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Anaesthesia Pharmacology Intensive Care and Emergency Medicine

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APICE 23

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Abbreviations

ACC	American College of Cardiology
ACEP	American College of Emergency Physicians
ADH_2	aldehyde dehydrogenase
ADP	adenosine diphosphate
AECC	American European Consensus Conference
AEDs	automated external defibrillators
AHA	American Heart Association
AKI	acute kidney injury
Akt	protein kinase B
ALI	acute lung injury
ALS	advanced life support
AMA	American Medical Association
AMSA	amplitude spectrum area
APACHE	Acute Physiology and Chronic Health Evaluation
ARDS	acute respiratory distress syndrome
ARDSNet	Health ARDS Clinical Trials Network
ARF	acute renal failure
ARF	acute respiratory failure
ATN	acute tubular necrosis
ATP	adenosine triphosphate
AV	alveolar ventilation
BLS	basic life support
BP	blood pressure
BUN	blood urea nitrogen
C	compliance
CABG	coronary artery bypass grafting
CARS	compensatory anti-inflammatory response syndrome
CBF	cerebral blood flow
CCO	continuous cardiac output
CCS	Canadian Cardiovascular Society
CD	Caesarean delivery

CI	confidence interval
CIP	critical illness polyneuropathy
CMSS	Council of Medical Specialty Societies
CO	cardiac output
COPD	chronic obstructive pulmonary disease
CPB	cardio-pulmonary bypass
CPP	cerebral perfusion pressure
CPP/Depth	coronary perfusion pressure and compression depth
CPR	cardiopulmonary resuscitation
CRF	chronic renal failure
CRPS	complex regional pain syndrome
CT	computed tomography
CVVH	continuous veno-venous haemofiltration
CVVHD	continuous veno-venous haemodiafiltration
Cw	total arterial compliance
DFP	dynamic functional profile
Dp/dt	contractility
DRG	disease related group
E	early filling velocity
e-	electron
E'	myocardial Doppler early velocity of the mitral annulus
EBM	evidence-based medicine
ECC	extracorporeal circulation
EECP	enhanced external counterpulsation
EEG	electroencephalogram
EMS	emergency medical services
EOC	emergency operation centres
EPO	erythropoietin
ESC	European Society of Cardiology
ESICM	European Society of Intensive Care Medicine
$etCO_2$	end-tidal CO_2
ETS	endoscopic thoracoscopic sympathectomy
f/VT	respiratory rate/tidal volume ratio
FADH2	flavin adenine dinucleotide (reduced)
FE	focused echocardiography
fR	respiratory frequency
FRC	functional residual capacity
GCS	Glasgow Coma Scale
GER	gastro-oesophageal reflux
GFR	glomerular filtration rate
GI	gastrointestinal
GRADE	Grading of Recommendations, Assessment, Development, and Evaluation
GRF	glomerular filtration rate
H+	proton
HACA	hypothermia after cardiac arrest

HIF	hypoxia-inducible-factor
HMO	Health Maintenance Organization
HNE	hydroxy nonenal
HR	hazard ratio
ICP	intracranial pressure
ICU	intensive care unit
IMM	inner mitochondrial membrane
IMS	intermembrane space
IOM	Institute of Medicine
ISF	International Sepsis Forum
IvIg	intravenous immunoglobulin
JAK	Janus tyrosine kinases
K+	potassium
KATP	mitochondrial ATP-sensitive K+
L	lung
LD	learning disabilities
LOS	length of stay
LST	life-sustaining technologies
LVEDA	left ventricular end-diastolic area
LYG	life-year gained
MAC	mechanical cough assist
MCI	mass casualty incident
MEES	Mainz Emergency Evaluation Scoring system
MG	myasthenia gravis
MIE	mechanical in exsufflator
MOF	multiple organ failure
MPTP	mitochondrial permeability transition pore
NADH	nicotinamide adenine dinucleotide (reduced)
nCPAP	noninvasive continuous positive airway pressure
NDE	near-death experience
NHE-1	sodium-hydrogen exchanger isoform-1
NHS	National Health Service
NICE	National Institute for health and Clinical Excellence
NIV	noninvasive ventilation
NMD	neuromuscular diseases
NPPV	noninvasive positive pressure ventilation
NRS	noninvasive respiratory support
OHCA	out-of-hospital cardiac arrest
OMM	outer mitochondrial membrane
P	pressure
P13K	phosphatidylinositide kinase
P4P	pay-for-performance
PAC	pulmonary artery catheterisation
$PaCO_2$	partial alveolar pressure of CO_2
PCI	percutaneous coronary intervention
PDK1	phosphoinositide dependent kinase-1

