For biphasic waveform defibrillators an initial energy dose of 120–200 J can be used. If needed, subsequent shocks can be delivered with the same or an escalating energy dose. There is no evidence that escalating energy shocks are more effective than nonescalating energy shocks.

Epinephrine remains the mainstay in drug therapy in all forms of cardiac arrest. Its vasoconstrictive action results in improved coronary and cerebral perfusion pressure. It is given if arrest persists after shock delivery in a dose of 1 mg and repeated if needed at 3- to 5-min intervals. Vasopressin in a single dose of 40 U can be given to replace the first or second dose of epinephrine, after which epinephrine is used if arrest persists.

Amiodarone is the drug of choice if an antiarrhythmic is needed for shock-refractory or recurrent VF/VT. In this situation it is given in a dose of 300 mg, with an additional 150-mg bolus if needed. If amiodarone is not available lidocaine can be given in a dose of 1–1.5 mg/kg, but it is not considered a first-line drug in this

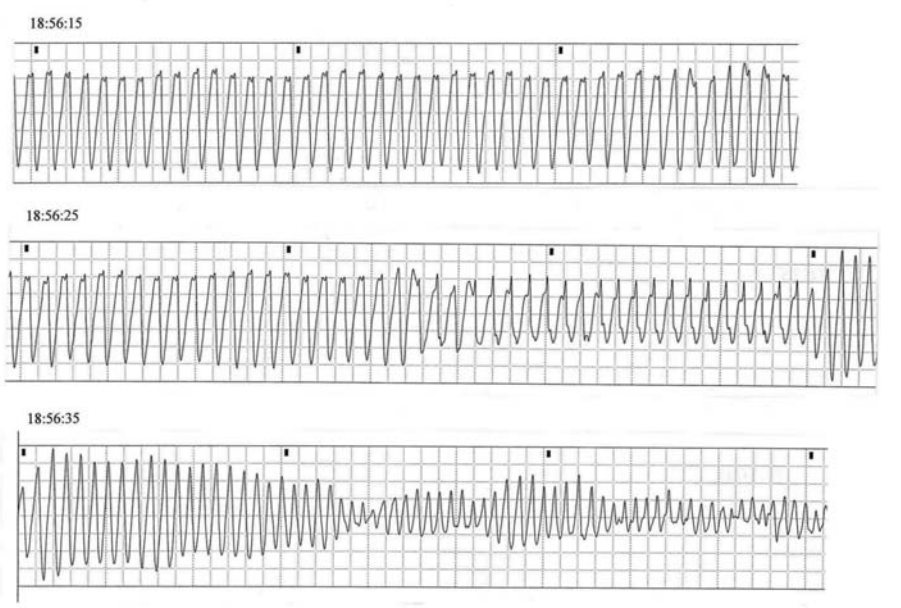

Fig. 11. Pulseless ventricular tachycardia with changing QRS morphology degenerating into ventricular fibrillation

setting, as in others as discussed above. If torsades de pointes is present magnesium sulphate in a dose of 1–2 g should be given.

Performance of effective chest compressions is of the utmost importance in the management of cardiac arrest, with minimal interruptions throughout. Drugs should be administered while CPR is in progress, and pauses in chest compressions should be brief and made only for shock delivery and endotracheal intubation, the latter intervention only if pauses in chest compression are necessary.

Conclusions

Therapeutic decisions in caring for patients with wide-complex tachyarrhythmias are based in each case upon an assessment of the diagnosis, the haemodynamic impact of the arrhythmia and the patient's underlying cardiac function. History, physical examination and the ECG should all be used in making the diagnosis and defining the appropriate treatment. Incorrect diagnosis can be not only ineffective but also dangerous, as it is for example when AV-node-blocking drugs are administered in patients with atrial fibrillation and WPW syndrome.

Ventricular tachycardia can be monomorphic or polymorphic; in the latter case a search should be made for QT-interval prolongation for diagnosis of torsades de pointes, which requires therapy different from that used for PVT without prolonged repolarisation. If a wide-QRS tachycardia cannot be diagnosed with certainty from the history or ECG amiodarone or procainamide can be used safely and effectively. Sotalol is also a useful drug. In all situations emergency cardioversion takes precedence if haemodynamic compromise is present or if drug therapy is ineffective. Use of more than one anti-arrhythmic drug increases the risk of proarrhythmic potential. Pulseless VT and VF are treated with minimally interrupted CPR, defibrillation shocks, epinephrine or vasopressin and amiodarone if needed for shock-refractory or recurrent VF/VT.

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OBSTETRICS AND PAEDIATRICS

Chapter 33

Obstetrics at high risk

R. Alexander, N. Volpe

Why Mothers Die 2000-2002–Report on confidential enquiries into maternal deaths in the United Kingdom
(http://www.cemach.org.uk/publications/WMD2000_2002/content.htm)

During this triennium, 391 maternal deaths were reported to the Enquiry, a slight increase on the 378 cases reported in 1997–99. Of the 391 deaths, 106 were classified as *Direct* and 155 as *Indirect* deaths, representing 27% and 40% of reported cases, respectively (Table 1). Thirty-six (9%) were classified as *Coincidental* and 94

Table 1. Number of maternal deaths reported to the Enquiry by cause; United Kindom 1985-2002

Chapter Cause	1985-87	1988-90	1991-93	1994-96	1997-99	2000-02*
***Direct* deaths (occurring during pregnancy and up to and including 42 days inclusive after delivery**						
2 Thrombosis and thromboembolism	32	33	35	48	35	30
3 Hypertensive disease of pregnancy	27	27	20	20	15	14
4 Haemorrhage	10	22	15	12	7	17
5 Amniotic fluid embolism	9	11	10	17	8	5
6 Death in early pregnancy total	22	24	18	15	17	15
Ectopic	16	15	8	12	13	11
Spontaneous miscarriage	5	6	3	2	2	1
Legal termination	1	3	5	1	2	3
Other	0	0	2	0	0	0
7 Genital tract sepsis	6**	7**	9**	14***	14***	11***
8 Other *Direct* total	27	17	14	7	7	8
Genital tract trauma	6	3	4	5	2	1
Fatty liver	6	5	2	2	4	3
Other	15	9	8	0	1	4
9 Anaesthetic	6	4	8	1	3	6
Total number of *Direct* deaths	139	145	128	134	106	106
***Indirect* deaths (up to and including 42 days after delivery)**						
10 Cardiac	22	18	37	39	35	44
11 Psychiatric	N/A	N/A	N/A	9	15	16
12 Other *Indirect*	62	75	63	86	75	90
13 *Indirect* malignancies	N/A	N/A	N/A	N/A	11	5
Total number of *Indirect* deaths	84	93	100	134	136	155
14 *Coincidental* deaths	*26*	*39*	*46*	*36*	*29*	*36*
15 *Late* deaths (42-365 days after delivery)						
Direct	N/A	13	10	4	7	4
Indirect	N/A	10	23	32	39	45
Coincidental	N/A	25	13	36	61	45
Total number of *Late* deaths	16	48	46	72	107	94

N/A = Not available
* deaths reported to the Enquiry only and excluding other deaths identified by ONS;
** Excluding early pregnancy deaths due to sepsis
*** Including early pregnancy deaths due to sepsis

(24%) as *Late*. The total number of *Direct* and *Indirect* maternal deaths reported to the Enquiry, 261, is higher than the 242 reported in the previous triennium. As first seen in the last report, the number of *Indirect* deaths now exceeds the number of *Direct* deaths. The overall maternal mortality rate for the United Kingdom for this triennium from deaths due to both *Direct* and *Indirect* causes is 13.1 maternal deaths per 100,000 maternities.

Table 2 gives the actual numbers of deaths and Table 3 shows the UK maternal death rates per million maternities by specific cause of death for the last six triennia.

Table 2. Definitions of maternal deaths

Term	Definition
Maternal deaths*	Deaths of women while pregnant or within 42 days of the end of the pregnancy, from any cause related to or aggravated by the pregnancy or its management, but not from accidental or incidental causes
Direct*	Deaths resulting from obstetric complications of the pregnant state (pregnancy, labour and puerperium), from interventions, omissions, incorrect treatment or from a chain of events resuiting from any of the above
Indirect*	Deaths resulting from previous existing disease, or disease that developed during pregnancy and which was not due to direct obstetric causes, but which was aggravated by the physiologic effects of pregnancy
Late*	Deaths occurring between 42 days and 1 year after abortion, miscarriage or delivery that are due to *Direct* or *Indirect* maternal causes
Coincidental (Fortuitous)**	Deaths from unrelated causes which happen to occur in pregnancy or the puerperium
Pregnancy-related deaths**	Deaths occurring in women while pregnant or within 42 days of termination of pregnancy, irrespective of the cause of the death

* = ICD 9
** = ICD 9/10 classifies these deaths as *Fortuitous* but the Enquiry prefers to use the term *Coincidental* as it a more accurate description. The Enquiry also considers deaths from *Late Coincidental* causes
*** = ICD 10

Table 3. Mortality rates by major cause of maternal death per million maternities; United Kingdom 1985-2002

Chapter	Cause	Rate per million maternities					
		1985-87	1988-90	1991-93	1994-96	1997-99	2000-02
2	Thrombosis and thromboembolism	14.1	14.0	15.1	21.8	165	15.0
3	Hypertensive disease of pregnancy	11.9	11.4	8.6	9.1	7.1	7.0
4	Haemorrhage	4.4	19.3	6.5	5.5	3.3	8.5
5	Amniotic fluid embolism	4.0	4.7	4.3	7.7	3.8	2.5
6	Deaths in early pregnancy	7.9'	7.6'	5.2'	6.8	8.0	7.5
7	Genital tract sepsis	4.4	5.5	6.4	6.4'	6.6'	5.5'
8	Total uterine trauma/other *Direct*	11.9	7.2	6.0	3.2	3.3	4.0
	Genital tract trauma	2.6	1.3	1.7	2.3	1.0	0.5
	Other *Direct*	9.3	5.9	4.3	0.9	2.3	3.5
9	Anaesthetic	2.6	1.7	3.5	0.5	1.4	3.0
10	Cardiac *Indirect*	9.7	7.6	15.9	17.7	16.5	22.0
11	Psychiatric *Indirect*''	–	–	–	4.1	7.1	8.0
12	Other *Indirect*	27.3	31.0	27.0	39.1	35.3	45.6
13	*Indirect* malignancies	–	–	–	–	5.1	2.5
2-13	Total *Direct* and *Indirect*	98.3	100.1	98.1	121.9	114.0	131.1
14	*Coincidental (Fortuitous)*	11.3	16.5	19.9	16.4	10.8	18.0
15	*Late*	*7.1*	*20.3*	*19.9*	*32.8*	*50.3*	*47.0*

' Including sepsis in early pregnancy;
'' until 1993-96 counted as *Coincidental* and note that these are only for suicides which occur during the first 6 weeks. A futher explanation od actual death rates from suicide can be found in the text. This table excludes cases identified by ONs but not notified to the Enquiry.

The main causes of death in pregnancy and delivery are thromboebolism, hypertensive disease, cardiac disease and haemorrhage. The first three will be discussed in further detail.

Thromboebolic disease

Pregnant women and, in particular, those with a history of thromboembolic disease are at appreciable risk during pregnancy. The reported incidence of deep vein thrombosis (DVT) and nonfatal pulmonary embolism varies considerably because of the peculiar diagnostic difficulties in pregnancy. Real-time ultrasound scanning combined with Doppler studies, being noninvasive, are the first-line diagnostic techniques for DVT in pregnancy [1]. The following are the recommendations of the American College of Obstetricians and Gynecologists:

- Pregnant patients with a history of isolated venous thrombosis directly related to a transient, highly thrombogenic event (orthopaedic trauma, complicated surgery) in whom an underlying thrombophilia has been excluded may be offered heparin prophylaxis or no prophylaxis during the antepartum period. However, they should be counselled that their risk of thromboembolism is likely to be higher than the normal population. Prophylactic warfarin should be offered for 6 weeks postpartum.
- Pregnant patients with a history of idiopathic thrombosis, thrombosis related to pregnancy or oral contraceptive use, or a history of thrombosis accompanied by an underlying thrombophilia other than homozygous for the factor V

Leiden mutation, heterozygous for both the factor V Leiden and the prothrombin G20210A mutation, or antithrombin-III (AT-III) deficiency should be offered antepartum and postpartum low-dose heparin prophylaxis.
- Patients without a history of thrombosis but who have an underlying thrombophilia and have a strong family history of thrombosis also are candidates for antepartum and postpartum prophylaxis. At the minimum, postpartum prophylaxis should be offered.
- Pregnant patients with a history of life-threatening thrombosis, with recent thrombosis, with recurrent thrombosis, receiving chronic anticoagulation, or patients with thrombosis found to be AT-III deficient, homozygous for the factor V Leiden mutation or prothrombin G20210A mutation, heterozygous for both the factor V Leiden and the prothrombin G20210A mutation should be given adjusted-dose heparin every 8 hours to maintain the activated partial thromboplastin time (APTT) at least 1.5 times control throughout the dosing interval. Low-molecular-weight heparin (LMWH) administered twice daily also is an alternative.
- Patients at risk for thrombosis should receive warfarin postpartum for 6 weeks to achieve an international normalised ration (INR) of approximately 2.0 to 3.0. Heparin should be given immediately postpartum with warfarin for at least 5 days until the INR is therapeutic.
- Patients with antiphospholipid syndrome and a history of thrombosis require adjusted-dose prophylactic anticoagulation.
- Patients who are candidates for either prophylactic or therapeutic heparin may be given enoxaparin or dalteparin during pregnancy. However, because of the lack of data regarding adequate dosing during pregnancy, antifactor Xa levels may be monitored.
- The safety of epidural anaesthesia with twice-daily dosing of LMWH is of concern and should be withheld until 24 hours after the last injection.
- Epidural anaesthesia appears to be safe in women taking unfractionated low-dose heparin if the APTT is normal.

The major concerns with heparin use during pregnancy are not foetal but maternal and include heparin-induced osteoporosis and heparin-induced thrombocytopoenia (HIT). Bleeding is also an issue. Warfarin derivatives cross the placenta. A skeletal embryopathy resulting in stippled epiphyses and nasal and limb hypoplasia can occur when warfarin is given between 6 and 12 weeks of gestation. Midtrimester exposure may result in optic atrophy, microcephaly and developmental delay. Bleeding can occur in the foetus at any time, resulting in a high foetal loss rate.

Management of hypertensive diseases of pregnancy

Hypertensive diseases of pregnancy are one of the most common direct causes of maternal death in the developed world. The largest single cause of death amongst women with pre-eclampsia and eclampsia in the United Kingdom is intracranial

haemorrhage, reflecting a failure of effective anti-hypertensive therapy. HELLP syndrome associated with pre-eclampsia is another cause of death.

Gestational hypertension occurs after 20 weeks of gestation and returns to normal within 3 months of delivery. It has none of the other features of pre-eclampsia. Eclampsia indicates the occurrence of seizures in a parturient who may have no underlying pathology. Pre-eclampsia is a complex multi-system disorder that may sometimes precede eclampsia.

The classic diagnostic triad for pre-eclampsia of hypertension, proteinuria and oedema is no longer considered useful. Oedema occurs in up to 80% of normotensive parturients and, conversely, pre-eclampsia can occur in the absence of proteinuria. There are several definitions of pre-eclampsia, but they generally involve hypertension occurring after 20 weeks with the involvement of at least one other organ system, for instance headache or epigastric pain. Hypertension in pregnancy is defined as a systolic pressure of 140 mmHg and /or a diastolic pressure of >90 mmHg.

Pathophysiology

Hypertension affects 10% of all pregnancies, and pre-eclampsia complicates approximately 2–8% in the UK. It also occurs more frequently in women who have previously suffered from pre-eclampsia. Other risk factors include diabetes, obesity, advanced age, nulliparity and a family history of pre-eclampsia. The presence of antiphospholipid antibodies and other autoimmune and chronic diseases increases the likelihood of pre-eclampsia.

Pre-eclamptic toxaemia (PET) is a multi-system disorder of endothelial dysfunction, characterised by widespread increased capillary permeability and generalised vasoconstricted hypovolaemic circulation with a lower cardiac output. However, the haemodynamic findings in pre-eclampsia are complex and vary widely between studies. Circulating catecholamines and administered vasoactive drugs may cause exaggerated responses. A high index of suspicion must be maintained even when the classic signs and symptoms are mild [2]. Patients with pre-eclampsia are at risk of developing pulmonary oedema. Early in the disease process the hypercoagulable state of normal pregnancy may be enhanced. Later on, both platelet activation and consumption are increased which can lead to significant thrombocytopenia (platelet count <100,000 mm^3) in approximately 15% of women with severe pre-eclampsia. Disseminated intravascular coagulopathy (DIC) occurs in 7% of cases of severe pre-eclampsia. Renal tubular function deteriorates relatively early in pre-eclampsia. The proteinuria of severe pre-eclampsia occurs later and reflects an ischaemic insult to the glomerulus. Normal individuals have an upper limit of proteinuria of about 100 mg/day, which is exceeded up to 500 mg/day. Most patients who develop oliguria respond to optimisation of the intravascular volume status. Abnormal liver function tests are frequently found in pre-eclampsia. More rarely, epigastric pain may be a symptom of tension on the capsule of the liver caused by oedema or intrahepatic haemorrha-

ge. HELLP syndrome is the well-recognised association of *H*aemolysis, *E*levated *L*iver enzymes and *L*ow *P*latelets. The neurological changes associated with severe pre-eclampsia include headaches, visual disturbances and hyperreflexia. This may culminate in seizures (eclampsia) due to cerebral vasospasm and reduced blood flow. Severity of pre-eclampsia is shown in Table 4.

Table 4. Severity of pre-eclampsia

Features of mild/moderate pre-eclampsia	*Features of severe pre-eclampsia*
Blood pressure >140/90	Blood pressure >160/110 mmHg
Proteinuria >300 mg/24 h	Proteinuria >5 g/24 h
Cerebral involvement (headache, visual disturbances)	Cerebral involvement (hyperreflexia, seizures)
	Oliguria <500 ml/24 h
	Increased serum creatinine level
	Pulmonary oedema
	Epigastric or right upper quadrant abdominal pain, evidence of hepatic injury (HELLP)
	Thrombocytopenia or disseminated intravascular coagulation
	Evidence of foetal compromise (IUGR or oligohydramnios)

Treatment

Treatment is focused on control of blood pressure, correction of intravascular volume, symptomatic organ support and prevention of complications. Delivery remains the only curative treatment for pre-eclampsia, and the disease process may still not resolve immediately.

Commonly used oral antiphypertensives include methyldopa, a centrally acting alpha-2 agonist, labetalol, a beta blocker, and nifedipine, a calcium channel blocker.

Hydrallazine or labetolol are commonly used for acute control of a rising diastolic pressure or resistant.

It is now accepted that magnesium sulphate ($MgSO_4$) is the anticonvulsant of choice in preventing and treating eclamptic fits [3]. Magnesium sulphate is usually administered as a slow intravenous bolus of 4–6 g and then as an infusion of 1–2 g per h to keep serum magnesium in the therapeutic range. The treatment of overdose is supportive in the first instance and also includes intravenous calcium (e.g. calcium gluconate 1 g). Magnesium therapy is often continued for at least 24 h post partum.

Clinical indicators of magnesium toxicity include the absence of tendon reflexes and decreased respiratory rate. ECG changes occur (P–Q interval prolonged, QRS complex widened), which may progress to conduction defects and cardiac arrest. The risks increase in the presence of oliguria, since magnesium depends on the kidneys for excretion (Table 5).

Table 5. Effects of rising plasma magnesium level

	mmol l^{-1}
Normal plasma level (NB most magnesium is intracellular)	1
Therapeutic range	2–3
ECG changes	3–5
Loss of deep tendon reflexes	5
Muscle paralysis, respiratory depression	6–7.5
Cardiac arrest	12

Assessment of the coagulation status of the blood is essential before regional anaesthesia, particularly in severe pre-eclampsia. Thrombocytopenia is a common corollary to severe pre-eclampsia, but there is no absolute level of platelet count that accurately predicts the occurrence of bleeding associated with regional anaesthesia. If the platelet count is less than 80,000 mm^3 then further assessment of the coagulation status is justified. The results of the PT, APTT and perhaps thrombo-elastography can be compared with the normal ranges for pregnant patients.

Where caesarean section is required the relative risks of general and regional anaesthesia must be assessed. Regional anaesthesia is usually considered safer, although cases must be assessed on an individual basis. The added risks associated with general anaesthesia include airway difficulties due to oedema (often aggravated by tracheal intubation), and the pressor response to laryngoscopy and extubation. If a working epidural is already present this should be extended for surgery. Spinal anaesthesia is currently controversial in PET [4, 5]—the anticipated potential risks of pulmonary oedema, profound cardiovascular instability, possibly from a fall in cardiac output [6], and the consequent recourse to i.v. fluids and vasoconstrictors suggest it is not a technique to be recommended in PET. However, limited data supporting the use of spinal anaesthesia in pre-eclampsia do exist [4, 5], although information from a larger number of patients, preferably in randomised prospective trials, is urgently required. Sequential CSE (low-dose spinal, then epidural top-ups) may prove useful. Fulminant PET (and the risk of an eclamptic seizure occurring during surgery) is considered a contraindication to regional block by some authors, but many anaesthetists would still choose a regional technique where possible. Even following an eclamptic convulsion, providing the patient has recovered the airway reflexes, is co-operative, and has been started on appropriate therapy (i.e. including magnesium sulphate) a regional technique may be considered preferable to general anaesthesia.

Where general anaesthesia is chosen, care should be taken to reduce the pressor response to laryngoscopy. Several techniques have been described to abolish this, including beta-blockers, opioids and/or i.v. lignocaine, but none is completely reliable. A bolus of $MgSO_4$ may be the most effective technique [7], although newer agents, such as esmolol and remifentanil, may find a role with further experience. Extubation may be particularly hazardous owing to aggravation of airway oedema leading to acute upper airway obstruction, and patients with fulminant pre-eclamp-

sia and suffering from marked oedema or airway compromise should be sent to the ITU for postoperative ventilation and stabilisation. Whether a regional or general anaesthetic technique is used for caesarean section, adequate recovery facilities are mandatory, and patients need high dependency nursing for at least 24 h.

Management of specific heart diseases in obstetrics

The parturient with heart disease, whether congenital or acquired, represents a challenge for even the experienced anaesthesiologist. The main goal in the management of these patients is to prevent further derangement of cardiac function during labour in a heart that is already stressed by the "physiological" changes of pregnancy with the potential to precipitate heart failure. This can be accomplished by effective anxiolysis, analgesia and anaesthesia. Ultimately, the aim of any anaesthetic intervention is to ensure the wellbeing of both mother and foetus. Accurate cardiovascular monitoring during labour and in the puerperium is essential in the management of all parturients with heart disease. Monitoring of ECG, blood pressure (preferably invasive) and SaO_2 is mandatory in patients with severe disease.

Mitral stenosis. This condition is usually the result of rheumatic heart disease. The main haemodynamic features are pulmonary congestion and reduced left-ventricular diastolic filling. Epidural analgesia for labour has been successfully used in these patients and has been shown to have little influence (and sometimes beneficial effects) on the haemodynamic picture. Pulmonary artery pressure monitoring (Swan-Ganz catheter) is strongly recommended by some authors [8] in patients with moderate-to-severe mitral stenosis. Many authors recommend epidural block as the technique of choice in providing anaesthesia for caesarean section in these patients [9–11]. Great care is needed in the administration of the block, and its cephalad spread should be restricted at the T-5 level.

Mitral regurgitation. In these patients an increase in systemic vascular resistance should be prevented. Epidural block is the technique of choice [12–14] for analgesia both in labour and for caesarean delivery [12].

Aortic stenosis. The key to the anaesthetic management of these parturients is the maintenance of both preload and afterload. Coronary perfusion is crucially dependent on the maintenance of diastolic pressure and time, and cardiac output is relatively fixed. Analgesia for labour is best provided by parenteral narcotics and by inhalation of nitrous oxide and oxygen. For the second stage of labour, pudendal nerve blockade can be used. Good analgesia has also been provided by intrathecal narcotics. General anaesthesia is the technique of choice for caesarean section.

Aortic regurgitation. These patients tolerate the circulatory overload produced by pregnancy very well, and most techniques of analgesia and anaesthesia have been used successfully. A decrease in left-ventricular afterload (such as occurs with neuraxial blockade) can lead to an improvement in cardiac function by reducing the regurgitant fraction.

Anaesthesia and analgesia in patients with congenital heart disease: tetralogy of Fallot. This condition is the most common cyanotic heart condition observed in

pregnant patients. Cyanosis is the result of a right-to-left shunt, the degree being determined by the amount of obstruction to right-ventricular outflow. One of the principal anaesthetic aims in managing these patients is to prevent an increase in this shunt. As with Eisenmenger's syndrome, the ratio of systemic to pulmonary vascular resistance is one determinant of the magnitude of the right-to-left shunt, and the level of cyanosis is also affected by changes in cardiac output (mixed venous oxygen saturation effect). All known techniques of analgesia and anaesthesia have been used with good results, but major regional blocks have to be used with caution owing to the risk of a severe decrease of systemic vascular resistance [9]. For caesarean section both light and deep levels of general anaesthesia have been advocated [12]. Tachycardia or infundibular spasm can be prevented by the administration of propranolol.

Eisenmenger syndrome. These patients present with pulmonary hypertension with right-to-left or left-to-right shunt at aortopulmonary, ventricular or atrial level. A decrease in the ratio of systemic to pulmonary vascular resistance results in increasing cyanosis. In these patients pregnancy and delivery are associated with a high mortality rate [15]. Epidural blockade using low concentrations of local anaesthetic has been used to produce satisfactory analgesia in labour [16, 17]. For caesarean section the anaesthetic technique of choice is general anaesthesia accomplished with drugs that do not depress cardiovascular function.

Coarctation of the aorta. The main cardiovascular consequence of coarctation is a chronically-increased left-ventricular afterload that causes hypertrophy of the left ventricle. Epidural blockade and intrathecal morphine have both been successfully used to provide analgesia in labour [7]. General anaesthesia is preferred for caesarean section [12].

Patients with cardiomyopathy. On the basis of anatomical and functional features cardiomyopathies can be classified as either dilated or hypertrophic. There is little information available on the anaesthetic management of patients with a cardiomyopathy in labour. In principle, depression of myocardial function should be avoided in patients with a dilated cardiomyopathy, but mild afterload reduction may be of benefit. In patients suffering from a hypertrophic cardiomyopathy, preload should be well maintained (to avoid systolic cavity obliteration) and beta agonists (whether used for tocolysis or cardiovascular reasons) should be avoided.

Peripartum cardiomyopathy (PPCM) is a relatively rare disease estimated to occur in 1 in 3,000–4,000 pregnancies [18]. Criteria for diagnosis include: (a) development of cardiac failure in the last trimester of pregnancy or within 5 months of delivery, (b) absence of a determinable aetiology for the cardiac failure, and (c) absence of demonstrable heart disease prior to the last month of pregnancy [19].

The diagnosis therefore, is largely one of exclusion, as the disease has no pathognomic features [20, 21]. The aetiology of PPCM remains poorly understood, with theories generally centred upon viral infection triggering autoimmune mechanisms in susceptible individuals [18, 19, 21].

Considerations about regional anaesthesia in these patients are similar to those in patients with other causes of heart failure. With regard to anaesthesia for caesarean section, general anaesthetic techniques involve either cardiodepressant

drugs, such as thiopentone and the inhalational anaesthetic agents, or high-dose narcotic techniques, which, while they maintain haemodynamic stability, may necessitate postoperative ventilation for both mother and infant. Epidural anaesthesia offers several advantages in addition to avoiding these problems.

Anaesthesia can be induced in a gradual and controlled manner and minimal change in haemodynamic parameters can be achieved if a pulmonary artery catheter is used to guide fluid and inotrope requirements. Small bolus doses or an incremental infusion of bupivacaine 0.5% with fentanyl 4–5 μg/ml is suitable for these purposes. In addition, major neuraxial blockade may actually improve myocardial performance by reducing the afterload on the left ventricle without impairing contractility, although not all authors agree [22].

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Chapter 34

Resuscitation of the newborn

D. Trevisanuto, N. Doglioni, F. Mario

It is estimated that 3–5% of newborn infants (about 4–7 million infants worldwide annually) require resuscitation at birth, making this one of the most commonly performed medical interventions [1].

There are many guidelines and international consensus statements that advise on how newborns should be resuscitated [2-4] (Fig. 1). However, previous experimental and clinical studies have suggested that there is minimal evidence in support of the practices currently recommended [1, 5–9], and these inconsistencies are magnified in the case of the resuscitation of extremely low-birthweight infants (ELBWI) [10]. In addition, in a recent study, Carbine et al. found that 54% of 100 resuscitations deviated from Neonatal Resuscitation Program (NRP) guidelines, showing that the application of NRP guidelines and skills in clinical settings is low [11]. Furthermore, current resuscitation guidelines make no distinction between

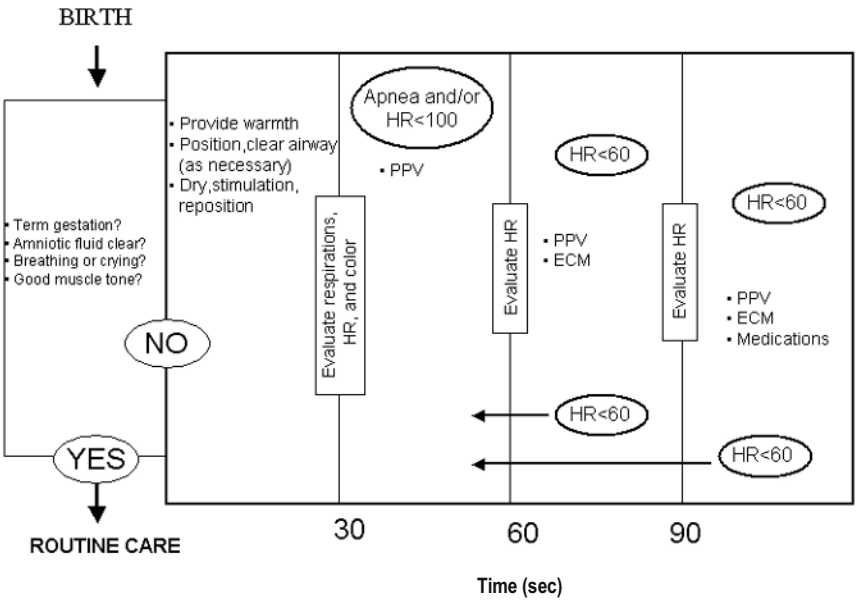

Fig. 1. Neonatal resuscitation flow algorithm. (*ECM* external cardiac massage, *HR* heart rate, *PPV* positive pressure ventilation)

the techniques for term and very premature infants [2–4], while it has been suggested that a different approach could be approved for the latter group [10].

International guidelines on neonatal resuscitation have been recently updated to take account of the articles published during the last 5 years evaluating specific interventions in the delivery setting [5]. They include the following areas (Table 1):

a) Initial evaluation;
b) Meconium aspiration syndrome (MAS);
c) Temperature;
d) Administration of oxygen;
e) Positive pressure ventilation;
f) Medications;
g) Withholding and discontinuing resuscitation.

Table 1. Major changes to the 2005 international guidelines for neonatal resuscitation

Area	Specific changes
Initial evaluation	Colour is not considered <30 s
Meconium aspiration syndrome (MAS)	Intrapartum oropharyngeal and nasopharyngeal suctioning is not indicated for infants born to mothers with meconium staining of amniotic fluid
Temperature	Polyethylene bags may help to reduce heat loss evaporation in VLBWI
Administration of oxygen	The standard approach is to use 100% oxygen. Employing either room air or 100% oxygen is reasonable
Positive pressure ventilation	Flow-controlled pressure devices are recognised as an acceptable method of administering positive pressure ventilation during resuscitation of the neonate, in particular the premature infant
Medications	Epinephrine: IV administration is the preferred route. Recommended dose for endotracheal route: 0.3–1.0 ml of 1:10,000 solution/kg
	Naloxone: is not recommended during the primary steps of resuscitation. Endotracheal route is not recommended
Withholding and discontinuing resuscitation	Discontinuation of resuscitation may be justified if there are no signs of life after 10 min of adequate resuscitative efforts

In this article, we examine the main changes contained in the international guidelines on neonatal resuscitation published in 2005. The recent paediatric literature that has allowed changes to the recommendations is reviewed.

Initial evaluation

International guidelines in 2000 included five questions (Term gestation? Amniotic fluid clear? Breathing or crying? Good muscle tone? Pink?) for the initial evaluation of each neonate [2–4]. These questions had to be asked within the first 30 s of each infant's life, and the answers determined whether the neonate would receive "routine" or "intensive" care. In the international guidelines issued in 2005 [5] the colour of the patient (pink?) is not considered in this phase. In a recent study, Kramlin et al. evaluated transcutaneous SaO_2 in 175 "healthy" neonates (gestational age 38±3 weeks; birth weight 2,953±865) during the first 5 min of postnatal life [12]. At 1 min of life the median (interquartile range) trancutaneous SaO_2 values were 63% (53–68%), confirming that clinical oxygenation (pink?) is not useful for the initial evaluation of the patient.

Meconium aspiration syndrome

Meconium aspiration syndrome (MAS) is frequently encountered in the delivery room [2–5]. In the presence of meconium-stained infants, the original guidelines suggested performing (a) suction of the nose, mouth and posterior pharynx before delivery of the shoulders, (b) direct laryngoscopy immediately after birth for suctioning of residual meconium from the hypopharynx and (c) intubation/suction of the trachea [2–4]. However, previous studies demonstrated that tracheal suctioning of the vigorous infant with meconium-stained fluid did not improve outcome and could cause complications [13]. The 2000 guidelines stated that intubation of the trachea in meconium-stained infants must be limited to patients with "absent or depressed respirations, decreased muscle tone, or heart rate <100 bpm" [2–4].

A recent randomised multicentre study demonstrated that the suction of mouth, nose and posterior pharynx before the delivery of the infant's shoulders did not change the incidence of MAS (relative risk 0.9, CI 0.6–1.3) [14].

Based on this study, the international guidelines of 2005 "No longer advise routine intrapartum oropharyngeal and nasopharyngeal suctioning for infants born to mothers with meconium staining of amniotic fluid" [5].

Temperature

The accepted standard for preterm infants and nonasphyxiated term infants is an environment that provides minimal heat loss and metabolic oxygen consumption. The Guidelines for Perinatal Care suggest that the environmental temperature in newborn care areas should be kept at 23.8–26.1°C [15]. A recent study showed that in Italy half of the level III centres fail to reach this standard [16]. Instead, a few centres are using the method of wrapping the infant's trunk in a polyethylene membrane to lower heat loss [16]. This method was demonstrated to be effective

in preventing heat loss evaporation in ELBWI by Vohra et al. and has already become part of clinical management in this high-risk population [17]. For this reason, international guidelines 2005 recommend that "additional warming techniques be used, such as covering the infant in plastic wrapping (food-grade, heat-resistant plastic) and placing him or her under radiant heat" [5].

On the other hand, guidelines advise avoiding hyperthermia, because animal studies indicate that this condition during and after ischaemia is associated with progression of cerebral injury [5, 18].

Finally, although animal and human studies seem to be promising in terms of brain damage prevention [19, 20], there is too little information available to justify recommending routine application of modest systemic or selective cerebral hypothermia after resuscitation of infants with suspected asphyxia.

Administration of oxygen

"Old" guidelines for neonatal resuscitation recommended provision of 100% oxygen at delivery [2–4]. Clinical studies have shown that room air is as effective as 100% oxygen for resuscitation of asphyxiated newborns and reduces the oxidative stress [21–23]. A meta-analysis of four human studies showed a reduction in mortality rate and no evidence of harm in infants resuscitated with room air compared with those resuscitated with 100% oxygen, although these results should be viewed with caution because of significant methodological concerns [24].

In a national survey, almost half the centres (44.6%) used oxygen concentrations lower than 100% for resuscitation of ELBWIs, showing a deviation from the NRP guidelines [25]. These data were comparable to those reported by O'Donnell et al. in a recent survey involving neonatologists from 13 countries [26].

Although the results of experimental and clinical studies suggest that it may be desirable to use lower oxygen concentrations [21–23], the 2005 guidelines state that "the standard approach to resuscitation is to use 100% oxygen" [5]. However, for the first time, they consider the possibility of using oxygen concentrations lower than 100%: "There is evidence that employing either of these practices (room air or 100% oxygen) during resuscitation of neonates is reasonable."

A recent study shows that pulse oximetry has not become an accepted standard of care during neonatal resuscitation [25]. Instead, a more aggressive use of the pulse oximeter in the delivery setting may facilitate the achievement of adequate blood oxygen levels, avoiding hyperoxia throughout and beyond the resuscitation process. The "new" guidelines consider the use of pulse oximetry to guide administration of a variable concentration of oxygen in the delivery room setting [5].

Positive pressure ventilation

The recommendations for assisted ventilation are similar to those in previous guidelines: initial peak inflating pressures of 30–40 cmH_2O at a rate of 40–60

breaths per minute [2–5]. Furthermore, the guidelines of 2005 outlined that "There is insufficient evidence to recommend an optimum inflation time" [5]. Self-inflating and flow-inflating bag-and-mask equipment and techniques remain the cornerstone of achieving effective ventilation in most resuscitations. However, for the first time, in the new guidelines the flow-controlled pressure-limited mechanical devices (e.g. T-piece resuscitators) are recognised as an acceptable method of administering positive-pressure ventilation during resuscitation of the newly born, and in particular the premature infant [5].

With regard to preterm neonates, previous guidelines did not make a distinction between the respiratory support desirable for term and/or very premature infants [2–4]. Owing to the aetiology of the respiratory failure, it is reasonable to postulate that very preterm infants may need a different resuscitation management than term infants [10, 27–31]. The guidelines of 2005 dedicate a specific chapter to assisted ventilation of preterm infants [5]. Although the level of evidence remains low or indeterminate for these statements, the following indications are reported: inclusion of positive end-expiratory pressure during application of positive-pressure ventilation, monitoring of administered pressures (initial inflation pressure of 20–25 cmH_2O) and use of continuous positive airway pressure in spontaneously breathing preterm infants after resuscitation [5].

The 2005 Guidelines state that endotracheal intubation may be indicated for special circumstances such as congenital diaphragmatic hernia or ELBWI, suggesting that this procedure is mandatory for these groups of patients [5]. Some experts advocate the intubation of all the VLBWI at delivery [2–4]; however, recent studies suggest that individualised intubation strategy is superior in this group of neonates [28, 29]. Furthermore, a recent survey showed that the intubation policy for ELBWI is based on an individualised strategy for the majority of the Italian centres (86.4%) [25].

Medications

The recommendations of 2005 changed for two drugs traditionally used for neonatal resuscitation [5]. First, based on the route of administration (IV or endotracheal), the dose of epinephrine was modified. In fact, if the endotracheal route is used, epinephrine doses of 0.01–0.03 mg/kg will probably be ineffective. Therefore, with 0.01–0.03 mg/kg per dose IV administration is the preferred route. While access is being obtained, administration of a higher dose (up to 0.1 mg/kg) through the endotracheal tube may be considered, but the safety and efficacy of this practice have not been evaluated. Second, the guidelines of 2005 stated that "Naloxone is not recommended during the primary steps of resuscitation" [5]. Furthermore, as there are no studies reporting the efficacy of endotracheal naloxone, this route is not recommended at this point.

Withholding and discontinuing resuscitation

Guidelines 2005 state that "A consistent and coordinated approach to individual cases by the obstetric and neonatal teams and the parents is an important goal" [5]. However, recent studies show that hospitals frequently have no written protocols for ethical aspects of neonatal resuscitation, the final decision is taken by the attending physician, and the parent's wishes are not adequately taken into account [32, 33]. Previous guidelines suggested that in particular circumstances it was reasonable to withhold resuscitation [2–4]. They included extreme prematurity, (gestational age <23 weeks or birth weight <400 g), anencephaly, and chromosomal abnormalities incompatible with life, such as trisomy 13 or 18. In the latest recommendations, all these circumstances are confirmed with the exception of trisomy 18 [5]. Based on previous guidelines [2–4], it was thought justified to discontinue resuscitation after 15 min of continuous and adequate resuscitative efforts when faced with infants showing no signs of life (no heart beat and no respiratory effort). In these circumstances, Guidelines 2005 limit this time to 10 min [5]. In Italy, 31.8% of the level III neonatal centres have no defined time for discontinuation of resuscitative efforts when faced with this clinical situation [32].

In conclusion, based on the results of recent randomised clinical trials, current guidelines for neonatal resuscitation have been changed. However, the level of evidence of some recommendations remains low, suggesting that further prospective research in this field is needed.

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Chapter 35

Regional anaesthesia in neonates

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The last decade has seen many advances in the management of pain in neonates, which are based upon an increased understanding of the neurophysiology of pain, combined with the development of clinical pain services, analgesic delivery devices and monitoring protocols.

The nervous system of neonates is characterised by the absence of full myelination and by poorly myelinated thalamocortical radiations. These elements must be considered as a reflection of immaturity but not as an indication of lack of function. The immaturity of the nociceptive system implies that young patients cannot localise pain as accurately as adults, and the corresponding perception of nociceptive sensation may be more widespread. The differences in subclasses of opioid receptors in neonates may contribute to a reduced ability to modulate nociceptive transmission.

Painful experiences in very-low-weight infants may result in significantly higher somatisation scores. This increased understanding of pain transmission and long-term pain consequences [1] underlines the need for a wide spectrum of strategies to achieve optimal patient pain relief.

Regional anaesthesia is commonly used as an adjunct to general anaesthesia or, most commonly, as a means of providing postoperative analgesia. Peripheral (both continuous or single shot) and central blocks (epidural or spinal) and the use of new low-toxicity local anaesthetics, sometimes combined with nonopioid additives, are current strategies of multimodal analgesia in neonates. When these procedures are applied to perform blocks it is essential to take account of the anatomical and physiological differences existing between neonates and children (Table 1).

Table 1. Anatomical and physiological considerations in neonates and children

	Neonates	Children 1 year
Dural sac	S-4	S2-S3
Spinal cord	L-3	L1
Intercristal space	L5–S1	L5
Lumbar lordosis	Absent	Present (acquired upright position)
CSF	4 ml/kg (50% in spinal canal)	4 ml/kg
Plasmatic level albumin/α-1 glycoproteins	Very low	Low

Peripheral nerve blocks

Standard peripheral blocks, such as paraumbilical, axillary, intercostal, inguinal, penile and femoral blocks and those of the fascia iliaca compartment, are the mainstay of analgesic management for neonatal surgery.

Peripheral nerve blocks may avoid the risks inherent in a central blockade and also its side-effects. Other advantages are: higher safety, less nausea/vomiting, less urinary retention, good postoperative analgesia that is long lasting, and the option of performing it even in anticoagulated or febrile patients.

However, peripheral nerve blocks require multiple injections and larger volumes of anaesthetic solution and have a longer onset time. Moreover, their limited effects in cavity surgery (thoracotomy/laparotomy) and their relatively short duration of action mean that they are less well suited to more major surgery.

A 'single-shot peripheral block' means a single injection of a local anaesthetic. This technique is now widely used in infants, but can provide analgesia for only a few hours. Another drawback of these blocks is the relatively high failure rate. For example, although inguinal hernia repair is one of the most common surgical procedures performed in neonates and premature infants, the precise anatomical positions of both the ilioinguinal and the iliohypogastric nerves are still not identified in this age group, and the relatively high failure rate of 10–25%, even when the technique is applied by experienced practitioners, could be due to a lack of specific spatial knowledge of the anatomy of these nerves in infants and neonates [2].

Direct ultrasonographic visualisation of the inguinal and iliohypogastric nerves might improve the quality of the block and reduce the risk of complications. The using of real-time imaging makes it possible to detect the precise location of the needle tip between the ilioinguinal and iliohypogastric nerves and to observe the spread of the local anaesthetic around both nerves. This allows the use of significantly smaller amounts of local anaesthetics while clinically effective blocks are still achieved. This is particularly relevant for neonates, who are at risk of local anaesthetic toxicity and higher free plasma concentrations of local anaesthetic agents in view of their lower plasma concentration of the binding protein alpha-1 acid glycoprotein. The results of a recent study are encouraging and demonstrate a further application of the use of ultrasonography in paediatric regional anaesthesia [3]; it is important, however, to underline that ultrasound imaging in neonates should be considered an important and ongoing part of training in regional paediatric anaesthesia, as it is a way of demonstrating the relevant anatomical differences of this age group and many of the structures that regional anaesthetists seek to avoid are clearly shown: the pleura, arteries and veins. It is for this reason that the availability of ultrasound may lead to changes in regional neonatal anaesthetic practice.

A **'continuous peripheral nerve block (CPNB)'** means a continuous infusion of local anaesthetic/s. CPNBs are even safer than central ones and are very effective for long-term pain control.