PEA	pulseless electrical activity
PEEPi	intrinsic positive end-expiratory pressure
PEI	individual educational plan
PEP	personalised educational plan
$PETCO_2$	partial pressure of end-tidal carbon dioxide
Pi	inorganic phosphate
PICU	paediatric intensive care unit
PIP	positive inspiratory pressure
PKCε	kinase C epsilon
PMN	polymorphonuclear neutrophils
PMR	percutaneous myocardial laser revascularisation
PPE	personal protective equipment
PRINCE	Pre-Resuscitation Intra-Nasal Cooling Effectiveness
PRISM	paediatric risk of mortality
PSV	pressure support ventilation
Q	coenzyme Q
QALY	quality-adjusted life-years
QI	quality improvement
R	resistance
RCT	randomised clinical trial
RES	reticuloendothelial system
ROSC	return of spontaneous circulation
Rp	total peripheral resistance
RS	respiratory system
RSBI	rapid shallow breathing index
RVSP	right ventricular systolic pressure
SATs	spontaneous awakening trials
SBT	spontaneous breathing trial
SBU	Swedish Board of Health and Welfare
SCA	sudden cardiac arrest
SCCM	Society of Critical Care Medicine
ScHARR	School of Health and Related Research
SCS	spinal cord stimulation
SH-2	src-homology domain-2
SIMV	synchronised intermittent mandatory ventilation
SSC	Surviving Sepsis Campaign
START	simple triage and rapid treatment
STEMI	ST-elevation myocardial infarction
SV	stroke volume
SVR	systemic vascular resistance
TBI	traumatic brain injury
TD	thermodilution
TEDA	thoracic epidural anaesthesia
TENS	transcutaneous electrical nerve stimulation
TMR	transmyocardial revascularisation
TNF-α	tumour necrosis factor-α

TOE	transoesophageal echocardiography
TVI	time-velocity integral
V	volume
$\dot{V}$	airflow
V/Q	ventilation to perfusion ratio
VAP	ventilator associated pneumonia
VCO_2	carbon dioxide elimination
VD	dead space ventilation
VE	minute ventilation
VF	ventricular fibrillation
VILI	ventilator-induced lung injury
VT	ventricular tachycardia
W	chest wall
WAEDM	World Association for Emergency and Disaster Medicine
WHO	World Health Organization
Zc	characteristic impedance

Part I
Continuing Medical Education

Can I Think what I Read?

1

P.D. Lumb

"Can I Think what I Read?" is an interesting question and an important consideration when approaching any information source. The real question must be "Can I trust the information and act on it in a professionally responsible manner"? Traditionally, material appearing in the scientific literature undergoes vigorous peer review that attempts to ensure validity, quality and relevance of any information accepted for publication. Often, the process requires the author to make significant modifications to the originally presented material, and the final submission may bear little resemblance to the first draft. However, and in order to dissect the question more fully, it is important to understand the publishing process and to determine the types of information available in the increasingly open world of electronic access to myriad data sources, the provenance of which is occasionally hard to identify.

The question of whether or not to publish may be as simple as a direct request to a potential author from an editor charged with fulfilling an obligation to cover a subject in either textbook or review article. This is a relatively simple task, the outcome of which is a work that is published under the auspices of peer review but with the caveat that the author is likely considered a content expert, thereby deserving the assignment, and that the peer review is more likely to be stylistic to ensure literary consistency within the global publication rather than for content accuracy. In an endeavour of this nature, the finished work is a reflection of the author and, as such, reflects that author's academic integrity and reputation. The information reflects current practice, incorporates recent outcomes verified in the literature but seldom presents groundbreaking or controversial information or introduces new practice concepts. It is interesting to follow the progress of a specialty by scanning the chapter titles and headings from its "standard" textbooks. Maturation is easily identified, and in anaesthesiology and critical care medicine, practice-based outcome, quality improvement and standards have all demanded equal attention to the more traditional subjects of physiology, pharmacology, toxicology and other favourite subjects that permit these specialists to become experts not only in the pathophysiology of critical illness but also in managing and maintaining the human–machine interface.

For any contracted article assigned to a content expert, the preparation and writing process parallels that of any document intended for exposure in the scientific community. The information must be correct, clinically valuable and verifiable and capable of the most in-

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tense scrutiny. However, while important, the content likely defines current practice rather than predicts new innovation. Despite this, the information must provide the conceptual framework in which the specialty's future progress will be grounded. Any standard text provides a common, effective clinical practice benchmark while having the capability of stimulating future innovation. This is contrasted with the non-contracted, research-oriented article that provides the stimulus for the questions posed in the remainder of this discussion. In other words, the question posed by the title takes on a new meaning. Can I begin to use and apply what I read in the literature, and what safeguards must I employ in my investigation of the literature prior to engaging the innovation in clinical practice? Recent examples of wholesale acceptance of apparently good ideas have, upon further reflection, required modification and tempering influences: tight control of blood glucose, use of steroids in sepsis, difficulties associated with implementing low tidal volume ventilation, and others. Indeed, it is interesting to note that some innovations with questionable benefit occasionally usurp all efforts to introduce clinically relevant standards that, if adopted, would apparently create significant patient care benefit and improve outcomes.