Many published studies demonstrate the efficacy and safety of analgesia via a peripheral catheter; no complications or side-effects linked to long-term infusions

have been described, and few accidental removals and little drug leakage have been described.

CPNBs are at least as efficient as epidural analgesia, but produce fewer side-effects [4]. The use of ropivacaine and levobupivacaine for CPNBs is particularly interesting in neonates, because of the lower cardiac and central nervous system (CNS) toxicity and differential sensory/motor blockade duration with these agents [5].

Ropivacaine is the drug of choice; it has the potential to produce a differential neural blockade with less pronounced motor block and induces less myotoxicity than bupivacaine [6].

There has so far been a lack of specific equipment for performance of such techniques in neonates, and practitioners have just used radial artery catheterisation sets, epidural kits, and central venous catheter sets. A specially designed set for paediatric CPNB has recently been developed. It is composed of a 20-G bevelled (15°) conducting needle 33 or 55 mm long sheathed in a plastic cannula and a 22-G, 400-mm-long catheter with a wire.

Data in the literature suggest that the starting bolus dose administered before a continuous infusion depends on the objective; 0.4–0.6 ml/kg of a low concentration (e.g. 0.2% ropivacaine) is generally used for intraoperative pain control and for postoperative analgesia. Lidocaine 1.5% can be added to a bolus of 0.2% ropivacaine. A continuous infusion is then administered using 0.125–0.25% bupivacaine or 0.2% ropivacaine at 0.1–0.3 ml kg^{-1} h^{-1}, which is equivalent to 0.2–0.4 mg kg^{-1} h^{-1}. A 25–30% reduction in local anaesthetic is recommended for infants months [7].

In a recent study, Ivani et al. [8] demonstrated better postoperative analgesia achieved when 2 μg/kg clonidine was added to ropivacaine for an ilioinguinal–iliohypogastric nerve block, but this observation was not supported by the results of the study published by Kaabachi et al. [9], which in fact failed to demonstrate a better postoperative analgesia following the addition of 1 μg/kg clonidine to 0.25% bupivacaine for ilioinguinal–iliohypogastric nerve blocks.

These different effects of a small dose of clonidine on the efficacy of nerve blocks may be explained by the differences in the type of nerve block, mixture injected and technique used, which probably influence the rate of absorption of the anaesthetic solutions injected.

Central blocks

Epidural

Epidural analgesia in combination with light general anaesthesia is a useful alternative for neonates undergoing major surgery, avoiding the adverse effects related to systemic administration of opioids and other agents. Apart from providing good intraoperative and postoperative analgesia, epidural blockade has beneficial effects on the humoral, metabolic, and haemodynamic responses to surgery and may improve postoperative respiratory performance.

In experienced hands, the complication rate of epidural analgesia is low. Serious complications have been described in small infants, including paraplegia and death. In most cases direct trauma is reported, and it seems probable that it is a result of difficulty in performing the epidural. Many authors share the opinion that only anaesthesiologists who are experienced in the technique should perform epidural anaesthesia in small infants and neonates.

Caudal epidural anaesthesia remains the most frequently performed regional anaesthetic technique in infants and children. This is a popular single-shot technique characterised by a high level of efficacy and safety. Of all central blocks, this is the one that has the lowest incidence of complications (0.7/1000 cases) [10].

In neonates and infants, the straighter column and less dense packing of the extradural space by fat and fibrous tissue allows catheters to be placed via the sacral hiatus, then threaded through to the thoracic region. This provides segmental thoracic analgesia, yet avoids the hazards associated with direct needling of the thoracic extradural space. Catheters may also be passed to low lumbar levels for lumbar blocks, so that the larger doses of local anaesthetic needed when the injection is performed at the sacral hiatus are avoided.

Correct cannula placement and catheter level should be checked to avoid high blocks and respiratory compromise or low blocks and inadequate analgesia. A number of techniques have been described for the confirmation of correct or intravascular placement, but the novel use of ultrasound to visualise the epidural catheter has a particularly high potential for improving safety and providing better quality analgesia [11, 12].

Toxicity of local anaesthetics affects the heart and the brain and is commonly produced as a result of inadvertent intravascular administration or administration of an excessive bolus dose.

Owing to the lower level of the plasma protein α1-acid glycoprotein, albumin, and lower bicarbonate reserves, neonates have a high risk of bupivacaine toxicities, such as cardiac dysrhythmia or respiratory arrest, which are more likely in neonates and infants than convulsions [13]. This can be avoided by using bolus doses and infusion rates that are within the recommended guidelines and by taking account of the pharmacokinetics of local anaesthetics in neonates. Pharmacokinetic studies of several local anaesthetics have been performed in neonates and have produced important information on the safe use of local anaesthetics in neonates. Pharmacokinetic studies on bupivacaine showed a reduction of clearance in neonates reaching mature values by 4–6 months of age. An infusion rate of 0.2 mg kg^{-1} h^{-1} provokes a continuous increase in the plasma concentration, which rises to the threshold for toxicity in about 72 h. Therefore, bupivacaine infusion rates of 0.4 mg kg^{-1} h^{-1} are safe in infants aged more than 6 months, but infusion rates in neonates should be no faster than 0.2 mg kg^{-1} h^{-1} [14].

Ropivacaine has a number of advantages that could be considered important in neonates. These include lower cardiotoxicity than are associated with equal concentrations of racemic bupivacaine and a higher threshold for CNS toxicity of the unbound concentration. The greater degree of block in nerve fibres of pain transmission than of motor function for a given concentration [15] would be of further benefit.

Plasma concentrations of unbound ropivacaine are expected to level off during an epidural infusion as ropivacaine is eliminated by liver metabolism with an intermediate to low hepatic extraction ratio (in adults as well as in children and neonates). Consequently, the plasma concentration of unbound ropivacaine at steady state will depend on the clearance of unbound ropivacaine. As a consequence of the age-related variations in clearance the unbound ropivacaine plasma concentrations are higher in neonates than in older age groups [16].

A study by Bosemberg et al. shows that plasma concentrations of unbound ropivacaine level off after a 24-h infusion in all age groups, including neonates. This is important and suggests that long-term epidural infusions of ropivacaine may be administered to both infants and neonates.

Furthermore, continuous epidural infusion of ropivacaine 0.2% (0.2–0.4 mg kg^{-1} h^{-1}) for 48–72 h provided satisfactory postoperative pain relief in infants aged 0–362 days.

Notwithstanding the use of different doses in different age groups, no age-related differences were found in the need for supplementary analgesia. A dose of 0.4 mg kg^{-1} h^{-1} of ropivacaine is generally recommended for continuous epidural infusion in children, but no studies have been performed in attempts to define the minimum effective infusion rates. However, because of the wider variability of plasma concentrations of ropivacaine in neonates, extreme caution should be exercised whenever neonates undergo surgery during the 1st week of life [17].

Finally, levobupivacaine is the newest local anaesthetic to be introduced into clinical practice. An open-label study performed by Chalkiadis [18] using 2mg/kg of 0.25% levobupivacaine in infants shows that there is a direct link between the immaturity of P450 CYP3A4 and CYP1A2 enzyme isoforms that metabolise this local anaesthetic in infants and a lower clearance than in adults. This lower clearance delays peak plasma concentration, which was noted to occur approximately 50 min after caudal epidural administration of levobupivacaine.

The low intrinsic toxicity of levobupivacaine makes it ideal as a local anaesthetic for paediatric use, but there are no data describing its pharmacokinetics in infants after caudal administration. A disadvantage of caudal blockade is the relatively short duration of postoperative analgesia.

Various additives to the local anaesthetic solution have been used in attempts to prolong the duration of anaesthesia following a single caudal epidural injection.

The addition of caudal clonidine to local anaesthetics has been considered useful to prolong the duration of anaesthesia and to reduce the postoperative need for analgesics in preterm infants. However, respiratory depression and postoperative apnoea are side-effects of clonidine [19].

Clonidine 1–2 μg/k and ketamine 0.5–1 mg/kg [20] increase the duration of analgesia from approximately 5 h to 10 h when combined with bupivacaine 0.1–0.25% or ropivacaine 0.08–0.2%.

Although clonidine-induced respiratory depression is uncommon in the dose range normally used (1–2 μg/kg), this adjuvant reduces the ventilatory response to carbon dioxide [21]. The consequent respiratory depression has been associated with differential recruitment of upper airway muscles and continuous activation

of laryngeal and pharyngeal muscles in animal studies. Clonidine has been shown to stimulate the central alpha-2 adrenoceptor, with a differential effect on baroreflex heart rate (HR) and vasomotor regulation. Alpha-2 adrenoceptor stimulation greatly augments baroreflex-mediated bradycardia and exerts a tonic inhibitory influence on respiratory rhythm in the awake goat. These effects can be reversed by selective alpha-2 adrenoceptor blockade [22].

Another study demonstrates that *S*-ketamine 0.5 mg/kg, when added to 0.2% caudal ropivacaine, provides better postoperative analgesia than clonidine without any clinically significant side-effects [23]. The combination of *S*+ ketamine and clonidine has been reported to provide satisfactory analgesia for up to 20 h. At the higher dosage levels both agents are associated with a greater risk of sedation, apnoea (particularly in neonates and infants) and nausea. Fentanyl, in contrast, does not prolong the duration of analgesia when added to a single-shot caudal block, but does significantly increase the incidence of nausea and vomiting. Other agents, such as buprenorphine, tramadol, neostigmine, and midazolam, are associated with an unacceptably high incidence of nausea and vomiting with minimal added benefit [24].

Spinal anaesthesia

Owing to improvements in neonatal care, increasing numbers of premature infants are surviving and could require surgical procedures. Apnoea of prematurity (AOP) is a concurrent issue for paediatric anaesthetists and is attributed to immaturity of the respiratory and central nervous systems. Numerous authors have provided case reports and case series detailing their experiences with spinal anaesthesia (SA) as an alternative to general anaesthesia to avoid the risk of AOP. By far the largest number of spinal anaesthesia are performed in infants who were born prematurely. The safety of the procedure and the high rate of success have extended the application of this anaesthetic technique to a wide variety of surgical procedures, such as pyloromyotomy, gastrostomy placement, myelomeningocele repair, cardiac surgery and genitourinary procedures. Moreover, spinal anaesthesia has been successfully applied in high-risk infants and for cardiac catheterisation, as documented by several case reports [25, 26].

Studies comparing general and spinal anaesthesia are available only for inguinal herniorrhaphy. The outcomes of interest have focused on the need for prolonged mechanical ventilation, apnoeic and/or bradycardic episodes, and length of hospital stay.

Relatively larger doses of local anaesthetics are required for spinal anaesthesia in infants than in adults and older children. The physiological/anatomical explanation for this is that the volume of CSF is larger in neonates than in children (4 versus 2 ml/kg) and the spinal cord and nerve roots are relatively greater in diameter in neonates.

Moreover there is a proportionally greater blood flow to the infant's spinal cord, leading to faster drug uptake from the subarachnoid space [27].

Lumbar puncture can be safely performed at the L4–L5 or L5–S1 interspaces. The *conus medullaris* terminates at the L-3 level in neonates (Table 1). Cutting-point needles (e.g. 22 or 25 G Quincke) are the ones most frequently used by paediatric specialists. For neonates, a spinal needle length of 25 mm is sufficient.

Spinal anaesthesia in neonates has been associated with minimal respiratory and haemodynamic changes [28–30]. Dohi et al. [31] studied haemodynamic stability during spinal anaesthesia in young children and premature infants and found little or no change in blood pressure (BP) or HR in response to sympathectomy. It was postulated that the lack of haemodynamic changes was due to the immaturity of the sympathetic nervous system in young children. The smaller relative blood volume in the lower extremities compared with adult proportions may account for the lesser degree of lower extremity venous pooling during sympathectomy and thus in turn for the fewer cardiovascular changes [32]. As with adults, certain associated conditions remain contraindications to spinal anaesthesia, including patient or parent refusal, uncorrected hypovolaemia, infection at the insertion site, untreated systemic sepsis and increased intracranial pressure [33].

Spinal anaesthesia is characterised by a high success rate of more than 80% [34].

Bupivacaine is a widely used local anaesthetic for neonates and has been used for spinal anaesthesia in neonates in some clinical trials [35]. The use of hyperbaric bupivacaine is suggested by the study of Kokki et al. [36]. They described a greater success rate of the block when they used bupivacaine in 8% of glucose than with isobaric bupivacaine in saline 0.9%. Frawley et al. suggest administering a dose of 0.8 mg/kg of levobupivacaine. Ropivacaine and levobupivacaine have recently been introduced, but their safety for spinal anaesthesia has still not been fully confirmed. Doses ranging between 0.75 and 1.25 mg/kg of an isobaric solution of levobupivacaine are suggested by the same dose range-finding study [37].

Investigators have employed tetracaine 0.5% in dextrose 5% (0.4–1 mg/kg), bupivacaine 0.5% (0.6–1 mg/kg), and bupivacaine 0.75% in dextrose 8.25% (0.6–1 mg/kg) for infants with body weight less than 5 kg. These dosing regimens will provide approximately 60–80 min of operating time. Return of hip flexion is observed within 2 h. The addition of adrenaline (epinephrine; 20–50 μg) to tetracaine solutions can prolong spinal anaesthesia by approximately 20 min [38].

Even though Craven's review recently published in *The Cochrane Database of Systematic Reviews* [39] shows no reliable evidence of the effects of spinal anaesthesia as against general anaesthesia on the incidence of apnoea, bradycardia, or oxygen desaturation in children born as preterm infants, we can consider SA a safe procedure that can be applied to avoid the risks associated with general anaesthesia.

An important drawback of neonatal SA is its short duration of action. The addition of clonidine has been proved to prolong bupivacaine SA with no immediate deleterious side-effects, but clonidine has not been reported in neonatal SA except in the recent study by Rochette et al. This observational study evaluated the clinical acceptability of clonidine in neonatal SA, which was induced by injection of 0.2 ml/kg of a solution prepared by adding clonidine 100 μg to 20 ml of 0.5% bupivacaine over 30 s, so that isobaric bupivacaine, 1 mg/kg, and clonidine, 1 μg/kg, were given. The results show that uncomplicated clonidine-related apnoea may be

acceptable with careful monitoring and encourage performance of a prospective, comparative study to evaluate the risk–benefit ratio of clonidine SA in newborns, underlining that clonidine may not affect postoperative desaturation in neonates [40].

Table 2. Suggested dosing regimens for spinal anaesthesia in neonates, infants and children.

Author and Ref	Age range	Agent	dose
Abajian et al. [41]	Less than 1 year	Tetracaine	0.22–0.32 mg/kg
Sartorelli et al. [42]	Less than 7 months	Tetracaine	0.5 mg/kg
Blaise and Roy [43]	0–3 months 3–24 months ›24 months 0–24 months ›24 months	Tetracaine: Bupivacaine:	0.4–0.5 mg/kg 0.3–0.4 mg/kg 0.2–0.3 mg/kg 0.3–0.4 mg/kg 0.3 mg/kg
Tobias et al. [44]	Neonate	Tetracaine	0.6 mg/kg
Tobias and Flannagan [45]	Neonate	Tetracaine	0.6 mg/kg
Kokki et al. [46]	2–5 years	Bupivacaine	0.5 mg/kg
Kokki and Hendolin [47]	2 months to 17 years	Lidocaine Bupivacaine	2–3 mg/kg 0.3–0.4 mg/kg
Melman et al. [48]	0.5 months to 15 years	Lidocaine	1.5–2.5 mg/kg
Parkinson et al. [49]	Less than 6 months	Bupivacaine	0.6 mg/kg
Rice et al. [50]	1–12 months	Lidocaine Tetracaine	3 mg/kg 0.4 mg/kg
Aronsson et al. [51]	1 day to 12 months	Tetracaine	0.5 mg/kg
Tobias and Mencio [52]	9 days to 12 months	Bupivacaine	0.5–0.6 mg/kg

Conclusions

Although considerable progress has been made in studying the safety, efficacy, dose–response relationships, and clinical outcomes associated with the use of analgesics and anaesthetics in neonates, there are still major gaps in our knowledge that hinder optimal clinical practice. Multicentre clinical trials with adequate sample sizes are needed to assess the occurrence of uncommon adverse effects and examine safety concerns. Ethical constraints demand the development of designs that permit immediate rescue while allowing examination of efficacy and dose–response relationships. Future studies should examine whether the optimal application of multimodal analgesia, as in adults, can improve clinical outcomes in neonates undergoing major surgery.

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Chapter 36

Locoregional anaesthesia in children

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Regional anaesthesia has become an essential component of modern paediatric anaesthesia. The two principal applications of regional anaesthesia are its intraoperative use to supplement light general anaesthesia and postoperative use for pain management. Key factors in encouraging the use of regional anaesthesia techniques have probably been the favourable outcomes observed in children undergoing combined general and epidural anaesthesia for major surgery, the routine practice of caudal and peripheral blocks to provide painless emergence and the efficacy of pain relief they provide in chronic and oncology patients.

The recent clinical introduction of new local anaesthetics with low systemic toxicity, such as ropivacaine and levobupivacaine, the wide use of nonopioid additives to local anaesthetics, and the use of ultrasonography to improve the success rate and efficacy of regional anaesthesia are topics that have been investigated in recent clinical trials and research. Finally, the interaction between general and regional anaesthesia has important clinical applications, and it can be considered the key to understanding the action of different drugs and the effect of their interaction on the anaesthetic state in children.

New local anaesthetics

Although local anaesthetics are generally quite safe and effective, they can have cardiovascular and nervous toxicity. This can occur after an excessive dose is administered or after accidental intravascular or intraosseus injection. Local anaesthetic toxicity is particularly relevant in infants and children. The relatively high doses that have to be administered to obtain clinical effects, in the presence of particular characteristics both anatomical and physiological, mean that the paediatric age group is especially vulnerable to adverse events related to anaesthetic administration. Moreover, the prime aim of single-shot administration of local anaesthetics is postoperative analgesia, so that long-acting anaesthetics must be used. Bupivacaine has been widely used for paediatric regional anaesthesia, but the choice is now shifting to ropivacaine and levobupivacaine. The last named has only recently been introduced into clinical practice, and several trials have been devoted to determining its safety and efficacy.

In animals levobupivacaine produced less cardiac and central nervous toxicity than bupivacaine. In healthy volunteers a comparison of levobupivacaine and

bupivacaine showed a smaller reduction of the stroke index and the ejection fraction after levobupivacaine. Similar toxic effects were found for levobupivacaine and ropivacaine [1]. The lower toxicity of levobupivacaine can be explained by a minor affinity for brain and myocardial tissues, so that a higher dose than of bupivacaine is necessary for it to be lethal.

However, regional anaesthesia is commonly performed in children who are already under general anaesthesia, and patients may tolerate high doses of anaesthetics before manifesting toxic effects. Furthermore, accidental venous injection of local anaesthetics cannot be detected with the test dose because of its proven low sensitivity. It is therefore very important to minimise the risk of toxic effects of local anaesthetics by using drugs with lower potential toxicity, such as levobupivacaine, particularly in children.

Pharmacokinetic properties of levobupivacaine in children are extrapolated from those of bupivacaine. A pharmacokinetic study of single-shot administration of 2 mg kg^{-1} of levobupivacaine via the caudal route has recently been performed, and it showed that the peak plasma concentration was reached after a mean of 30 min [2]; children aged less than 3 years had a delayed peak plasma concentration. In all patients the plasma concentration was in the safe range for bupivacaine, but no recommendations exist at present on the safe plasma concentration of levobupivacaine in children. The same authors performed a pharmacokinetic study after a single administration of levobupivacaine in infants less than 3 months old [3]. This study showed that clearance of levobupivacaine in infants is half than in adults; this is explained by immaturity of the two isoforms of cytochrome P450 that are involved in the metabolism of levobupivacaine. No pharmacokinetic studies have been performed after continuous infusion of levobupivacaine in children.

The potency of levobupivacaine has been tested in women in labour. Lyons et al. compared the minimum local anaesthetic concentration (MLAC) of levobupivacaine and racemic bupivacaine and demonstrated that the potency ratio of levobupivacaine to bupivacaine was 0.98 and unlikely to have any clinical relevance [4]. Some clinical trials have recently been published on caudal single-shot administration of levobupivacaine in children. It has been demonstrated that levobupivacaine is effective and well tolerated.

In an open study, 2 mg kg^{-1} of levobupivacaine was effective in 90% of children less than 2 years old [5]. In a randomised double blind study levobupivacaine 0.25% was compared with ropivacaine 0.2% and bupivacaine 0.25%. The three drugs were comparable in terms of intra- and postoperative pain relief, but ropivacaine produced a less marked and durable postoperative motor block [6]. Onset time, intraoperative analgesia, postoperative pain relief and duration of analgesia were comparable for levobupivacaine 0.25% and ropivacaine 0.25% in the randomised double-blind study performed by Astuto et al. [7]. Locatelli et al. compared levobupivacaine 0.25%, ropivacaine 0.25% and bupivacaine 0.25 in a phase III controlled trial. The three drugs were comparable for clinical efficacy and motor block, but the duration of analgesia was longer with bupivacaine than with levobupivacaine or ropivacaine [8]. Ivani et al. investigated the effects of three different

Table 1. Clinical trials performed on levobupivacaine (*L*), compared with bupivacaine (*B*) and ropivacaine (*R*) after caudal administration in children

First author [ref]	Drug	Dose	Age	Kind of surgery	Duration of analgesia	Early motor block	Conclusions
Taylor [5]	L 0.25%	2 mg kg^{-1}	<2 years	Circumcision	7.3 h	—	Similar to bupivacaine
Ivani [9]	L 0.125% L 0.2% L 0.25%	1 ml kg^{-1} 1 ml kg^{-1} 1 ml kg^{-1}	1–7 years	Subumbilical	60 min 118 min 158 min	0 patients 4 patients 8 patients	0.2% is the best clinical option
Astuto [7]	L 0.25% R 0.25%	1 ml kg^{-1}	2–6 years	Subumbilical	302±29 min 230±38 min	— —	Comparable onset and duration
Locatelli [8]	L 0.25% R 0.25% B 0.25%	0.5–1 ml kg^{-1}	<10 years	Minor	1.7 (0.4) h 1.6 (0.6) h 2.45 (0.6) h	B longer than L and R ($P< 0.01$)	B longer than L and R ($P< 0.05$)
Breschan [24]	L 0.2% R 0.2% B 0.2%	1 ml kg^{-1}	1–7 years	Minor	5.75 h 5.7 h 5.35 h	Less for L and R (2 h)	Comparable analgesia
Ivani G [6]	L 0.2% R 0.2%	1 ml kg^{-1}	1–7 years	Minor	308 min 380 min	8 patients 5 patients	Comparable analgesia

concentrations of levobupivacaine (0.125%, 0.2% and 0.25%) [9]. A dose–response relationship was found for duration of postoperative analgesia, and the number of patients who experimented early postoperative motor block in the three groups. Based on the results of this clinical trial, Ivani suggested that 0.2% is a good concentration of levobupivacaine to use for caudal block in children.

In the final analysis, these clinical trials show that levobupivacaine, ropivacaine and bupivacaine have similar clinical properties when given at the same dose and concentration in children, as shown in Table 1. In contrast, ropivacaine has been demonstrated to be less potent than bupivacaine and levobupivacaine in adults. The possible explanation for the difference in potency between children and adults is that in children caudal block is performed under general anaesthesia. General anaesthesia could modify the clinical effect of central blocks, and different techniques of general anaesthesia could have different effects on postoperative analgesia. Moreover, the local anaesthetic concentration used in clinical practice may reach the upper portion of the dose–response curve, where potency differences are obscured. A double blind, controlled, phase III study on the minimal local anaesthetic concentration (MLAC) of levobupivacaine under standard conditions of general anaesthesia (1 MAC of sevoflurane) is in progress in our clinic. The authors believe that the results of this trial will be highly relevant to our understanding of the potency differences between the two local anaesthetics and the relationship with sevoflurane anaesthesia.

Nonopioid additives to local anaesthetics

Various agents are currently used as adjuncts to regional anaesthesia. Combination of these additives with local anaesthetics prolongs the duration of the block, with improved postoperative analgesia, as shown in several clinical trials. Moreover, opioid administration and the well-known side effects of opioids (respiratory depression, nausea, vomiting, pruritus) can be avoided.

Clonidine

Clonidine has an analgesic activity that is mediated by α_2-adrenergic receptors at both spinal and supraspinal sites. The first extradural administration was reported in 1984; since then various studies have demonstrated a prolonged duration of analgesia in children when it is combined with local anaesthetics: the addition of 1–2 $\mu g\ kg^{-1}$ of clonidine given via the epidural route increases the duration of 1–2 h achieved with local anaesthetics alone. In a recent clinical trial the results of adding three different doses of clonidine (1, 1.5 and 2 $\mu g\ kg^{-1}$) to 0.125% bupivacaine were compared, and after the 2 $\mu\ kg^{-1}$ dose a significantly longer period of analgesia was demonstrated, with no significant respiratory or haemodynamic side-effects [10]. Contradictory results have been reported concerning peripheral nerve blocks [11]. Moreover, clonidine has other potential benefits, including reduced postoperative agitation, shivering and vomiting. On the other hand, administration of higher

dosages of clonidine is associated with a potential risk of apnoea, particularly in neonates. Finally, a pharmacokinetic study was performed; it demonstrated that epidural and intramuscular administration of the same dose was followed by a similar peak plasma concentration, but no correlation was found between the analgesic effects produced by epidural administration and systemic absorption.

Table 2. Guidelines for nonopioid additive administration via the caudal epidural route in children

Drug	Dose	Site of action	
Clonidine	1–2 μg kg^{-1}	Agonist of α_2-adrenergic receptor	Sedation, respiratory depression
***S*-Ketamine**	0.5 mg kg^{-1}	Blocker of NMDA receptor	Rare
Midazolam	50 μg kg^{-1}	Agonist of GABA receptor	Sedation
Neostigmine	2 μg kg^{-1}	Muscarinic receptor	Nausea, vomiting

S-Ketamine

Ketamine is an *N*-methyl-d-aspartic acid (NMDA) blocker that decreases the activation of dorsal horn neurones. Other neuronal systems may also be involved in the antinociceptive action of ketamine, as blockade of norepinephrine and serotonin receptors attenuates the analgesic action of ketamine in animals [12]. Ketamine not only produces analgesia after systemic administration, but also exerts a profound analgesic effect at spinal cord level in animal preparations [13].

There is still some concern about the safety of extradural ketamine, because of the reported risk of neurotoxicity. It appears that *S*(+)-ketamine, which is available in a preservative-free formulation, has a low potential for causing neurotoxicity. While its pharmacokinetic properties are similar to those of the racemic mixture, *S*(+)-ketamine has approximately twice the analgesic potency of the racemate [14].

Ketamine has been used as the sole agent to produce caudal block in children [15]. Moreover, addition of 1–2 μg kg^{-1} of clonidine to 1 mg kg^{-1} of ketamine via the caudal route significantly prolongs analgesia: for 24 h, as demonstrated by Hager et al. [16]. De Negri et al. have shown that the addition of 0.5 mg kg^{-1} of *S*-ketamine to caudal ropivacaine 0.2% prolongs the duration of postoperative analgesia in children significantly beyond that attained with ropivacaine plus clonidine 2 μg kg^{-1} or ropivacaine alone [17].

In conclusion, ketamine has the important advantage that accidental intravascular or intramuscular injection does not produce cardiovascular or neuronal toxicity such as is seen with local anaesthetics. At a dose of 0.5 mg kg^{-1} *S*-ketamine significantly prolongs the duration of analgesia beyond the duration achieved with added clonidine, and clinical side-effects are rare. Doses of 1 mg kg^{-1} or more produce systemic side-effects [18].

Other additives

Midazolam is a benzodiazepine that interacts with γ-aminobutyric acid (GABA) receptors in the brain and spinal cord. These receptors have an important role in modulation of the nociceptive response. A dose of 50 μg kg^{-1} prolongs the duration of analgesia yielded by bupivacaine in children [19].

Neostigmine prolongs the duration of analgesia when it is administered with local anaesthetics, at a dose of 2 μg kg^{-1}. Its mechanism of action is unclear and probably involves muscarinic receptors in the spinal cord. Neostigmine produces dose-dependent nausea and vomiting and the presence of paraben and methylparaben in the solution could result in a neurotoxic effect [20].

Ultrasonography and paediatric regional anaesthesia

The key requirement for successful regional anaesthetic blocks is the distribution of local anaesthetics around the nerve structures. Morgan affirmed, in a personal communication, that regional anaesthesia always works if the anaesthetists *"put the right dose of the right drug in the right place."*

The loss-of-resistance technique is usually used to check needle-tip penetration into the epidural space, and catheter insertion is traditionally achieved blind. Ultrasonography (US) can be used to identify neuraxial structures during insertion and placement of epidural catheters and to identify peripheral nerves. Moreover, US can be particularly useful for teaching trainees who are inexperienced in anaesthesia. During the performance of caudal block the ultrasound probe can be positioned cephalad to the injection site in the transverse plane, approximately at the tip of the needle. Dilatation of the caudal space and localised turbulence are noted on the ultrasound screen when placement is successful. Roberts et al. [21] studied 60 caudal blocks in children monitored by US imaging and conclude that US is a reliable indicator of correct performance for caudal block. They found US was safe, quick to perform, and useful insofar as it provided additional information on anatomy.

Similarly, ultrasonographic guidance of peripheral nerve blocks of both the upper and the lower extremities reduces the number of complications and improves the quality of the blocks. Willschke et al. [22] have demonstrated that US-guided ilioinguinal/iliohypogastric nerve blocks can be achieved with significantly smaller volumes of local anaesthetics and that the intra- and postoperative requirements for additional analgesia are significantly lower than with conventional method.

In summary, direct visualisation of the distribution of local anaesthetics with the aid of US can improve the quality of the block and avoid the complications of upper/lower extremity nerve blocks and neuraxial techniques in real time. The theoretical and practical advantages over conventional guidance techniques, such as nerve stimulation and loss-of-resistance procedures, are significant, particularly in children [23]. Considering their enormous potential, these techniques should have a role in the future training of anaesthetists.

Conclusions

Regional anaesthesia techniques are widely used in paediatric anaesthesia, and postoperative analgesia is the primary aim. As they involve insertion of needles and catheters and the administration of drugs, primarily local anaesthetics, every precaution should be taken to ensure the safety of the patients. Furthermore, in children regional anaesthesia is usually performed under general anaesthesia. There are many reasons to support performing regional blocks under light general anaesthesia, and the background of several decades and the wide number of clinical trials performed can be considered criteria of evidence-based medicine for safe practice.

Owing to their effectiveness, regional techniques should be used with discrimination, using adequate and well-established concentrations of local anaesthetics so as not to blunt abnormally high degrees of pain and motor functions. Local anaesthetics with lower intrinsic toxicity, such as levobupivacaine, the addition of adjuvants to allow use of less concentrated local anaesthetics and the potential help US can provide in identifying correct placements of local anaesthetics are topics of great interest and much debated. On the one hand, no drug or medical practice is free of potential side-effects and complications, particularly with neuraxial administration. It would thus be good to be able to demonstrate that the use of invasive techniques translates into improved care and outcome, avoiding the risk of neurotoxicity. On the other hand, the current position may be that regional anaesthesia is safe provided it is carried out by an anaesthetist with proven experience in paediatric practice.

We conclude that with sound judgment and appropriate scientific knowledge, in many instances regional anaesthesia is the best technique to provide adequate intraoperative and postoperative pain relief in paediatric patients.

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Chapter 37

Management of CRRT in paediatrics

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Acute renal failure (ARF) is defined as the cessation of renal function with or without changes in urinary output. The incidence of ARF in paediatric intensive care units is highly variable, ranging from 2% to 8%, and is often associated with severe medical or surgical illness [1]. Whereas patients with intrinsic renal abnormalities as the basis for their renal failure have mortality rates below 10%, patients with secondary ARF have mortality rates higher than 50% [2].

If conventional therapy fails to control fluid and metabolic balance, extracorporeal renal replacement therapy (RRT) has to be instituted. Whereas acute peritoneal dialysis was the RRT of choice in the 1970s and 1980s, some patients benefited from acute haemodialysis (HD). Over the last two decades improvements in vascular access, the availability of equipment for use specifically in neonatal and paediatric patients and improved techniques, together with enhanced understanding of paediatric critical care medicine, have improved care for infants and children with multiple-organ system failure (MOSF) requiring RRT [3–9]. Continuous renal replacement therapy (CRRT) has become an important supportive therapy for critically ill infants and children with MOSF.

Methods

Schematics representing spontaneous and pump-driven haemofiltration and haemodiafiltration are shown in Fig. 1.

Haemofiltration

The treatment of ARF with haemofiltration can take the form of continuous arteriovenous haemofiltration with or without HD (CAVH/CAVHD) or of continuous venovenous haemofiltration with or without dialysis (CVVH/CVVHD).

Continuous arteriovenous haemofiltration (CAVH). When this technique is applied blood is driven through the highly permeable haemofilter by the patient's arteriovenous pressure gradient, producing an ultrafiltrate that is partially or totally replaced by an appropriate replacement solution.

Slow continuous ultrafiltration (SCU). Slow continuous ultrafiltration (SCU) is a form of CAVH/CVVH that is not associated with fluid replacement.

Continuous venovenous haemofiltration (CVVH). Blood is driven through a

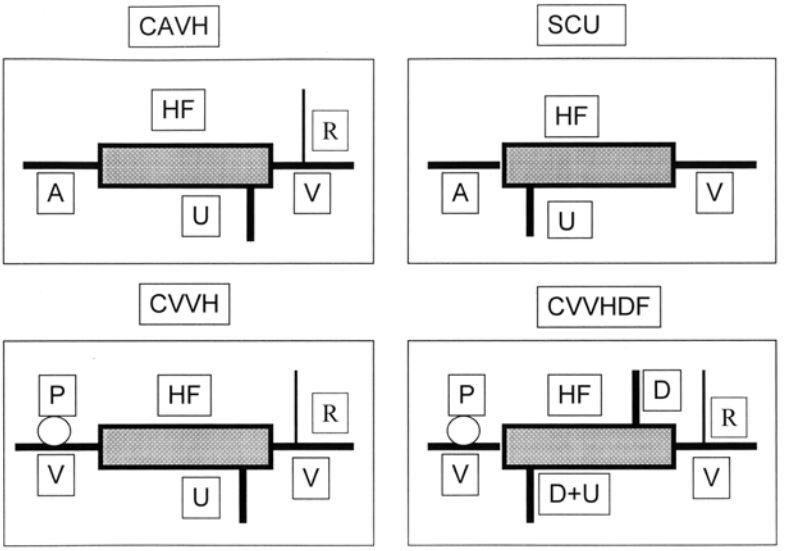

Fig. 1. Schematics illustrating different techniques of continuous renal replacement therapies (*A* artery, *V* vein, *HF* haemofilter, *U* ultrafiltrate, *R* replacement fluid, *D* dialysate, *P* pump, *CAVH* continuous arteriovenous haemofiltration, *SCUF* slow continuous ultrafiltration, *CVVH* continuous venovenous haemofiltration, *CVVHDF* continuous venovenous haemodiafiltration)

highly permeable haemofilter by a roller pump. The ultrafiltrate produced is partially or totally replaced according to the clinical requirements.

Continuous haemodiafiltration (CHDF). During this technique the CAVH or CVVH circuit is modified by the addition of slow countercurrent dialysate flow into the ultrafiltrate-dialysate compartment of the haemofilter. CHDF can be applied in the spontaneous or pump-driven mode.

Machines

Whereas in the past HF machines were not well adapted for small infants, nowadays a variety of machines offer a variety of blood flow rates, warning systems, accurate ultrafiltration controllers, venous and arterial pressures and blood leak detectors. The Baxter, Braun, Medica and Fresenius machines allow for individual choice of HF membranes whilst the Gambro Prisma uses a single HF membrane that is a fixed part of an HF cassette.

Membranes

The choice of membrane for CRRT depends on the machine, whether the need is for convective or diffusive clearance, and the size of the child. The Gambro Prisma has a membrane (AN-69) that is part of the cassette that comes with the machine.

The membrane has been shown to be biocompatible, and it can be used for either convective or diffusive clearance. Alternatively, polysulphone (Renaflow II® 400, 700 Baxter Inc., D150 Hemofilter®, Medica Inc.) and polyamide (FH 22®, Gambro Inc.) membranes are also biocompatible and offer a variety of sizes (0.042 m^2 to 0.6 m^2, filling volume 3.7–48 ml) with the same convective and diffusive flexibility.

Vascular access

Vascular access for CRRT depends on the size of the child and the necessary blood flow rates [10]. Data are given in Table 1. Access is needed to maintain blood flow rates in the range of 10–100 ml/min (4–6 ml kg^{-1} min^{-1}). Triple-lumen access might be helpful in the setting of citrate anticoagulation, where a third lumen might be beneficial for calcium infusion to avoid systemic hypocalcaemia.

Table 1. Vascular access for continuous venovenous haemofiltration in infants and children

	Body weight (kg)	*Catheter size*[a]	*Site of insertion*
Neonates	3 kg	5 Fr SLC	Internal jugular vein
		6.5 Fr DLC	Femoral vein
Infants	3–10 kg	7.0–8.0 Fr DLC	Internal jugular vein
			Femoral vein
			Subclavian vein
Children	10–15 kg	8.0 Fr DLC	Internal jugular vein
	15–30 kg	9.0 Fr DLC	Femoral vein
	>30 kg	11–12 Fr DLC	Subclavian vein

SL single lumen, *DL* double lumen, *Fr* French
[a]Catheters: GamCath® 6.5/8/11/12 Fr; Medcomp Hemo-cath® 8/11.5 Fr; Medcomp Duo-Flow®9 Fr, Medcomp Tri-Flow® 11.5 Fr

Anticoagulation

Unfractionated heparin has been the mainstay of anticoagulation for CRRT. Patients with a normal coagulation status initially receive a heparin bolus of 50–100 IU/kg, which is followed by a continuous infusion of 10–30 IU kg^{-1} h^{-1} into the arterial line of the extracorporeal device to target an ACT of 180–220 s or a PTT of twice the normal value [11]. The advantage of heparin is that it can be easily controlled with bedside ACT monitoring. In patients at high risk of bleeding prostacyclin (Flolan®, Welcome, London, UK) might be given at a rate of 5–20 ng kg^{-1} min^{-1} as the sole antithrombotic agent or in combination with low-dose heparin (5 IU kg^{-1} h^{-1}). Recently, citrate anticoagulation has been introduced as an alternative to heparin anticoagulation in some cases [12, 13]. When calcium is bound with citrate the blood loses its ability to coagulate, so that the patency of the haemofiltration circuit is maintained. The usual target for the ionised calcium of the circuit is 0.25–0.4 mmol/l. To prevent citrate toxicity in the patient, calcium is then infused with a target ionised calcium level of 1.1–1.3 mmol/l. The use of

citrate anticoagulation might result in metabolic alkalosis, because 1 mmol of citrate converts to 3 mmol of bicarbonate in the presence of normal hepatic function or citrate toxicity expressed as rising total calcium and decreasing ionised calcium levels caused by decreased hepatic citrate clearance.

Solutions

Both lactate- and bicarbonate-based solutions result in the same degree of effective clearance, but plasma lactate levels are higher in patients treated with lactate-based solutions. Small infants and patients with hepatic failure may not be able to convert lactate to bicarbonate, and the use of lactate-based dialysis solution might result in hyperlactaemia or worsen lactic acidosis. Today, a variety of bicarbonate-based dialysate and haemofiltration solutions (Hemosol BO®, Prismasol 2®, Prismasol 4®) are on the market and need not to be prepared by the hospital pharmacy. In addition, calcium-free dialysate solutions are available for citrate anticoagulation (PrismOcal®, Prismocitrate10/2®).

Nutrition in ARF

Critically ill infants and children with ARF are often inadequately nourished, because many suffer from multiple organ dysfunction syndrome. In addition, fluid restriction further compromises overall nutrition. During CRRT glucose and amino acids are lost. Separate studies have shown that normal enteral or parenteral nutrition results in a negative protein balance. Maxvold et al. showed in a prospective study that during CVVHD and CVVH use of a dialysate or prefilter ultrafiltrate substitution with 2,000 ml h^{-1} 1.73 m^{-2} resulted in an average loss of approximately 10 g/1.73 m^2 of amino acids (about 10% of protein intake) associated with a negative nitrogen balance at a parenteral amino acid intake of 1.5 g/kg per day [14]. Bellomo et al. increased the amino acid intake in adults undergoing CVVHDF to 2.5 g/kg per day and noted that nitrogen balance was improved but the overall nitrogen balance remained negative [15].

Start of CRRT

A debate that will continue for decades is when to begin CRRT [16]. Arguments for early intervention are easier access, more CRRT training for the staff, lower serum urea nitrogen, and less fluid accumulation. Arguments against early intervention are the lack of any prospective data showing that early intervention affects outcome and the additional risk to the patient when the access is placed and through fluid removal. Like many therapies and procedures, infrequent use increases anxiety when a modality is employed and it then carries an increased risk of complications. This anxiety may be offset with more frequent use of CRRT, which will allow for more familiarity and experience with the modality.

CRRT data

In 2005 Goldstein et al. published the first results of the Prospective Paediatric CRRT Registry in *Kidney International*; the patient base included paediatric patients with multiple organ system failure who had been treated between 2001 and 2003 [17]. The main demographic, clinical and RRT data of this prospective study and our own data of 20 years' experience with CRRT in paediatric patients are given in Tables 2 and 3. The most common causes of CRRT were sepsis (ppCRRT Registry 39.2%, PICU Graz 19%) and cardiogenic shock (ppCRRT Registry 20%, PICU Graz 52%). The most common comorbid underlying illnesses included status following bone marrow transplantation (n=18) and solid organ transplantations (n=8). The primary reasons for CRRT initiation were treatment of fluid overload and electrolyte imbalance (54.1%), treatment of fluid overload only (29.2%), treatment of electrolyte imbalance (8.3%), treatment to prevent fluid overload or electrolyte imbalance (5.0%), and others (3.3%). Most (83.3%) of the patients were mechanically ventilated, and 76 patients were receiving both mechanical ventilation and inotropic agents at the time of CRRT initiation. Survival rates were not different for patients receiving one (40% survival), two (55%) or three or more (45%) inotropic agents at CRRT initiation. Survival rates were significantly better for patients with <20% fluid overload (FO) (ppCRRT Registry 58% survival; PICU Graz 58%) than for those with >20% FO (ppCRRT Registry 40% survival, PICU Graz 23% survival) at CRRT initiation (p<0.002). In addition, survival rates were significantly better for patients who were able to attain their former dry weight during their

Table 2. Demographic, clinical and RRT data recorded by the Prospective Paediatric CRRT Registry Group and the PICU, Medical University of Graz

	ppCRRT (2001–2003)	*PICU Graz (1985–2006)*
Patients	157	114
Patients with MOSF	120	100
Survivors	51.7%	51%
Age (years)	8.5±6.8	4.1±6.1
Body weight (kg)	11.1±25.5	15.6±17.9
Patients being mechanically ventilated	100	92
Patients being mechanically ventilated and taking inotropes	76	88
Inotropes	1.5±1.1	2.0±0.3
PRISM Init CRRT	16.4±7.7	16.6±14
PICU days to CRRT	7.3±14.1	1.84±1.34
AN69 filter	88	24
Polysulphone filter	28	41
Polyamide filter	0	35

PICU paediatric intensive care unit, *MOSF* multiple organ system failure, *CRRT* continuous renal replacement therapy, *ppCRRT* prospective paediatric CRRT Registry Group

Table 3. Clinical and RRT data recorded by the Prospective Paediatric CRRT Registry Group and in the PICU, Medical University of Graz

	ppCRRT	*2001–2003*	*PICU Graz*	*1985–2006*
	N	*Mortality rate (%)*	*N*	*Mortality rate (%)*
Patients	120	51.7%	100	52%
Cardiac surgery	24	47%	52	48%
Sepsis	47	39%	19	58%
BMT/Tx	24	67%	15	80%
Fluid overload				
<20%		42%	82	42%
>20%		60%	18	77%
Vasopressors			29	68%
CVVHD	69	56%	0	
CVVH	35	42%	35	65%
CVVHDF	12	42%	24	35%
CAVH/SCU	0	0	35	40%
ECMO+HF	0	0	6	83%

PICU paediatric intensive care unit, *MOSF* multiple organ system failure, *CRRT* continuous renal replacement therapy, *ppCRRT* prospective paediatric CRRT registry group, *BMT* bone marrow transplantation, *Tx* solid organ transplantation, *CVVHD* continuous venovenous haemodialysis, *CVVH* continuous venovenous haemofiltration, *CVVHDF* continuous venovenous haemodiafiltration, *CAVH* arteriovenous haemofiltration, *SCU* slow continuous ultrafiltration, *ECMO* extracorporeal membrane oxygenation, *HF* haemofiltration

CRRT course (76% survival) than for patients who did not return to their dry weight during the CRRT course (36%, $p<0.001$).

The majority of patients recorded in the ppCRRT Registry received CRRT with an AN 69 membrane, whereas in our study more patients were treated with polysulphone and polyamide membranes. The majority of the ppCRRT Registry patients were treated with a diffusion-only-based CRRT modality (CVVHD), whereas in our study the 76 patients were treated with a convection-based CRRT modality. Patient survival did not differ significantly between CRRT modalities in the ppCRRT Registry patients (CVVH 58%, CVVHD 44%, CVVHDF 58%). No association was observed between survival rates and whether CRRT clearance was <2,000 ml/h per 1.73m^2 or >2,000 ml/h per 1.73m^2. In our retrospective study patients receiving a combined diffusion and convection-based CRRT modality had the highest survival rates (65%).

Conclusions

Advances in RRT in the last few years have resulted in the availability of multiple RRT modalities for the treatment of ARF in the PICU. CRRT, with the use of venovenous access and its advantages in haemodynamically unstable patients, is gaining greater acceptance. The choice of RRT modality should be based on the clinical status of the patient, the resources available in the institution and the cost of therapy. However, further prospective studies are required to find the optimal timing of RRT initiation and the best RRT modality.

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Chapter 38

Severity scores in paediatric intensive care units

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The practice of paediatric critical care has matured dramatically in the course of the past three decades. Knowledge of the pathophysiology of life-threatening processes and the technological capacity to monitor and treat paediatric patients suffering from them has advanced rapidly during this period. Along with the scientific and technical advances has come the evolution of the paediatric intensive care unit (PICU), in which special needs of critically ill or injured children and their families can be met by paediatric specialists. All critically ill infants and children cared for in hospitals, regardless of the physical setting, are entitled to receive the same quality of care [1].

Mortality risk scoring systems are integral to the provision of modern intensive care, providing a measure of performance both between and within individual intensive care units over time [2]. A valid scoring system must predict mortality accurately while adjusting for case mix and disease severity [2–4], but also requires data capture that is feasible in clinical practice [4].

Severity scores were first developed for adult intensive care units (ICUs) and subsequently, in 1988, the first specific paediatric score was published: the Pediatric Risk of Mortality (PRISM) score [5]. Almost 10 years later, in 1997, a new paediatric score was developed by an Australian group of PICUs: the Paediatric Index of Mortality (PIM) [6]. Adjourned versions of these scores were then published, the latest one, in 2003, being the PIM2, a revised version of the PIM score [7].

The common paediatric intensive care scores identify physical ICU admission as a crucial event, and may utilise data captured before or after ICU admission, or

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a combination of both [8]. A tacit assumption in these scores is that ICU care begins when the patient enters the ICU.

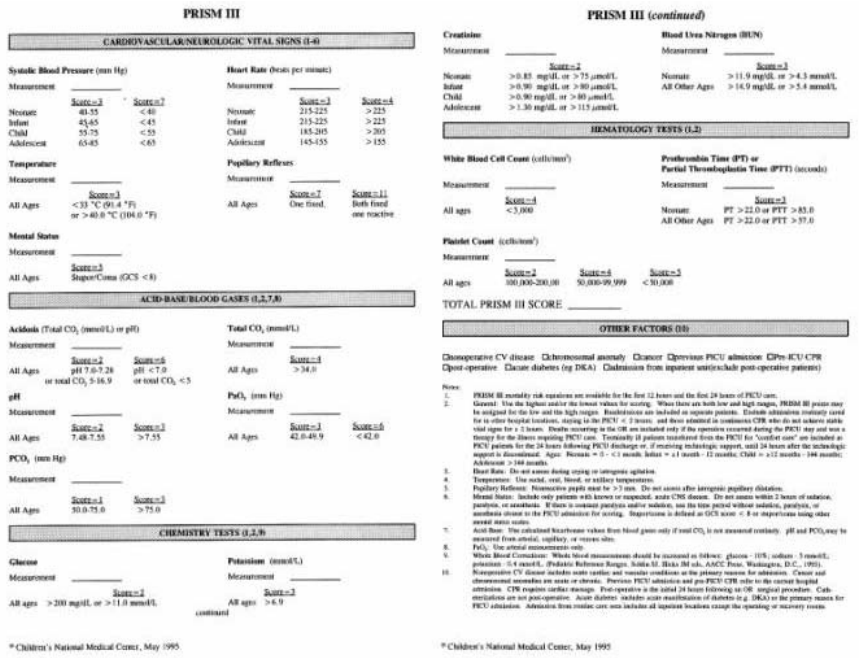
The purposes of using such scores vary; they include comparison of severity of illness between different treatments in clinical trials and comparison of quality of care between PICUs using standardised (that is, severity of illness-adjusted) mortality rates. Both the PRISM and the PIM scoring system families have been developed and carefully validated in tertiary PICUs [5–7, 9]. They differ in the amount of information required to calculate the risk of death, the duration of the observation period, and the time point used to define when observation should commence.

PRISM was derived from data collected in PICUs in the United States between 1980 and 1985 [5]. PRISM points are accrued from abnormalities in physiology occurring during the first 24 h after intensive care admission. Age, operative status and the PRISM score are used to predict the risk of death. PRISM III was derived from data collected in units in the United States in 1993 and 1994 [10]. With this revision, the method of assigning points for abnormalities in physiology was refined and variables that adjust for treatment given before intensive care admission and for five specific diagnoses were added. PRISM has been widely used internationally, and the model discriminates accurately between death and survival.

PIM was developed from data collected between 1994 and 1996 in seven PICUs in Australia and one in the United Kingdom [6]. PIM2 was developed from data collected between 1997 and 1999 in 13 ICUs in Australia, New Zealand and the United Kingdom [7]. PIM and PIM2 use data collected at the time of intensive care admission or the time of first contact with intensive care medical staff. The simplicity of the models makes it easier to collect accurate data routinely on large numbers of intensive care patients. Figures 1 and 2 describe PRISM III and PIM2, respectively.

In 1994 a study adopting the PRISM score was conducted in Italy on the paediatric population admitted to both paediatric and adult ICUs [11]. The score showed good sensitivity and specificity in predicting, on an individual basis, which children would die and which would survive (discrimination), but the number of observed deaths was significantly higher than predicted by the score. However, this might be due to poor performance of the Italian ICUs included in that survey, since the study found higher overall mortality (11.4%) than in other countries.

Since 1994 no other multicentre national study has been conducted in Italian children, neonates and premature babies admitted to ICUs. Therefore, the Italian Society of Paediatric and Neonatal Anaesthesia and Intensive Care Medicine decided to perform an observational, prospective, multicentre study with the aim of assessing the validity of the PIM2 score in Italian PICUs. In this manuscript we will present preliminary data relating to the first 2,500 children enrolled in the study.



PRISM III

CARDIOVASCULAR/NEUROLOGIC VITAL SIGNS (1-4)

Systolic Blood Pressure (mm Hg)

Measurement _____

	Score=3	Score=7
Neonate	40-55	<40
Infant	45-65	<45
Child	55-75	<55
Adolescent	65-85	<65

Heart Rate (beats per minute)

Measurement _____

	Score=3	Score=4
Neonate	215-225	>225
Infant	215-225	>225
Child	185-205	>205
Adolescent	145-155	>155

Temperature

Measurement _____

	Score=3
All Ages	<33 °C (91.4 °F) or >40.0 °C (104.0 °F)

Pupillary Reflexes

Measurement _____

	Score=7	Score=11
All Ages	One fixed.	Both fixed one reactive

Mental Status

Measurement _____

	Score=5
All Ages	Stupor/Coma (GCS <8)

ACID-BASE/BLOOD GASES (1,2,7,8)

Acidosis (Total CO_2 (mmol/L) or pH)

Measurement _____

	Score=2	Score=6
All Ages	pH 7.0-7.28 or total CO_2 5-16.9	pH <7.0 or total CO_2 <5

Total CO_2 (mmol/L)

Measurement _____

	Score=4
All Ages	>34.0

pH

Measurement _____

	Score=2	Score=3
All Ages	7.48-7.55	>7.55

PaO_2 (mm Hg)

Measurement _____

	Score=3	Score=6
All Ages	42.0-49.9	<42.0

PCO_2 (mm Hg)

Measurement _____

	Score=1	Score=3
All Ages	50.0-75.0	>75.0

CHEMISTRY TESTS (1,2,9)

Glucose

Measurement _____

	Score=2
All ages	>200 mg/dL or >11.0 mmol/L

Potassium (mmol/L)

Measurement _____

	Score=3
All ages	>6.9

continued

* Children's National Medical Center, May 1995

PRISM III (*continued*)

Creatinine

Measurement _____

	Score=2
Neonate	>0.85 mg/dL or >75 μmol/L
Infant	>0.90 mg/dL or >80 μmol/L
Child	>0.90 mg/dL or >80 μmol/L
Adolescent	>1.30 mg/dL or >115 μmol/L

Blood Urea Nitrogen (BUN)

Measurement _____

	Score=3
Neonate	>11.9 mg/dL or >4.3 mmol/L
All Other Ages	>14.9 mg/dL or >5.4 mmol/L

HEMATOLOGY TESTS (1,2)

White Blood Cell Count (cells/mm³)

Measurement _____

	Score=4
All ages	<3,000

Prothrombin Time (PT) or Partial Thromboplastin Time (PTT) (seconds)

Measurement _____

	Score=3
Neonate	PT >22.0 or PTT >85.0
All Other Ages	PT >22.0 or PTT >57.0

Platelet Count (cells/mm³)

Measurement _____

	Score=2	Score=4	Score=5
All ages	100,000-200,00	50,000-99,999	<50,000

TOTAL PRISM III SCORE _____

OTHER FACTORS (10)

☐noncperative CV disease ☐chromosomal anomaly ☐cancer ☐previous PICU admission ☐Pre-ICU CPR ☐post-operative ☐acute diabetes (eg DKA) ☐admission from inpatient unit(exclude post-operative patients)

Notes:

1. PRISM III mortality risk equations are available for the first 12 hours and the first 24 hours of PICU care.
2. General: Use the highest and/or the lowest values for scoring. When there are both low and high ranges, PRISM III points may be assigned for the low and the high ranges. Exacerbations are included as separate patients. Exclude admissions routinely cared for in other hospital locations, staying in the PICU < 2 hours, and those admitted in continuous CPR who do not achieve stable vital signs for ≥ 2 hours. Deaths occurring in the OR are included only if the operation occurred during the PICU stay and was a therapy for the illness requiring PICU care. Terminally ill patients transferred from the PICU for "comfort care" are included as PICU patients for the 24 hours following PICU discharge or, if receiving technologic support, until 24 hours after the technologic support is discontinued. Ages: Neonate = 0 - <1 month; Infant = ≥1 month - 12 months; Child = ≥12 months - 144 months; Adolescent ≥144 months.
3. Heart Rate: Do not assess during crying or iatrogenic agitation.
4. Temperature: Use rectal, oral, blood, or axillary temperatures.
5. Pupillary Reflexes: Nonreactive pupils must be >3 mm. Do not assess after iatrogenic pupillary dilatation.
6. Mental Status: Include only patients with known or suspected, acute CNS disease. Do not assess within 2 hours of sedation, paralysis, or anesthesia. If there is constant paralysis and/or sedation, use the time period without sedation, paralysis, or anesthesia closest to the PICU admission for scoring. Stupor/coma is defined as GCS score ≤ 8 or stupor/coma using other sound metric scales.
7. Acid Base: Use calculated bicarbonate values from blood gases only if total CO_2 is not measured routinely. pH and PCO_2 may be measured from arterial, capillary, or venous sites.
8. FiO_2: Use arterial measurements only.
9. Whole Blood Correlations: Whole blood measurements should be increased as follows: glucose - 10%; sodium - 5 mmol/L; potassium - 0.4 mmol/L. (Pediatric Reference Ranges. Schlis SJ. Hicks JM eds. AACC Press. Washington, D.C., 1995).
10. Nonoperative CV disease includes acute cardiac and vascular conditions as the primary reason for admission. Cancer and chromosomal anomalies are acute or chronic. Previous PICU admission and pre-PICU CPR refer to the current hospital admission. CPR requires cardiac massage. Post-operative is the initial 24 hours following an OR surgical procedure. Cardioversion are not post-operative. Acute diabetes includes acute manifestation of diabetes (e.g. DKA) or the primary reason for PICU admission. Admission from routine care area includes all inpatient locations except the operating or recovery rooms.

* Children's National Medical Center, May 1995

Fig. 1. PRISM III score variables

1. Systolic blood pressure, mmHg (unknown=120)[1]
2. Pupillary reactions to bright light (>3 mm and both fixed=1, other or unknown=0)[2]
3. PaO_2, mmHg (unknown=0)FIO_2 at the time of PaO_2 if oxygen via ETT or headbox (unknown=0)
4. Base excess in arterial or capillary blood, mmol/l (unknown=0)
5. Mechanical ventilation at any time during the first hour in ICU (no=0, yes=1)[3]
6. Elective admission to ICU (no=0, yes=1)[4]
7. Recovery from surgery or a procedure is the main reason for ICU admission (no=0, yes=1)[5]
8. Admitted following cardiac bypass (no=0, yes=1)[6]
9. High risk diagnosis. Record the number in brackets. If in doubt record 0.
   - [0] None
   - [1] Cardiac arrest preceding ICU admission[7]
   - [2] Severe combined immune deficiency
   - [3] Leukaemia or lymphoma after first induction
   - [4] Spontaneous cerebral haemorrhage[8]
   - [5] Cardiomyopathy or myocarditis
   - [6] Hypoplastic left heart syndrome[9]
   - [7] HIV infection
   - [8] Liver failure is the main reason for ICU admission[10]
   - [9] Neuro-degenerative disorder[11]
10. Low risk diagnosis. Record the number in brackets. If in doubt record 0.
    - [0] None
    - [1] Asthma is the main reason for ICU admission
    - [2] Bronchiolitis is the main reason for ICU admission[12]
    - [3] Croup is the main reason for ICU admission
    - [4] Obstructive sleep apnoea is the main reason for ICU admission[13]
    - [5] Diabetic keto-acidosis is the main reason for ICU admission

Fig. 2. PIM2 score variables

Methods

The study was conducted over 1 year, from 1 March 2004 to 28 February 2005, and all 23 existing Italian PICUs were invited to take part. All consecutive patients admitted, from newborns (including premature babies if over 32 weeks of gestational age and with weight =1,500 g) to 16-year-old children, were enrolled. For each patient age, sex, reason for admission (medical, elective surgery, emergency surgery, cardiac surgery, neurosurgery, injury), diagnosis on admission (respiratory failure, heart disease, neurological disease, sepsis, metabolic disease, postsurgical observation, others), presence and nature of any chronic disease, immune status, length of stay (LOS), diagnosis on discharge, and outcome (survival or death) were considered. The severity score we applied was PIM2 [7], which was applied at each patient's admission.

No limits were imposed for the PICU stay. Patients still in the PICU at the end of the study were recorded as 'alive'. Data were collected by each PICU through a dedicated electronic database (Access®, Microsoft Corporation) and sent to the coordinating centre (Children's Hospital Vittore Buzzi, Milan). For reasons of privacy, patients' data were kept anonymous and each child was identified by the centre of origin and his or her admission number. Before the start of the study, the study instruments and procedures were tested on site for 1 month in each centre (i.e. software function, appropriate data entry, correct mailing).

Excel (Excel®, Microsoft Corporation) and Statistical Package for the Social Sciences (SPSS vers.13.0. Chicago, Ill.) were used for data management and analysis.

We used discrimination and calibration measures to assess the performance of the PIM2 score in our population. Discrimination is the ability of the score to predict the outcome on an individual basis, and calibration is its ability to predict the actual number of deaths observed in the whole population or in specific subgroups. For discrimination we calculated the area under the receiver operating characteristics (ROC) curve, and we used the Hosmer-Lemeshow goodness-of-fit test to assess the calibration across different deciles of risk [12].

The 95% confidence intervals (CI) of SMRs were calculated with the test-based method [13] and the *p*-values were derived from the one degree of freedom Chi-square calculated as ([observed deaths–expected deaths]^2/expected deaths).

Results

Of the 23 units, 5 had to be excluded because of deficient data collection and/or transmission. Table 1 shows a summary description of the PICUs in the study. There were 10 in the north of the country (centres 1–10), 5 in central Italy (11–15) and 3 in the south (16–18). Ten units were in children's hospitals, and the other 8 were in the paediatric departments of general hospitals. The average number of beds was six, and only 3 units had ten or more. Most of the units accepted both medical and surgical patients, from newborns to 16 years old.

Table 1. Description of PICUs (*G* general hospital, *P* paediatric hospital, *Ne* neonates, *Pe* paediatric patients)

Centre no.	Hospital	Type of unit	No. of beds	Newborn	Medical	General surgery	Cardiac surgery	Neuro-surgery	Trauma	Paediatric intensivist available 24 h
1	G	Ne-Pe	10	X	X	X	X	X	X	
2	P	Pe	4		X	X				X
3	P	Ne-Pe	6	X	X	X			X	X
4	G	Ne	4	X	X	X				
5	P	Ne-Pe	6	X	X	X		X	X	X
6	P	Pe	12		X	X	X	X	X	X
7	P	Ne-Pe	4	X	X	X			X	X
8	G	Pe	4			X				X
9	G	Ne-Pe	6	X	X	X		X	X	X
10	G	Pe	6	X	X	X		X	X	X
11	G	Pe	6		X	X			X	X
12	P	Pe	4		X	X		X	X	X
13	P	Ne-Pe	6	X	X	X		X	X	X
14	G	Pe	6		X	X		X	X	X
15	P	Pe	8		X	X			X	X
16	P	Pe	10		X	X			X	X
17	P	Pe	8		X	X			X	X
18	G	Ne-Pe	5	X	X		X			

Eight centres remained involved in the survey for only 6 months instead of the whole year, for administrative reasons. In all, 3,429 consecutive children were enrolled. A total of 54 children were excluded because they were outside the age limits, and 109 because their data were incomplete. A preliminary analysis of 2,500 children is reported. The female-to-male ratio was 0.68; the median age was 10 months (mean 35.8); there were 118 premature babies; and 793 children (24.2%) were less than 1 month of age. Among medical patients, the most frequent diagnosis on admission was respiratory failure. Surgical patients accounted for 46.4% of the entire population and trauma patients, for 6.8%. The median LOS in the PICU was 2 days (mean 5.8, range 0–365 days); 4.5 % had a shorter LOS than 24 h, and 31% were discharged after 1 day.

The mean PIM2 score predicted 147.0 deaths (5.8%), while 131 deaths were actually observed (5.2%). In 40% of these children (52) death occurred within the first 24 h after admission. Among medical patients 27.2% had a chronic disease, with an absolute mortality rate of 14.6%. The difference between observed and predicted deaths was not significant, and the ratio of observed to expected deaths gave a standard mortality rate (SMR) for the entire sample of 0.89. The value of the area under the curve is 0.89, with a 95% CI of 0.86–0.91. Observed and expected mortality across deciles of mortality risk groups, according to the Hosmer-Lemeshow test,

showed good calibration, since the differences between observed and expected deaths across the deciles of risk were not significant (χ^2 9.86; 8 *df*, p=0.26) for the entire sample or for each single decile of predicted mortality risk.

Discussion

PRISM and PIM scores were developed in specific countries (respectively in the USA and Australia) and can be applied virtually worldwide, although it is essential to test their performance in a large cohort of the country that intends to adopt them. Scores cover an intrinsic description of the healthcare system, PICU organisation, and case-mix of the population used to create it. Thus, poor calibration in other settings, with over- or underprediction of mortality, is the result of substantial differences in the way healthcare is organised. Some authors suggest calculating new coefficients specific to each population in order to improve performance [14], but this compromises the ideal of comparisons between different countries.

When applied to other countries, statistical analysis should test discrimination and calibration. Discrimination is verified by calculation of the area under the ROC curve, while calibration is tested with a goodness-of-fit test for deciles of risk.

This study evaluated the ability of the PIM2 score to predict mortality in Italian PICUs. A previous study in the early 1990s did not validate the PRISM score [11]. For the present study we chose the PIM2 score because it is the most recent severity score published for children and has a free algorithm to calculate mortality risk, while other scores require a licence; in addition, the small number (10) of variables makes it very simple to collect the data needed.

Our preliminary results seem to show good discrimination and good calibration of the score. The area under the ROC curve (0.89) was very close to the 0.90 reported in the original article (95% CI 0.89–0.91) [7]. In the overall population, the PIM2 score predicted 147.0 deaths, while we actually observed 131 with an observed-to-expected ratio (SMR) of 0.89, which is not significantly different from unity. The score maintained its validity across the different levels of severity when the population was stratified according to the PIM2 risk score into ten progressive categories (deciles). The numbers of observed deaths were not statistically different from the predictions in all ten strata or when a summary measure of the significance was obtained with the Hosmer-Lemeshow test.

The study that used the PRISM score in Italian ICUs in 1994 revealed an observed mortality that was significantly higher than that predicted although the discrimination power was satisfactory [11]. Paediatric absolute mortality was much higher (11.4%) in the Italian PRISM Study than in the present study (5.2%). The two Italian study cohorts were similar in age, type of admission, co-morbidities, and geographic distribution of units, and the only striking difference was in the features of the ICUs; 10 of the 21 units enrolled in the PRISM study (47.6%) were adult units, a mean of 21 children per year being admitted to these adult–paediatric units and 91 to paediatric units. In our study, all units were specifically paediatric ICUs, and the mean number of children per year per unit was 181.

In all the subgroup analyses in the PRISM study the lack of fit of the model was due to higher mortality than expected in the low-risk categories (which amounted to 89% of the cohort). For these reasons, we presume that differences between observed and expected deaths were only partially related to the validity or otherwise of the PRISM score. Insufficient experience and skill in treating paediatric patients, probably because of the small number of cases managed per year, seems to be the main reason. As reported in the literature, paediatric patients need to be cared for in dedicated units in children's hospitals or in paediatric departments [15–17]. Competence and skill in treating paediatric patients increase with centralisation of paediatric critical care and the numbers of patients observed [18, 19].

One reason why critically ill children are admitted to adult units is the inhomogeneous distribution of Italian PICUs through the country: there seem to be enough in the north but not nearly enough in the south, and in the last 10 years nothing has really changed. Between 13% and 22% of children from the south of Italy are treated in hospitals in the north [20], while many children in the south are treated in adult ICUs.

The validity of the PIM2 score might be explained by some intrinsic characteristics that render it less affected by the setting and the demographic and clinical features of the population admitted to the PICU. One of the main characteristics of this score is that all the variables have to be recorded within the first hour of admission. As 40% of deaths occurred in the first 24 h the PIM2 seems to be better than other scores that require collection of data over 12–24 h. In our study both the discrimination and calibration through deciles of risk were appropriate. Assessing the performance of the PIM2 score is an important step for Italian paediatric critical care medicine. The need to work together on epidemiological and clinical studies is pressing, because most units are small (4–6 beds) and have no more than 200–400 admissions per year. PIM2 provides a valid mortality index for multicentre national studies and may help to improve child health policies throughout the country.

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Chapter 39

Analgesia and sedation during mechanical ventilation in paediatrics

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In paediatric intensive care units (PICU) critically ill children experience various stimuli perceived as disturbing, frightening and dangerous. Maintaining a good level of comfort while preserving safety is a main part of the care in mechanically ventilated patients and the use of sedatives and analgesics is recommended in these circumstances [1, 2].

The child can experience pain due to medical illness, surgical procedures, trauma, placement of central and arterial lines, drains, endotracheal tube, noninvasive ventilation devices. Physical therapy, dressing changes, prolonged immobility are other causes of pain. Moreover unfamiliar people and environment, noises (voices, alarms, ventilators), lights, handling, thirst, pain, cold, sleep deprivation, fear of death make the child anxious and agitated. Agitation can result also from hypoxaemia, hypoglicaemia, hypotension, pharmacological adverse effects, withdrawal syndrome.

The aim of sedation in the PICU is to obtain a good relief from pain and discomfort. The benefits are reduction of stress response (metabolic rate, oxygen consumption), pulmonary dysfunction (chest wall and diaphragm rigidity), desynchronisation with the ventilator, risk of dislodging tubes or lines, adverse psychological effects, parental anxiety. Other important goals of the treatment are sleep pattern improvement and amnesic effect [3].

Sedation assessment

The evaluation of adequacy of sedation demands reliable tools for the paediatric population. The level of optimal sedation can vary in the different situations. Usually the child should be somnolent, responsive to environment but untroubled by it, with no excessive movement, or sedated as needed to the point of no distress. Avoiding oversedation allows the child's ability to communicate with parents and caregivers and rules out the risk of respiratory depression and haemodynamic instability. In cases of raised intracranial pressure (head injury, encephalopathy) a state similar to deep anaesthesia is required.

The Comfort scale (Table 1) is a physiologic-behavioural eight dimensional subscore scale based on observation of alertness, calmness/agitation, respiratory response, physical movement, blood pressure, heart rate, muscle tone, facial ten-

sion [4]. Between inadequate sedation and excessive sedation, the target range of optimal sedation is defined as scores of 17 to 26 [5]. The Comfort scale demonstrates good reliability and validity as a postoperative pain instrument in a population of neonates and toddlers after major abdominal or thoracic surgery [6].

Table 1. The Comfort Scale [4]

ALERTNESS	
Deeply asleep	1
Lightly asleep	2
Drowsy	3
Fully awake and alert	4
Hyper-alert	5

CALMNESS/AGITATION	
Calm	1
Slightly anxious	2
Anxious	3
Very anxious	4
Panicky	5

RESPIRATORY RESPONSE	
No coughing and no spontaneous respiration	1
Spontaneous respiration with little or no response to ventilation	2
Occasional cough or resistance to ventilator	3
Actively breathes against ventilator or cough regularly	4
Fights ventilator; coughing or choking	5

PHYSICAL MOVEMENT	
No movement	1
Occasional, slight movement	2
Frequent, slight movement	3
Vigorous movement limited to extremities	4
Vigorous movements including torso and head	5

BLOOD PRESSURE (MAP) BASELINE	
Blood pressure below baseline	1
Blood pressure consistently at baseline	2
Infrequent elevation of 15% or more	3
Frequent elevation of 15% or more	4
Sustained elevation ≥ 15%	5

HEART RATE BASELINE	
Heart rate below baseline	1
Heart rate consistently at baseline	2
Infrequent elevation of 15% or more	3
Frequent elevation of 15% or more	4
Sustained elevation ≥ 15%	5

MUSCLE TONE	
Muscle totally relaxed; no muscle tone	1
Reduced muscle tone	2
Normal muscle tone	3
Increased muscle tone and flexion of fingers and toes	4
Extreme muscle rigidity and flexion of fingers and toes	5

FACIAL TENSION	
Facial muscle totally relaxed	1
Facial muscle tone normal; no facial muscle tension evident	2
Tension evident in some facial muscles	3
Tension evident throughout facial muscles	4
Facial muscles contorted and grimacing	5

The Ramsay scale (Table 2) measures three levels of awake states and three levels of asleep states [7]. It is based on responsiveness to glabellar tap or loud auditory stimulus and, though a simple method, the scale has been criticised for repeatedly disturbing approach to the patient [5].

Table 2. The Ramsay Scale [7]

1	Awake	Patient anxious and agitated or restless or both
2	Awake	Patient cooperative, oriented and tranquil
3	Awake	Patient responds to commands only
4	Asleep	A brisk response to a light glabellar tap or loud auditory stimulus
5	Asleep	A sluggish response to a light glabellar tap or loud auditory stimulus
6	Asleep	No response to a light glabellar tap or loud auditory stimulus

Parkinson and Huges compare two regimens of sedation using a scoring system originally described by Ratcliffe [8, 9]. This arousability scale is based on the response of the child to tracheal suctioning, ranging from no response to patient who is awake, restless and distressed when not disturbed (Table 3).

Table 3. Sedation Scale (Ratcliffe) [9]

1	No response to tracheal suction. There is no movement when tracheal suctioning is performed. The patient is asleep.
2	Cough and small limb movement and/or grimace in response to tracheal suction. There is brief movement of limbs or face when tracheal suctioning is performed, but not eye opening. The patient rapidly settles back to presuction state (asleep).
3	**Agitation with major limb movement or crying in response to tracheal suction.** There is marked movement of limbs which may be purposeful (hands up towards tube or face) with crying (lacrimation) and/or eye opening when tracheal suction is performed. The patient may take longer to settle after suction (1-2 min). The patient is asleep when he/she is not being stimulated.
4	Patient is awake and moving but is not agitated when not disturbed. The patient is awake for part or all of the time. He/she may move, open eyes or be trying to communicate, but does not seem distressed when not stimulated (i.e. not being suctioned or having blood taken, etc.).
5	**Patient is awake and restless or distressed when not disturbed.** The patient is restless, moving around with or without eyes open; he or she may be crying, sweating and unable to settle, lines and tubes may be pulled. He or she is awake for most of the time.

None of these methods is usable when the child suffers from abnormalities of neurological or muscular function, severe mental retardation, multiorgan dysfunction, or when a neuromuscular blockade is needed.

The bispectral index (BIS) monitor derives a number ranging from 0 (isoelectric) to 100 (fully awake) from a modified electroencephalogram. BIS proves a reliable measure of sedation in the PICU during mechanical ventilation [10, 11], particularly during administration of neuromuscular blocking agents [12], and during procedural sedation with children [13]. On the other hand BIS shows a moderate correlation with the clinical sedation scores in a population of mechanically ventilated surgical adult patients, specially at deeper sedation levels, suggesting that BIS is unsuitable for monitoring sedation in a heterogeneous group of surgical patients in the intensive care unit (ICU) [14]. A BIS value ranging from 45-50 to 70 correlates with adequate sedation.

Definition of a sedation endpoint for each patient, regular assessment of level of sedation and response to therapy, sedation assessment through a validated scale are recommended [1]. Nonetheless a review of current practice in UK paediatric intensive care reports that only a minority of units formally assesses sedation levels and observes that locally devised sedation scoring systems are in fact widely used [15].

Sedation therapy

Sedation of agitated critically ill patients should be started only after providing adequate analgesia and treating reversible physiological causes of agitation [1]. First, the patient's comfort may be increased by stabilising fractures, avoiding urinary retention, treating hyperpyrexia etc. Comfort should also be provided by proper positioning, environment modification, massage and other nonpharmacological measures, as reassurance, parental presence, distraction, music therapy, play therapy.

When administering a sedation therapy, having defined the suitable level of sedation for each patient, a continuous or intermittent treatment is started. The efficacy of the therapy should be regularly assessed and documented and the therapeutic plan titrated and reassessed on the basis of the patient's needs, as clinical variations, necessity of invasive procedures, tolerance and physical dependency influence timing and amount of drugs to be administered. Moreover the great variability observed in the responses of critically ill patients may result from their pharmacokinetic and pharmacodynamic behaviour, as this is influenced by renal/hepatic dysfunction, hypoproteinaemia, changes in drug distribution and volume of distribution, pharmacological interactions. The development of withdrawal has to be recognised and treated too.

Usually sedation is a combination of a hypnotic agent (benzodiazepines, propofol, barbiturates) and an analgesic one (opioids). On the basis of particular features of the patient, other agents like ketamine and α_2- adrenergic agonists can be an alternative to conventional sedation in mechanically ventilated children (Table 4).

Table 4. Starting doses of agents for PICU sedation

Agent	Starting doses [References]
Midazolam	0.05 to 0.15 mg. kg $^{-1}$. h $^{-1}$ [17]
Lorazepam	0.1 to 0.33 mg. kg $^{-1}$. h $^{-1}$ [23]
Propofol	1 to 3 mg. kg $^{-1}$. h $^{-1}$ [17, 29]
Thiopental	1 to 2 mg. kg $^{-1}$. h $^{-1}$ [17]
Fentanyl	2 to 3 μg. kg $^{-1}$. h $^{-1}$ [17]
Morphine	10-30 μg. kg $^{-1}$. h $^{-1}$ [17]
Ketamine	20-80 μg. kg $^{-1}$. h $^{-1}$ [38]
Clonidine	1 μg. kg $^{-1}$. h $^{-1}$ [44]
Dexmedetomidine	0.25 to 0.75 μg. kg $^{-1}$. h $^{-1}$ [17]

Benzodiazepines

Benzodiazepines (BDZ) are the most popular sedative drugs used in the PICU, often combined with opioids [3, 16, 17]. They share the same GABA-ergic mechanism of action with propofol and barbiturates, resulting in hyperpolarisation of the neuronal membrane. BDZ produce anxyolisis, amnesia, sedation, muscle relaxation and have anticonvulsant properties. BDZ lack analgesic properties, though they are frequently administered as adjuvants of analgesics. Potential adverse effects are hypoventilation/apnoea and hypotension. Continuous infusions can produce oversedation and prolongation of sedative effects, due to accumulation of parental drug or its active metabolites. Tolerance and paradoxical agitation are also described.

Midazolam

Midazolam is a parenteral drug characterised by faster onset time and shorter duration than other BDZ such as diazepam and lorazepam. Midazolam is metabolised by the hepatic cP450 mainly to the active compound 1-OH- midazolam, then by the glycuronil-tranferase to 1-OH-midazolam-glucuronide, that is excreted renally.

A wide experience with midazolam for sedation in PICU states a bolus dose of 0.25 mg. kg $^{-1}$ followed by a continuous infusion of starting doses ranging from 0.05 to 0.15 mg. kg $^{-1}$. h $^{-1}$ [17]. Depending on age (due to the immaturity of enzyme systems), underlying illness (due to the organ dysfunction) and drug interactions, midazolam shows a marked interpatient variability in dosage requirements to produce sedation in critically ill paediatric patients [18]. Lower midazolam elimination was observed by de Wildt et al. [19] as compared to other studies [20] in a population of PICU patients. Midazolam is not recommended for the sedation of critically ill preterms, as association with a bad outcome has been observed [21].

Lorazepam

Lorazepam has not been so extensively used in PICU, although it is less involved in drug interactions and is better metabolised to inactive glucuronide compound in advanced liver diseases. Infusion rates range from 0.1 to 0.33 mg. kg $^{-1}$. h $^{-1}$ [22]. Rectal administration may be more effective and safer than rectal diazepam in the treatment of status epilepticus in children, but there is no evidence to prefer intravenous lorazepam in these cases [23]. The slower onset and longer half-life make it less suitable to treat acute agitation, less titratable as a continuous infusion, preferred for prolonged sedation. Withdrawal and accumulation of the diluent propylene glycol [22, 24] are described.

Propofol

Propofol is a GABA-ergic alkyl phenol compound diluted in a long-chain triglycerides oil-based emulsion, introduced into anaesthesia practice for the induction and maintenance of anaesthesia. Its pharmacological features (rapid onset and offset, absence of cumulative effects) makes it one of the agents of choice for sedation in ICU. In paediatric practice dosage is inversely related to age. Peripheral vasodilation, negative inotropic and vagotonic properties suggest caution when propofol is administered to haemodynamically instable patients. Myoclonic activity specially in children is also reported. Nonetheless propofol remains an effective agent in the treatment of refractory status epilepticus and intracranial hypertension along with barbiturates.

In 1992 Parke et al. report a fatal "propofol infusion syndrome" in PICU patients sedated with propofol [25], followed by analogous observations [26]. The clinical course of the syndrome includes metabolic acidosis, lipaemic serum, brady-arrhytmia, rhabdomyolisis, hepatic and renal failure up to death for cardiac failure unresponsive to resuscitative measures. Further reports hypothesised the disruption of fatty- acid oxidation by impaired entry of long-chain acylcarnitine esters into the mitochondria and failure of the mitochondrial respiratory chain as causal mechanism [27, 28]. Despite the concerns about safe use of propofol in the PICU, Cornfield et al. speculate that propofol can be safely and effectively used for sedation in critically ill patients for extended periods of time if not exceeding 67 $\mu g. kg^{-1}. h^{-1}$ [29]. Surveys in Australia/ New Zealand [30] and UK/North America [31] indicate that propofol is still used for continuous sedation in the PICU, although an unpublished randomised trial of the FDA advises against this therapeutic practice [32]. In the PICU it is advisable to restrict the use of propofol to specific circumstances like refractory status epilepticus, increased intracranial pressure, procedural sedation. Starting doses range from 1 to 3 $mg. kg^{-1}. h^{-1}$ [17].

Thiopental

Barbiturates are classified on the basis of their chemical structure or their duration of activity. The short-acting agent thiopental (ethyl-1-methilbutyl-barbiturate, pentobarbital) is commonly used for anaesthesia induction and endotracheal intubation. It shares with propofol the mechanism of action and the depressing effects on neurological and cardiovascolar function. This can limit its use in haemodynamically instable patients. Moreover the barbiturate solution is alkaline, leading to incompatibility with other solutions and necessitating a separate infusion site. The main role of barbiturates in the PICU is the treatment of refractory status epilepticus and of raised intracranial pressure, beyond the usefulness as a second-line agent when sedation with first-line agents (BDZ and opioids) is inadequate despite increasing dosage [17]. Introducing continuous thiopental sedation provides effective sedation and enables neuromuscular blocking agents to be discontinued. Potential complications like blood pressure instability, oversedation and drug reaction lead sometimes to discontinuation of the drug [33]. Starting doses range from 1 to 2 $mg. kg^{-1}. h^{-1}$ [17].

Opioids

Acting on specific receptors (μ, κ, δ) placed in the nervous system, opioids provide dose-related analgesia and some degree of sedation, without ensuring amnesia. Their combination with BDZ or propofol is advisable when amnesia is required, e.g. during neuromuscular block. The dosage of opiods is lower in newborns, for a specific sensitivity due to pharmacokinetic and pharmacodynamic reasons. Any way titration to the desired effect is necessary in every patient, as interpatient variability is common. Potentially dangerous adverse effects are frequent with opioids: respiratory depression may be of concern when partial respiratory support is given, clouding of consciousness may hamper the neurological assessment. In the PICU the widespread use of opioids refers mainly to fentanyl and morphine [3, 16]. To date evidence about the proper use of remifentanil in the PICU is not yet available.

Fentanyl

Fentanyl is the opioid of choice in children who undergo surgery for congenital heart disease, as its limited cardiovascular impact allows to administer it even in high doses in this patient population. Another effect supporting its use is the ability to modulate pulmonary vascular resistance and prevent pulmonary hypertensive crisis. The complication of chest-wall rigidity, specific to the syntetic opioids, is a centrally mediated reaction generally occurring when an high dose is given rapidly. This phenomenon is rarely observed in the PICU, where fentanyl is usually administered by continuous infusion because of its short half-life. However fentanyl demonstrates a context-sensitive half-life, so that the duration of its effect is prolonged when it is administered over an extended period of time [17, 34, 35]. Starting doses range from 2 to 3 $\mu g. kg^{-1}. h^{-1}$ [17].

Morphine

Morphine is another opioid frequently used in the PICU, metabolised in the liver to morphine-6-glycuronide (M6G), an active metabolite to be excreted with urine. As compared with fentanyl, morphine can produce a potentially harmful hypotensive effect in hypovolaemic patients, due to hystaminergic vasodilation and blunting of sympathetic response and epynephrine levels. Moreover immunosuppressive effects of morphine are demonstrated [36]. The binding to receptors on immune cells involved in the inflammatory and pain response may be deleterious, though the actual role of this phenomenon in the PICU is still to be estimated. When compared to fentanyl, morphine results associated with more sedation, less chest-wall rigidity and slower developing of tolerance. Starting infusion rate is 10-30 $\mu g. kg^{-1}. h^{-1}$ [17], although in newborns the initial dosage has to be reduced to 25-30% [37].

Ketamine

Ketamine is a phencyclidine derivative acting as a NMDA (N-methyl-D-aspartate) antagonist, producing a state of "dissociative anaesthesia" by combination of a potent analgesic effect with amnesia, in the absence of depression of respiratory driving and of cardiovascular function. Favourable effects on ventilation, arterial pressure and heart rate are mediated through the release of endogenous catecholamines. The interaction of ketamine with opioid receptors could be the source of its dysphoric effect (vivid and unpleasant dreams). The hypothesis that ketamine should increase pulmonary vascular resistance and intracranial pressure remains controversial, although these effects seem related more to poor control of ventilation.

Ketamine is metabolised in the liver to norketamine, an active compound which is further hydroxylated and then excreted by the kidney. Besides the currently used racemic mixture [S (+) and R (-)], the S (-) enantiomer acts as a doubly potent more selective compound, limiting the adverse effects of the original substance.

Ketamine has recently been revalued, particularly in the field of regional paediatric anaesthesia [38]. It can play a role also in ventilated children, when spontaneous ventilation has to be preserved (e.g. during a non-invasive approach), in status asthmaticus, in patients adversely affected by other agents, when drug rotation is sustained during long-term sedation, as a bolus during painful procedures. Starting doses of continuous infusion are 20-80 $\mu g. kg^{-1}. h^{-1}$ [38]. Combination with midazolam or promethazine is reported [17, 39].

Alfa$_2$- adrenergic agonists

Alfa2- adrenoreceptors are found in the central and peripheral nervous system and in autonomic ganglia. Peripheral pre-synaptic receptors activation inhibits the release of norepinephrine, while central post-synaptic receptors stimulation inhibits sympathetic activity. Alfa$_2$-adrenergic agonists act centrally by the decrease of noradrenergic output from the locus caeruleus, resulting in an inhibitory effect leading to sedation and anxiolysis. This mechanism, including the activation of the GABA system, produces a non-REM similar sleep, the lack of which seems to be a cause of delirium during prolonged sedation by other agents (BDZ, propofol, barbiturates). Moreover analgesic properties derive to these agents from the regulation of substance P release, by means of a spinal cord mediated mechanism [40]. Beyond their clinical applications in the field of cardiovascular diseases (hypertension) and psychiatric disorders (opiate addiction), the role of α_2- adrenergic agonists in human anaesthetic and pain relief practice has been well recognised. Adverse effects as hypotension and bradycardia are possible.

Clonidine

Clonidine was firstly proposed for the treatment of postoperative and oncologic pain by the epidural route, either in adults [41, 42] and in children [43]. In the last

decade paediatric regional anaesthesia has taken advantage both of its sedative and analgesic effects. Ambrose et al. found that clonidine in combination with midazolam at 1 μg. kg $^{-1}$. h $^{-1}$ is not associated with significant changes in heart rate, arterial pressure or cardiac index, beside exhibiting a significant opiod sparing effect [44]. In children with single-organ (respiratory) failure, oral clonidine at the dose of 3-5 μg. kg $^{-1}$ every 8 h in combination with morphine and lorazepam, supplies a safe and effective sedation and allows opiod and benzodiazepine sparing [45]. In long-term sedation clonidine is part of differentiated cycling drug regimens [39].

Dexmedetomidine

Dexmedetomidine is an α_2-agonist drug licensed in USA by FDA for adults post-operative care sedation, characterised by an 8-fold affinity for the α_2-adrenoceptors than clonidine and by a favourable pharmacologic profile for the sedation of postsurgical patients during mechanical ventilation [46].

In 2001 Venn and Grounds compare dexmedetomidine with propofol in 20 adult patients requiring sedation in the first hours after surgery. They find this agent to supply a comparative depth of sedation and extubation times, with the advantage of a better quality of the sedation features [47]. The preliminary experience with dexmedetomidine in paediatrics encourages its use for sedation in mechanically ventilated children [48]. Doses range from 0.25 to 0.75 μg. kg $^{-1}$. h $^{-1}$ [17].

Conclusions

Providing sedation to critically ill children is mandatory to supply both enough comfort and a good adaptation to the intensive care in non collaborative patients. Pharmacological and non pharmacological measures suitable for the age are available.

A combination of midazolam with fentanyl or morphine is the most extensively adopted sedation regimen in the PICU. The choice of lorazepam is limited to long-term sedation, yet the risk of accumulation of propylene-glycol should always be recalled.

While recognised as safe for anaesthesia and procedural sedation, propofol is not recommended for current sedation under the age of 16, except in specific situations such as refractory status epilepticus. Barbiturates can be an alternative in these cases.

Other agents like ketamine and α2- agonists may have a sparing opioid effect and are useful in the prevention and treatment of tolerance and withdrawal syndrome.

So far reports on the use of remifentanil in paediatrics are limited to anaesthesia, but its use could be advocated when rapid awakening for neurologic assessment is needed.

Neuromuscular blocking agents have possible indications in PICU patients, although their administration shows controversial aspects in infants and children [49,50].

Tolerance, withdrawal and physical dependency are common after long-term

sedation in the PICU. The awareness of this issue imposes defined strategies of prevention and treatment [51].

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COMPUTING

Chapter 40

Latency reduction in clinical and translational research[1]

C.-H. Huang

Better healthcare information technology may make better healthcare possible. However, there seems to be less penetration of information technology in healthcare than in any other major industry.

A recent article (*Time*, June 2005) summarised the e-health revolution in the past two decades. In the 1990s, software systems were developed to allow insurance claims to be recorded and processed on computers. Products have also been developed with the aim of making it possible for doctors to run paperless medical practices; among other things, this involves booking appointments online, creating e-prescriptions and, most importantly, collecting X-rays, laboratory results and medical histories in a single database accessible to physicians and patients. Using tablet PCs and examination templates, physicians can enter all the data they once wrote out by hand, leaving more quality time to spend with the patients. These medical records can then be viewed by the patients at home via their doctor's website. Websites are also developed to manage family's health history. Information can be collected, stored and shared with any physician who is taking part in the programme. Hardware devices are also being developed to facilitate portable, accessible records. For example, patients can get the results of physical examinations and ECGs and other data loaded onto a thumb drive that plugs into a PC. Records can be updated on visits to specialists and beamed to other doctors. Patients can also download personal information, such as details of allergies, previous surgery, chronic conditions, and the drugs they are currently taking onto a smart card. Such cards could be life-saving when emergencies occur away from patients' normal areas.

The establishment of regional health information organisations is another step forward. An organisation of this type serves patients, and also area doctors, hospitals, laboratories, pharmacies, insurers, employers and consumers. If a resident makes an emergency-room (ER) visit on a Saturday, the ER doctor can call up the patient's records from his or her primary care physician. There are risks involved in computerising personal health information, and privacy advocates are especially concerned that once patient records are online it will be much easier for sensitive information to fall into the hands of, say, insurance companies or potential employers. Yet, since regional health organisations came into being, the medical

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community has been rapidly plugging into the new world of electronic health records.

Healthcare-related research and practice often produce tremendous amounts of data. These data are usually geographically distributed among hospitals, clinics, research laboratories, radiology centres, etc. For research, training or clinical purposes, physicians and medical researchers often need to consult and analyse medical data from various different sites. The on-demand integration/extraction and automated analysis of these data in a real-time manner will yield a significant level of convenience and is therefore increasingly needed. However, owing to the sensitive nature of these data and the lack of an effective and flexible integration approach, medical data are currently often stored and archived inside each data producer (hospitals, clinics, laboratories, etc.), and are usually disconnected from the outside world to enforce security issues.

The massive computing power that can now be accessed can be applied to help doctors in making diagnoses and treatment decisions. With the advent of the internet, it became possible, theoretically, to communicate new standard practices to doctors within months rather than 15 years, which is the current lag-time between discovery and practice. In addition, pharmaceutical companies with access to anonymous health data could improve and speed up drug development. The dynamic networking technology of today will have the potential to allow hospitals in rural areas to access expensive medical equipment in peer medical institutes securely in a real-time manner. All this sheds light on a new generation of e-health that could potentially improve healthcare quality.

Grids represent a rapidly emerging and expanding technology that allows geographically distributed resources (CPU cycles, data storage, sensors, visualisation devices, and a wide variety of internet-ready instruments) that are under distinct control to be linked together in a transparent fashion. The power of the grid lies not only in the aggregate computing power, data storage and network bandwidth that can readily be brought to bear on a particular problem, but in its ease of use. Since resources in a grid are pooled from many different domains, each with its own security protocol, ensuring the security of each system on the grid is of paramount importance. The potential of the grids for serving as a general-purpose research platform also results from the following facts, as pointed out in [1]:

- The internet is reasonably mature and able to serve as a fundamental infrastructure.
- Network bandwidth has increased to the point of being able to provide efficient and reliable services.
- Storage capacity has now reached commodity levels where a terabyte of disk can be purchased for roughly the same price as a high-end PC.
- More and more instruments are becoming Internet aware.
- Clusters, supercomputers, storage and visualisation devices are becoming more easily accessible.
- Applications have been parallelised.
- Collaborative environments are moving out of the alpha phase of implementation.

Dynamic coalitions for healthcare research and practice

The *Health Grid Initiatives* conducted at the University of Connecticut (UConn) are aimed at advancing the application of modern information technology to various disciplines within life science research and practice by promoting and reinforcing awareness of the advantages linked to the development and deployment of modern grid technologies towards an infrastructure for automated information integration, extraction and analysis [2–4]. The information infrastructure is based on a campus-wide computational and data grid, an ongoing effort begun in 2004. Another ongoing effort is the development of general-purpose middleware support for secure transfer of sensitive medical data over the computing infrastructure. The educational programmes associated with the Health Grid Initiatives include the development of new, and re-development of current, courses to incorporate inventions coming out of the research, a new cross-disciplinary *e-health* minor, and new degree courses emphasising the application of information technology to different disciplines within the life sciences. In addition, an annual scientific meeting, the international *Bio-Grid Workshop*, is held each year in conjunction with the research and education enterprise.

Toward the clinical end, a grid-enabled expert system for medical image retrieval from geographically distributed sites has been designed as a prototype system to study the special needs from grid-enabling clinical projects. The expert system is equipped with a request parser and is able to retrieve image files from distributed sites, where different medical data management systems are used and different security level checks are applied. The expert system provides a web portal as the interface for a physician to select the *magnetic resonance image* (MRI) sequence corresponding to a given patient and request for similar images. A set of ranked MRI sequences is returned so that the physician can visualise these cases and read the corresponding diagnoses. The expert system is parallelised and grid enabled using the grid-enabling *API*s (application interfaces) currently available. Based on this prototype system, we further study the computation load distribution, data migration frequency, bandwidth consumption rate, user statistics, ease of use of the web portal and the completeness of the current APIs.

This study will facilitate the investigation of a dynamically re-configurable and fault-tolerant general-purpose *health grid*, allowing task-oriented integration and sharing of (internet-aware) medical resources that are geographically remote from one another. Such a dynamic coalition forms a virtual collaborative organisation. Interested institutes can participate in any virtual organisation simply by the following steps:

(1) Register for the virtual organisation
(2) Register the IP addresses of the local resources to be shared
(3) Define strategies administering local and grid-level resources
(4) Parallelise and grid-enable related applications
(5) Implement (or install) a grid portal.

Clinical research projects currently at the planning stage to be grid enabled include

(1) The *Clinical-Genomic Information Exchange* project
(2) The *Remote Medical Data Visualisation* project
(3) The *Remote Intensive Care* project
(4) The *Translational Research on Rare Diseases* project.

Let us take the remote intensive care project as an example. There has been a severe shortage of intensive care specialists in the United States—fewer than 6,000 at a time when nearly 5 million patients are admitted to ICUs each year. Typically, hospitals rely on nurses to notice a problem with a patient. Then the nurse has to page a physician, who runs to the ICU to check on the patient. With the monitoring devices and in-room cameras connected to the health grid, physicians can check any patient's ventilator, intravenous medication and anything else wherever they are and at any time. This allows critical care doctors and nurses to monitor dozens of patients at different hospitals simultaneously, much as an air traffic controller keeps track of several aeroplanes. The professionals watching from afar alert those on duty at the hospitals to changes or problems through videoconferencing equipment at the nurses' stations. This greatly enhances the quality of intensive care in a way that could not be equalled even if on-site staffing establishments were doubled or tripled, by enabling hospitals to make the best use of a limited number of intensive care doctors.

Current project staff include faculty members from the Schools of Engineering, Medicine, Allied Health, Dental Medicine and Education. An invitation to a medical professional to participate in the initiatives will start with the medical network administrators at the John Dempsey Hospital affiliated with the UConn Health Center or at major hospitals in Connecticut, such as the Hartford Hospital, the Connecticut Children's Medical Center, Saint Francis Hospital and the Yale Medical Center, etc.

While promoting and reinforcing awareness of the possibilities and advantages linked to the development, deployment and evaluation of grid technologies towards the automated integration and analysis of health information in a broad sense, part of the research effort will be directed towards further exploration of research issues arising from the health grid, as a potential solution, via on-campus interdisciplinary collaboration on grid-enabling research projects as well as the integration tests with two international research teams from Japan and UK.

Architectures proposed in the health grid infrastructure will allow formation of a general-purpose data manager, taking advantage of classical theory (transactions concept) and proposing solutions to implement a secure and high-performance (medical) data manager by breaking down transactions into concurrent tasks and requests. Further equipped with customised web portals and application-specific user interface, this infrastructure may potentially provide a solution to secure and on-demand integration/analysis of life science data in a broader sense, including information from the population level (social healthcare) to the individual (clinical practice) and molecular (genetic and proteomic information) levels.

The educational programmes introduce the interdisciplinary research work associated with the Health Grid Initiatives to undergraduate/graduate students in the early stages of their academic careers, to spark their interest, and to medical

professionals and biomedical researchers who may benefit from modern information technology and infrastructures. In the long run, we expect to produce software engineers who are prepared to formalise and solve problems emerging from life science disciplines and to produce life science researchers and professionals with robust information processing techniques.

Technical details of the research programmes associated with the Health Grid Initiatives will not be elaborated here. Rather, the sections below describe the educational activities, outreach programmes and supporting facilities in conjunction with the research enterprise.

Education and outreach

In conjunction with the research enterprise, several educational development programmes are being developed, and an annual scientific meeting on health-grid-related topics is outlined. Specifically, a series of cross-disciplinary courses emphasising the application of information technology in life science research and practice (in the short term and throughout a semester) are being developed at the University of Connecticut as part of a new, self-contained *e-health* minor open to students and professionals at educational institutes and to healthcare providers in Connecticut. This programme will produce software engineers prepared to formalise and solve emerging medical and health applications, as well as clinical scientists and professionals with secure information processing techniques. In addition, an annual international workshop, initiated in 2003, on developing, deploying and evaluating grid techniques for life science research and practice, is conducted as part of the health grid activities. The goal is to reinforce and promote awareness of the possibilities and advantages linked to grid technologies in bioinformatics, clinical informatics, bio-imaging, and public health informatics.

Academic programme development

Undergraduate and graduate education

Our development programme will produce course materials for a redeveloped undergraduate *Introduction to e-Health* course. This is an initial step towards implementation of an undergraduate e-health minor to supplement the UConn degrees in Computer Science and Medicine. The course will involve fundamental concepts of health informatics, as well as a (reasonably) comprehensive introduction to the formal aspects of information processing techniques. The e-health minor will also include a course on advanced grid computing, an (existing) course introducing medical and health informatics and a capstone senior design course focusing on portable implementation of parallel algorithms for biomedical and healthcare problems. The minor is intended to produce software engineers who are prepared to formalise and solve emerging medical and health applications, and also

clinical scientists and professionals with secure information processing techniques.

Two new graduate courses, *Advanced Computational Biology* and *Medical Informatics*, are being offered in the School of Engineering, jointly with the department of Neuroscience at the UConn Health Center and the School of Allied Health of UConn. The campus-wide computing and information infrastructure will serve as the platform for class projects.

Degree courses in biomedical software development

In a collaborative effort with fellow faculty members of the School of Allied Health at the University of Connecticut and the UConn Health Center, we are working on the development of a new family of undergraduate courses (and a 5-year Master of Engineering course) that will prepare students for development of area-specific software for life science research and practice. These programmes will integrate a B.S. in a life science discipline, with course work offered by the Computer Science and Engineering Department, producing life science professionals and researchers with expertise in a chosen information technology discipline. These graduates will lead development teams in the production of life science applications in their chosen area of expertise. This programme falls under a broad University initiative for e-health and information technology. The role of information technology in the life science sector, especially that of classical applications such as modelling and simulation, can hardly be overestimated [5]. It is not surprising that these techniques have evolved into highly area-specific tools and methods [6–9].

The minor mentioned above will be available to all undergraduate students in the School of Engineering, School of Allied Health and the UConn Health Center. It is intended to supplement the students' degrees with cross-disciplinary expertise. Aside from an integrated capstone project to be discussed below, the minor will consist of existing courses, including stochastic analysis, introduction to scientific computing, numerical analysis and an adapted collaborative software engineering course, which is described below. The M.S. degree mentioned above will consist of a full B.S. gained in each department of the Health Center, the courses referenced above, five graduate courses approved by the chosen department, and an independent course on information processing. Both programmes culminate in an integrated application design project, appearing in the undergraduate minor as a capstone design project and appearing in the M.S. course as a combination capstone and Master's degree project. To prepare students for these projects, these tracks will include a family of new software engineering courses (one for each area of bio/medical/health), which will simultaneously expose the students to software engineering tools and methods and to algorithmic tools and techniques specific to their chosen area.

Each course will be co-instructed by a professor from the School of Engineering and a professor from the associated department of the Health Center, who will be responsible for the relevant topic above. This division is intended to allow the programme maximum portability, as it alleviates the need for an instructor specialised in both fields.

Drawing on the expertise of a representative from each participating depart-

ment, material for this new family of software engineering courses will be developed to

(1) Insulate software engineering material from area-specific material in a suitable manner to maximise portability
(2) Provide an introduction to computational methods relevant to the specific life-science discipline
(3) Provide an introduction to life-science informatics
(4) Lead the students through the development of a large, area-specific application

Outreach

In 2003 we initiated the Annual International Workshop on Biomedical Computations on the Grid (Bio-Grid), which is currently funded by the NIH. The aims of the Bio-Grid Workshop are to promote and reinforce awareness of the possibilities and advantages linked to the development, deployment and evaluation of grid technologies in broadly biology-related research and practice [10–19]. Events from 2003–2006 have been held in Tokyo (Japan), Chicago (US), Cardiff (UK) and Singapore, respectively, all featuring invited keynote speeches and technical programmes of peer-reviewed papers as well as plenary sessions.

Specifically, the workshops concentrate on all aspects of grid-enabled infrastructures, test beds, management and security for support of such research areas as

(1) Tele-systems for diagnostic, prognostic and therapeutic applications
(2) Health data storage and retrieval
(3) Social healthcare
(4) Pharmaceutics and clinical trials
(5) Computerised epidemiology
(6) Collaborative and proprietary health grids
(7) Data mining and visualisation of health data
(8) Text mining of healthcare information bases
(9) Healthcare information retrieval and integration
(10) Distributed medical database management and integration
(11) Integrative bioinformatics and medical informatics systems
(12) Medical imaging: management, analysis, processing and simulation
(13) Translational research
(14) Molecular modelling for drug design
(15) Topics in basic biology

a. Computational genomics/proteomics
b. Genetic linkage analysis
c. Molecular sequence analysis
d. Phylogeny reconstruction
e. Determination of protein structures
f. Identification of genes and regulatory patterns
g. Genetic/biochemical networks and systems biology.

In addition to the focus areas, research articles reporting original results of developing, deploying and evaluating grid techniques in novel topics in bioinformatics, clinical informatics, bio-imaging and public health informatics are also solicited.

This workshop will continue to be held as part of the Health-Grid Initiatives.

Facilities

Facilities available in support of the above-mentioned initiatives include the following.

Departmental facilities

The Information Technology Engineering Building (ITEB) is the home of the Computer Science and Engineering Department. It houses newly renovated laboratory space for graduate students in close proximity to many faculty offices. Computing equipment for this space includes 40 Pentium II Windows NT systems, a Windows NT server, and 20 Sun Ultra workstations. Graduate students working on funded projects have first priority for these facilities, as this fosters the serendipitous communication that is so crucial for effective research progress.

Instructional facilities

ITEB houses many of our computer science undergraduate laboratories, including several high-tech classrooms, which have PCs connected to the Internet, Barco projectors for both PC and VCR, satellite down-links and area cable television.

Research laboratories

Much computer science research activity is hosted in the Taylor L. Booth Engineering Center for Advanced Technology (BECAT). This Center houses 15 research laboratories equipped with workstations, PCs and several high-performance computing systems and servers, including a SparcCenter 2000 parallel computing system with 24 processors and a scalable BECAT grid consisting of over 24 nodes supporting grid and cluster middleware architectures. The BECAT's 100 Mbit/s FDDI token ring serves as a backbone for the School of Engineering computing network.

Other facilities

In support of the initiatives, the project staff has unlimited access to the high-end parallel machines provided by the *Connecticut Institute for Supercomputing and Visualization* (CISV, under BECAT at UConn), and also to additional computing resources off campus, including

- *A 64-processor SGI Altix 3700*

The newly purchased and installed SGI Altix system consists of (1) an 8-processor SGI Altix 350 with 8 GB memory as the front-end server and (2) a 64-processor SGI Altix 3700 Bx2 supercomputer with 64 GB memory. These twin systems will be networked to the School's existing SGI Onyx-4 Visualisation System to provide a complete compute-to-visualisation package for researchers and students within the School.

- *A 64-processor SGI Origin 3800*

The Origin 3800 has the revolutionary SGI NUMAflex computing model in its underlying architecture. All system components can be upgraded, maintained, and re-deployed independently. It is built on the SGI NUMA architecture and IRIX 6.5 operating system. This SGI Origin 3800 has the following characteristics: 64 R12000 processors running at 400 MHz MIPS R12010 Floating Point Chip FPU, 32 GB of RAM, and more than 300 GB of fibre channel disk space.

- *A 64-processor Dell Pentium cluster*

This cluster consists of 3830 Pentium III (1.27 GHz) processors and 206 Pentium 4 (2.4 GHz) processors. The Dell Pentium cluster features the performance of 5.8 trillion operations per second, more than 2 trillion bytes (TB) of RAM, 160 TB of disk storage, and 16 TB raid array for data storage.

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CRITICAL CARE BLEEDING

Chapter 41

New frontiers in critical bleeding

S. Busani, L. Donno, M. Girardis

Massive bleeding: 'the lethal triad'

The exact definition of critical haemorrhage remains a matter of debate, but the majority view is that it can be defined as bleeding requiring emergency intervention to avoid the patient's death or tissue/organ loss (e.g. liver, uterus) [1–3]. The first step in critical haemorrhage is the control of bleeding source by means of surgery, radiological or endoscopic intervention and medical therapy in patients with inherited or acquired coagulopathies. Unfortunately, these strategies are sometimes not available or do not allow definitive control of bleeding, particularly in the case of severe trauma patients. In fact, massive bleeding remains one of the main causes of death in trauma patients, and it is usually caused by a combination of vascular injury and coagulopathy [4]. In these patients, together with diffuse injuries, secondary coagulopathy is a key factor in failed bleeding control. The causes of this coagulopathy are multifactorial, and both hypothermia and acidosis can worsen haemostasis function further [4–5]. Cosgriff et al. [6] indicate that trauma patients transfused with more than 10 units of packed red blood cells and the combination of injury severity score >25, pH<7.10, temperature <34°C and systolic blood pressure <70mmHg have a 98% chance of developing a severe coagulopathy (PT and aPTT twice the normal values). Among these different risk factors, hypothermia and acidosis have been identified as the two main ones involved in the development of coagulopathy [6].

Hypothermia: The patient affected by massive bleeding faces a high risk of developing hypothermia, which in human beings occurs at a core temperature lower than 35°C [7]. In trauma patients the reasons for hypothermia are numerous and include reduced heat production because of haemorrhagic shock and decreased oxygen consumption, evaporative loss resulting from wet clothing and convection and radiation heat losses because of body exposure. Nevertheless, the major part of heat loss usually comes from resuscitation with fluids at room temperature [5]. Hypothermia has adverse effects on coagulation, as it causes platelet dysfunction, alteration of coagulation enzyme kinetics, disruption of fibrinolytic balance, and prolongation of clotting time. It has been demonstrated that at a temperature of 33°C, the impairment in coagulation processes is equivalent to a 33% factor IX deficiency, a situation that sounds more impressive if referred to as 'B haemophilia'. Moreover, a greater degree of clot lyses, attributed to the impairment of intrinsic inhibitors of fibrinolysis, such as PAI or α2-antiplasmin, occurs at lower

temperatures [8]. Wolberg et al. [9] recently reported that plasma enzyme activities were not significantly reduced in vitro at 33°C, while platelet aggregation and adhesion were strongly reduced; below 33°C both enzyme activities and platelet activation were reduced. This suggests that bleeding observed in mildly hypothermic patients results primarily from a platelet adhesion defect and not from reduced enzyme activity or platelet activation, whereas at lower core temperatures both mechanisms are present [9].

Acidosis: Massive haemorrhage can lead to intracellular derangement in oxygen and substrate utilisation, causing metabolic acidosis. A strong correlation between the development of coagulation abnormalities and degree of hypotension has been observed in various studies. It has also been demonstrated that hypoperfusion is associated with a consumption coagulopathy, prolongation of aPTT and decreases in factor V activity and microvascular bleeding [10]. Meng et al. report that the activity of factor VIIa, the VIIa/TF complex and of the Xa/Va complex are strongly reduced as pH approaches 7 [11]. The enzyme activities of individual coagulation factors are reduced by 90% at this pH. The high concentration of hydrogen ions interferes with the interaction between coagulation factors and the phospholipids exposed on the activated platelets that form the rafts supporting the highest levels of activity of the coagulation factor complexes [12].

In spite of improvements in pre-hospital trauma resuscitation, the so-called lethal triad (coagulopathy, acidosis and hypothermia) is a challenge to the intensive care doctor in terms of early recognition and treatment of these dreadful complications [5]. Prevention of hypothermia by keeping the patient dry and covered is mandatory in the pre-hospital setting; the patient should also be provided with a warm environment and warmed fluids immediately on admission to the hospital. The prevention of hypotension and hypoperfusion and correction of possible acidosis with bicarbonate infusion to maintain pH >7.2 are crucial to avoid impairment of the haemostasis. Source control and the standard support therapy, including temperature and pH correction, are the cornerstones of treatment in severe bleeding, but unfortunately they are sometimes unavailable or cannot stop the ongoing haemorrhage. Therefore, over recent decades clinical research has focused on drugs and techniques that might be useful in particular circumstances, such as on the battlefield and in other pre-hospital settings, and in the case of uncontrollable haemorrhage.

Massive bleeding: novel therapies

Numerous drugs and different strategies have been proposed or re-evaluated for their usefulness in the management of bleeding. The next few paragraphs will be devoted to describing (i) drugs acting as *local* therapy that could be useful in controlling the source of bleeding and (ii) the role of *activated recombinant factor VII (rFVIIa)* as systemic therapy to manage uncontrollable bleeding and intracerebral haemorrhage (ICH).

Local therapies: As described above, massive haemorrhage is responsible for

half of the deaths in trauma patients, and the main cause of death, particularly in injured soldiers, is noneffective control of the bleeding at source following penetrating trauma. To overcome this problem, a few *local* treatments have been developed and applied in the case of military casualties, with the aim of stabilising life-threatening injuries. The most attractive local haemostatic agent currently utilised by the United States Military Force in Afghanistan and Iraq is QuickClot. Quickclot is displacing traditional tourniquets and gauze dressings in battlefield casualties because it can be applied to wounds of the head, neck and torso, all sites where traditional techniques are impossible to apply [13]. This new haemostatic agent is a zeolite-based granular material that can be externally applied directly to any wound; every soldier with minimal medical training can apply QuickClot with the aim of inducing formation of a blood clot. This material acts as a sorbent that dehydrates the haemorrhaging blood (producing an exothermic reaction), adheres and conforms to the injured tissue, modifies the local electrolyte conditions, heats the surrounding tissue and induces haemostasis [13]. Heat generation is related directly to the reaction of QuickClot to blood and inversely to haematocrit. The main, and considerable, side-effect of this new material is the release of large amounts of heat, which tends to burn healthy tissues. The maximum temperature measured in swine wounds during QuickClot application was 57°C [17]. New strategies are on study to modify the original zeolite composition in order to reduce the amount of heat released [13]. QuickClot is not degradable and must be debrided from wounds following haemorrhage control [5]. Some anecdotal reports have demonstrated that this material can reduce blood loss and mortality in lethal femoral artery injury in swine [14] and that it can also be applied intracorporeally to control haemorrhage in a coagulopathic surgical field during a surgical procedures after major trauma [15]. A recent paper reported the successful use of QuickClot in a man with an uncontrollable epistaxis following a punch biopsy of the nasopharynx [16].

Another interesting local treatment is a dressing called HemCon, a biodegradable derivative of chitin derived from shrimp shells. The primary haemostatic mechanism is an electrostatic interaction with blood elements [17]. The HemCon chitosan-based haemostatic dressing is approved by the US Food and Drug Administration for haemorrhage control. A very recent paper reported the efficacy of HemoCon dressings in combat casualties in the pre-hospital setting. Dressings were utilised externally on the chest, groin, buttock and abdomen in 25 cases; on the extremities in 35 cases; and on neck or facial wounds in 4 cases. In 97% of the cases, use of the HemCon dressing resulted in cessation of bleeding or improved haemostasis [18].

The modified rapid deployment hemostat (MRDH), another type of local dressing, consists of poly-*N*-acetyl glucosamine, which is a derivative of marine microalgae [5]. The exact mechanism of action of MRDH is still unknown, but it has been reported that it is able to control bleeding in hypothermic coagulopathic swine after traumatic liver avulsion [19]. Among ten trauma patients with hypothermia, acidosis and coagulopathy undergoing abbreviated laparotomy, MRDH application provided immediate haemostasis in all cases but one [20].

In trauma patients and in combat casualties the above new dressings seem to

be very promising in the control of an external source of bleeding, particularly in selected body regions where haemorrhage is difficult to manage by standard procedures (e.g. neck, chest, groin). Nevertheless, clinical experiences with these new techniques is still only anecdotal, so that at present the efficacy and safety of these products are completely unknown.

Activated Recombinant Factor VII (rFVIIa): rFVIIa has aroused great interest for the management of bleeding since it was first felt to be indicated in haemophiliac patients with inhibitors of factor VIII or IX to control/prevent overt bleeding. More recently, rFVIIa has been used as an 'off-label' treatment in bleeding patients with native or acquired defects of haemostasis: excessive oral anticoagulant therapy, thrombocytopenia, inherited Glanzmann thromboasthenia, Bernard Soulier syndrome, Von Willebrand disease, hepatic dysfunction, orthotopic liver transplantation and many other clinical settings [21–23].

The reason for this great interest on rFVIIa as a pan-haemostatic agent derives from its mechanism of action at therapeutic doses. Initiation of haemostasis involves the formation of a complex between tissue factor (TF) and activated factor VII (FVIIa) after injury. In physiological conditions TF is found in the subendothelium and is only exposed to circulating blood after tissue damage, although it can be expressed by several types of cells as a consequence of thrombogenic stimuli. The TF–VIIa complex then activates both factors IX and X and catalyses the autoactivation of more FVII; this chain of events is now known to be the main physiological pathway leading to the haemostasis in vivo. On these grounds, rFVIIa has been widely used for the treatment of bleeding episodes, and the literature offers a rapidly growing body of papers strongly suggesting that rFVIIa should be considered as an effective and safe adjunctive haemostatic treatment for severe bleeding that is unresponsive to conventional therapy [22, 23]. However, a few crucial points remain to be clarified concerning the use of rFVIIa: (i) optimal time of administration, (ii) optimal dosage and (iii) safety. In addition, the solutions to these problems are probably different for each category of bleeding patients; for instance, the optimal rFVIIa dosage seems to be lower for a patient with intracerebral haemorrhage (ICH) than for a cirrhotic patent with massive oesophageal bleeding.

In this light, two important randomised trials on trauma and ICH patients have recently been published. In the randomised double-blind trial on bleeding control in severely injured trauma patients, Boffard et al. [24] demonstrated the partial efficacy and safety of rFVIIa. Patients with severe trauma were randomised to a placebo group or to a rFVIIa group in which they received three intravenous injection boluses of 200, 100 and 100 μg/kg. The first dose was administered after transfusion of the 8th unit of red blood cells (RBC), and the second and third doses, 1 h and 3 h after the first dose, respectively. In the trial, 134 penetrating trauma patients and 143 blunt trauma patients were studied; in blunt trauma the RBC transfusion was significantly smaller with rFVIIa than in the Placebo group, and the proportion of patients needing massive transfusion (defined as >20 units of RBC) was also lower. No statistical differences were detected in the number of RBC transfused in penetrating trauma. The most important endpoint of this study was not achieved: the 48-h survival rate of the patients treated with rFVIIa was not

different from that in patients who received placebo. In any case, the safety profile of the drug was established in these trauma populations with a very high dosage of rFVIIa (300 μg/kg): six adverse thromboembolic events were reported by the investigators in their rFVIIa-treated patients and six were detected in placebo-treated patients.

ICH is a particular type of critical bleeding in which a very small amount of blood can determine a bad outcome. Therefore, the prevention of haematoma enlargement by ultra-haemostatic therapy should be a primary issue in the management of ICH patients. From the pathophysiological point of view, it has recently been reported that ICH expands over time because of persisting bleeding from the primary source and mechanical disruption of the surrounding vessels [25]. In this context, rVIIa seems very attractive, because of its rapid 'pan-haemostatic' effect, and a recent randomised trial confirms this hypothesis. Mayer et al. [26] have highlighted the observation that rVIIa used within the first 4 h after the onset of ICH limits the growth of haematoma and decreases the mortality or severe disability rate from 69% to 53% of patients. A small increase (from 2% to 7%) in the incidence of adverse thromboembolic events (e.g. myocardial ischaemia and cerebral infarction) was observed in patients treated with rVIIa, but the overall frequency of fatal or serious adverse events did not differ from that with placebo. Therefore, rVIIa can be considered a first-line therapy for use to improve survival and functional outcome in patients with ICH.

In conclusion, novel therapies are now available to manage critical bleeding both locally and by systemic therapy. However, most of these are still used as 'compassionate' treatment, and the published experience available is only preliminary. Therefore, in our opinion, in patients affected by severe bleeding patients the maximum effort should be reserved to prompt control of the bleeding source and accurate application of standard support therapy to prevent or correct disturbances of haemostasis.

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Chapter 42

Evaluation of performance of ICUs

J.R. Le Gall

The performance of an intensive care unit (ICU) has different aspects. For many years ICU performance was synonymous with standard mortality ratio (SMR). Nowadays, however, other aspects of performance are taken into account, which are concerned with the patients', families', nurses', doctors' and providers' points of view. Several studies, on the other hand, have demonstrated the relationship between organisation and performance. Improving ICU performance requires that we shift from a paradigm that concentrates on individual performance to a different paradigm that emphasises the need to assess and improve ICU systems and processes. Various observations illustrate the importance of ICUs. One third to one half of Americans spend time in an ICU during their final year of life, and one fifth die there [1]. Quite apart from the death rates, suffering is common among ICU patients [2]; and substantial dissatisfaction among the relatives and friends of ICU patients indicates that suffering is not limited to the patients. In addition, the economic costs of ICU care are staggering. Certain subsets of iatrogenic complications in ICUs occur in 31% of patients and are severe in 13% of patients. Errors were observed in 1% of all the activities performed each day in patients in an Israeli ICU, with a higher rate among physicians than among nurses [3]. Poor communication, teamwork, and problem solving are common among ICU staff and are perceived as being more prevalent and important by ICU nurses than physicians [4]. Another problem is the variation in practice and outcomes that is not explained by patient or illness characteristics. For example, the odds ratio across 34 ICUs for use of pulmonary artery flotation catheters was found to vary by 38% according to patients' race and by 33% according to their insurance status, but by 200–400% according to how the ICU was organised and staffed [5]. Given the frequency of death in ICUs, it is particularly troubling that ICUs suffer from major deficiencies in terms of palliative and end-of-life care. ICU patients and their surrogates are often dissatisfied with the amount, nature, and clarity of communication with caregivers [6].

Defining ICU performance

Assessing performance requires the quantification of parameters that are relevant to patients, society and the hospital. For example, nosocomial infections are common and deadly complications of ICU care. Effective hand hygiene has a

proven role in reducing nosocomial infections [7], so that the rate at which ICU personnel perform recommended hand hygiene is an appropriate secondary index of ICU performance. The ICU readmission rate is a questionable indicator of ICU performance. For readmission to be a meaningful indicator would require that a detrimental outcome that occurred after the patient left was due to a problem present prior to the original ICU discharge and would not have occurred had the patient remained longer in the ICU [8]. Although daily costs are reduced by transferring patients from the ICU to ward beds, premature transfers lead to worse outcomes. Reductions in the lengths of stay and short-term mortality rates may merely reflect a shift of the place of death from one location to another, with no real net improvements. Thus, using short-term mortality rate or length of stay as outcomes can lead to erroneous conclusions [9]. The collection of data on post-hospital survival and QOL is laborious, which undoubtedly contributes to the low usage of these important measures. Combining these into a measure of long-term survival that is adjusted for the QOL, such as quality-adjusted life-years, is even more labour intensive. A variety of questionnaire-based tools have been developed for quantifying patients' QOL. The most commonly used is the Medical Outcomes Study 36-item short form [10]. Complication and error rates are often used as measures of ICU performance. These are relevant because of potential causal relationships of such adverse events with increased mortality, morbidity or costs [11]. Symptom control and end-of-life decision-making are important aspects of ICU care. There is much room for improvement in this area. Because ICU care is expensive, resource consumption should be part of the assessment of ICU performance at every institution. The best measure that balances simplicity and information content is length of stay in the ICU, although, this has limitations. Other measures whose acquisition requires a lot of effort include total monetary charges or costs, usage of various diagnostic and/or therapeutic procedures and the therapeutic intervention scoring system (TISS) score [12]. It is important for ICU beds to be used effectively, because they are an expensive and limited resource. In practice, ICU triage decisions are often inefficient, but they can be made more effective without adverse medical consequences [13]. The importance of satisfaction among patients and their families as measures of ICU performance is highlighted by data [6] documenting that poor communication and dissatisfaction are common. The satisfaction of all those who work in an ICU is another key component of ICU performance. Job dissatisfaction contributes to higher rates of staff turnover [14]. One large class of performance measures quantifies the processes, procedures and functions going on within the ICU or linking the ICU to the rest of the hospital. In Table 1 we have summarised and classified the different aspects of ICU performance. They may be classified as structures (particularly management), processes (such as appropriateness of medical intervention) and outcomes (not only SMR, but also quality of life and family and staff satisfaction).

Table 1. The various aspects of ICU performance

Structures	Size and technological availability of ICUs	
	Management: conflict management abilities	
	Effectiveness of ICU bed utilisation	
Processes	Appropriateness of medical intervention	
	Rate of nosocomial infection	
	Frequency of processes/procedures/functions involved in ICU care	
Outcomes	Medical	Survival rates ICU, hospital, long term
		Long-term functioning and quality of life among survivors
	Ethical	Patient satisfaction
		Families' satisfaction
		Concordance of desired and actual end-of-life decisions
	Institutional	Staff satisfaction
		Degree of burnout syndromes
	Economic	Satisfaction of others in the hospital with the ICU
		Resource consumption by ICU, hospital and posthospital cost
		Effectiveness of care

The earliest studies of ICU performance

The two earliest studies on evaluation of ICUs were published in 1976 (by a French group proposing a way to evaluate the prognosis of ICU patients [15]), and in 1982 (the first time comparison of hospital mortality in US and French ICUs [16]).

In 1976, Rapin et al. [15] published "Les chances de survie des malades hospitalisés dans un service de réanimation" [in French: The chances of survival of patients hospitalised in an ICU]. In order to define criteria of prognosis for patients hospitalised in intensive care units, 2,105 cases of patients treated over 4 years for acute life-threatening illnesses were reviewed. According to the severity of the patients' initial illness or illnesses, three groups were defined: group I in which each patient had one initial illness, which was assumed to be reversible (55.3%); group II, in which each patient had several initial illnesses, also assumed to be reversible (27.7%); and group III, in which each patient had one or several initial illnesses, with at least one of them presumed irreversible (17%). The total mortality was 31.3%, and the rate was significantly lower in women than in men. Mortality by the above groups was 8.7% in the first, 42.7% in the second ($p<0.0001$), and 83% in the third ($p<0.0001$). In each group the prognosis was influenced by the type of initial disease (respiratory, circulatory, renal or metabolic, septic, neurological and hepato-digestive failure). In groups I and II mortality was greater when high risk factors were present and rose with advancing age, but remained below 50%. In group III mortality was the same whether or not high risk factors were present, was not influenced by age, and was always near 90%. Over the 4 years, the mortality declined significantly in group II, from 57% to 29%. It was concluded that treatment of life-threatening acute visceral failure in an ICU has a poor result when this failure is associated with a chronic or presumably irreversible disorder. In other cases the presence of a high

risk factor, particularly old age, is not a contraindication to treatment in an ICU.

In 1982, Knaus et al. [16] published the first international comparison of hospital mortality among ICU patients in USA and France. In this study, for the first time a severity score was used to describe the patients. The authors showed that the hospital mortality increased from 5% to 75% with worsening severity of the patients' illness. On the other hand, they did not find a statistically significant difference in the adjusted mortality between USA and France.

The Standard Mortality Ratio (SMR)

The SMR is the comparison between the probable hospital mortality (P) and the observed hospital mortality (O). The probability of mortality is estimated by a model using a severity score [17, 18]. This approach is valid only when used with models characterised by excellent calibration and discrimination [19]. The recently devised scores are objective, built up from logistic regression. In their order of publication, they are APACHE III [20], SAPS II [21] and MPM II [22].We will take SAPS II as an example.

The SAPS II

In 1993, Le Gall et al. [21] published a New Simplified Acute Physiology Score (SAPS II) based on the European North American Multicenter Study. They compared the SMRs in the countries taking part. All of them had a SMR close to 1, which was expected, since they were involved in development of the SAPS II. What was more striking was the difference in hospital mortality according to the countries. Two groups of countries were observed. In the first group (France, Italy, Spain and UK) the hospital mortality rate was around 30%. In the second group (Austria, Belgium, Finland, Germany, The Netherlands, Switzerland and North America) the hospital mortality ratio rate was close to 20%. Does this mean that the first group was performing less well than the second one? Obviously not, since the SMR was around 1 for every country. It is probable that the patients in the second group were less severely ill, so that the ICUs in these countries were treating patients who in other countries would be admitted to the recovery room.

Obsolescence of the probability models

During subsequent years many studies were performed and showed when models were applied to different populations that the calibration of the models was poor. Another observation was that the SMR was declining over years. Considering, for instance the SMR according to the SAPS II model, Glance et al. [23] showed that for 24 ICUs studied the SMR was always lower than 1 (0.406–0.773). We can only suggest hypotheses to explain this: obsolescence of the models, changing case mix, different selection criteria for admission.

Nevertheless it was mandatory to improve the statistical qualities of the models, or even propose new models.

Improvement of the probability models

Several attempts to improve the probability models have been published.

Customisation

Customisation of the models is changing the equation of probability without altering the severity score. This method is simple, and its use has been proposed both for specific applications and for countries. Le Gall and Lemeshow have proposed customising the SAPS II and the MPM II for patients with early septicaemia [24]. Moreno [25] and Metnitz [26] have published customised models.

Expanded models

Knaus et al. [27] proposed an expanded model for septicaemia patients, adding acidosis, cirrhosis and other variables to the APACHE II score.

Table 2. Expanded Simplified Acute Physiology Score (SAPS II)

	Value	Points
SAPS II		0.059*IGSII
Age	<40 years 40–59 years 60–69 years 70–79 years >79 years	0 0.3810 0.6017 0.7860 1.1379
Sex	Male Female	0.2500 0
Length of hospital stay before ICU admission	<24 h 1 day 2 days 3–9 days >9 days	0.0383 0 0.0350 0.3407 0.7957
Patient's origin	From outside From the wards From another hospital	0 0.3520 0.2173
Length of stay in ICU	<24 h 1 day 2–3 days 4–9 days 9 days	0.9352 0.3063 0.0482 0 0.0251
Central or Swan-Ganz catheter	No Yes	0 0.2126

Sedation	No Yes	0 0.1086
Neurological failure	No Yes	0 0.4343
Circulatory failure	No Yes	0 0.9177
Renal failure	No Yes	0 0.3608
Haematological failure	No Yes	0 0.2106
Hepatic failure	No Yes	0 0.7084

Logit = –9.1703+0.4125 * score + 3.4517 * log(score+1)

Le Gall et al. [28] proposed an expanded SAPS II adapted to the French population (Table 2). The added variables were collected on each patient's first day in the ICU. Age and sex were entered, as were the length of hospital stay before ICU admission, patient's location before ICU and clinical category (medical or surgical). No diagnosis was included, apart from any medical drug overdose. This was done for three reasons: the SMR of these patients was 0.2 according to the original SAPS II model; the percentage of patients with this diagnosis varied from 0 to 40% according to the ICUs; and it is simple, obvious, and easy to collect on the first day in the ICU.

Repetitive scoring

Some researchers have emphasised that the first few days in the ICU are decisive in determining the outcome, and particularly the first 3 days.

Larche et al. [29] observed the development of the Logistic Organ Dysfunction (LOD) model [30] during cancer patients' first 3 days in the ICU. They showed that the difference between LOD 3 and LOD 1 determined the prognosis.

Timsit et al. [31] proposed a score based on SAPS II and LOD collected during the first 3 days in the ICU. They called this composite score the TRIOS, and its calibration was excellent.

The most recent scores

The SAPS III has been developed from work with a worldwide database relating to 19,577 patients. The score itself comprises three parts: chronic variables, acute variables, including sepsis and its characteristics, and physiology. The probability of ICU and hospital death is obtained by adding diagnoses to the model. The evaluation of ICU performance is adapted to each ICU according to its case-mix [32, 33]. APACHE IV [34] uses the ICU day 1 information from a specific US database of 13,618 consecutives admissions. It is very similar to APACHE III, but new variables have been added and different statistical modelling used. Future studies

will show whether the new scores (SAPS III, APACHE IV) perform better than the oldest ones (SAPS II, APACHE II and III).

Some reflections on SMR and benchmarking

As quoted by Garland in his outstanding review "*Improving the ICU*" [35],"If there are reasons to suspect substantial differences in case-mix variables between the cohorts being compared, then some adjustment should be made for these differences. In the real world, however, the resources needed to collect data and adjust for the case mix often exceed those resources that are available, requiring dependence on unadjusted data. Such limitations should not lead to nihilism and inaction. Although unadjusted data could be misleading, they cannot possibly be more misleading than having no performance data at all. Similarly, adjustments made with the currently available, but imperfect, methodologies are better than raw data. Although benchmarking the performance of an ICU against others is desirable, the simplest performance comparison is between successive time intervals." We must also mention the excellent paper by Boffelli et al. "*Improving the ICU, the GIVITI experience*" [36]. These authors analysed 55,246 patients and showed that Italian ICUs performed better in 2005 than in 2004.

Other aspects of performance

The patient's points of view

The points of view of dying and surviving patients are obviously different. With reference to dying patients many studies have been published about the management of death in ICUs. A book edited by Curtis and Rubenfield, entitled "*Managing death in the Intensive Care Unit, the transition from cure to comfort*", has recently been published. What is important for surviving patients is the quality of life. Among the numerous papers devoted to this subject, we may quote the article published by Herridge et al. [37]. Looking at the 1-year outcomes of ARDS survivors, they found that 40 (49%) of 82, 1-year survivors had returned to work. Furthermore, of these 40 patients, 31 (78%) had returned to their original work. When, on the other hand, the authors considered the patients' ability to exercise and their health-related quality of life they found that at 1 year after ICU discharge 89% of survivors had normal physical functioning and 88% had a normal social functioning.

The family's points of view

Many studies have been published on outcome for the patient's family. Let us quote a study by Azoulay et al. [38] on family members' desire to share in the decision-making process. Poor comprehension was noted in 35% of family members. Among ICU staff members, 91% of physicians and 83% of nonphysicians believed that

families should be offered the option of being involved in decision-making but that only 39% of patients had actually involved family members in decisions. A desire to share in decision-making was expressed by only 47% of family members, and only 15% of family members actually shared in decision-making. Effectiveness of information influenced this desire.

Burnout syndrome

Nurses and the doctors working in ICUs may suffer from the burnout syndrome that reflects the exhaustion caused by the physical and psychological burdens their work entails. One study by Embriaco et al. [39] showed that 46.5% of 959 intensive care specialists interviewed at 1 day had high-degree burnout. Some of the risk factors for burnout found were: female sex, too many duties, too few holidays and conflicts between doctors or with nurses.

Relationship between management and performance

Good management makes for good performance. The first study published on this relationship was that by Shortell et al. [40]. Based on data collected from 17,440 patients across 42 ICUs, the study examines the factors associated with risk-adjusted mortality, risk-adjusted average length of stay, nurse turnover, evaluated technical quality of care and evaluated ability to meet family member needs. Findings revealed by the APACHE III methodology for risk adjustment were that: (1) technological availability is significantly associated with lower risk-adjusted mortality (beta = 0.42); (2) diagnostic diversity is significantly associated with greater risk-adjusted mortality (beta = 0.43); and (3) caregiver interaction comprising the culture, leadership, coordination, communication, and conflict management abilities of the unit is significantly associated with lower risk-adjusted length of stay (beta = 0.34), lower nurse turnover (beta = 0.36), higher rated technical quality of care (beta = 0.81), and better rated ability to meet family members' needs (beta = 0.74). Furthermore, units with greater technological availability are significantly more likely to be associated with hospitals that are more profitable, involved in teaching activities, and have unit leaders who are taking an active part in hospital-wide quality improvement activities.

A French study conducted by Azoulay et al. in 920 families [41] showed the positive factors influencing patients' families' satisfaction. These were: family members of French descent, patient-to-nurse ratio ≤ 3, information provided by junior physicians, and family helped by their usual doctor. The negative factors were: family feeling they received contradictory information, family not knowing the specific role of each caregiver, inadequate ratio of desired/allowed time with the patient.

Conclusions

In the evaluation of an ICU's performance, the SMR is a necessary (but not sufficient) instrument. The SMR must be calculated from customised or expanded scores. The first 3 days in the ICU determine the outcome.

The evaluation of performance must take account of the patients', families' and staff members' points of view. We must stress that good management makes for a well-performing unit.

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