Perhaps this is a more relevant statement in terms of the question "When does implementation of innovation become necessary"? The sequence of events – from innovator through early adopter, members of the early and/or late majority and laggard – is well documented, but the reasons for the change-associated challenges sometimes overlook the impact of the literature and its adaptability and influence on behaviour. Indeed, Berwick suggests that "the term 'laggards' probably misstates the group's value and wisdom. They should perhaps be called traditionalists, sea anchors, or archivists, to emphasise that they are often making choices that are wise and useful to the community or organisation. They are the physicians who swear by the tried and true" [1]. Therefore, in order to answer the question of thinking what we read, it is important to define the context of the publication and its intent, provenance and peer-review integrity. The answer is complex and defines one of the dilemmas of the modern healthcare professional: "How do I maintain relevance"? The question is predicated on the reality and understanding that the process of lifelong learning must be the anticipation of all physicians; more important, therefore, is the selection and appropriateness of the information included in the educational process.

In some respects, the answer is based on the insight and self-classification of the reader with respect to the information to be accessed. Both reader and author need to understand the process through which information moves from concept through writing and peer review to publication. The injunction "caveat emptor" is as important in medical science as it is in purchasing any other product. Authors need to consider the audience they wish to reach: Will it be a group of generalist practitioners, theoreticians, applied researchers, a mixture of all or the general public who may be searching increasingly available and sophisticated information sources? Will the manuscript be submitted for peer review or appear in an online, direct access site? Readers need to consider all the preceding and also develop insight into the varieties of sources that satisfy these unique, sometime integrated and – always in one manner or another – competitive interests. It is also important to consider the reader's need for information and style of acquisition. In the current state of really simple syndication (RSS) feeds, many busy practitioners rely on abstract scanning to determine the necessity for further investigation or in-depth reading of the article with reference checking and further investigation. In order to accommodate this need, editors are careful to require that an abstract is a brief, precise, specific and honest representation

of the material contained in the main article. The abstract should stand alone; it is the authors attempt to sell the reader and encourage further investigation. Unfortunately, and by design, there is insufficient detail for the reader to accept the conclusions as presented and adopt them without investigating their provenance; this requires digestion of the full text article at a minimum. Further investigation and additional reading of related articles is necessary prior to adopting new information or techniques into clinical practice. In this setting, the question becomes one of self-determined responsibility on the part of the reader to undertake the discipline of the responsible reader. Frequently, the author's conclusions provide an important contextual basis for the reader's ability to classify the information. Here the author should provide insight into whether the information represents either an important advance or best practices in the current context and suggest future directions for new research or practice initiatives. In all areas, the author should represent the work's shortcomings and develop the foundation for investigating future questions. The basics are: What has been done before and is current? What was done in the current investigations? What was accomplished? It is important to understand that negative results are sometimes more important than apparent innovations.

The concept of partnership between author and audience (reader) is an interesting one. First, exposure to literature is the requirement to learn to read in one's native alphabet and language. There is no question about provenance, and the student deviates from the programme at her or his peril. It is interesting, therefore, to recognise that the current response to the professional literature is a requirement for evidence-based reading. In another paradigm, that translates to suspicion. If this is a requirement to evaluate the current literature, where in our educational or cultural heritage does the courage to question the printed word evolve? Perhaps the first occasion occurs when the student questions the validity of the novel and understands the concept of fantasy and escape. Unfortunately, this understanding and scepticism appears subdued when the practitioner is confronted with a lead article from a highly regarded source with an astronomic impact factor. In this instance, the assumption is that the article's provenance has been vetted and that the information can be accepted at face value. This is neither the intent nor the objective of peer review. Rather, manuscripts that survive the peer review process present to the reader information that has been subjected to review by content experts who evaluate and critique all aspects of the submission, including the hypothesis, experimental design, statistical analysis and conclusions. The process is rigorous, and the majority of articles submitted for publication fail to meet the necessary standard. It is not unusual for a journal to have an acceptance rate of 30% (or less) of submitted articles. Despite the rigor of the process and the expertise of the reviewers, there is no guarantee that the published information is either accurate or credible. Perhaps a more important concern is not the timeliness of the information but its relevance, applicability and durability following implementation.

It is in this context that the requirement for a critical understanding or continuous evaluation of the evidence base of published information becomes critically important. The corollary is that once published does not mean sacrosanct. The courage to challenge defines the next set of experiments or investigations that must be performed to continuously validate/redefine the original hypothesis.

The unique tension and paradox in scientific literature is that the quality and sophistication of the reader defines the credibility of the publication. This leads to certain preconceptions or conditions that define quality but not necessarily veracity. Is this an oxymoron

or a legitimate concern? A journal's quality is judged in a variety of ways, the impact factor being one. This measurement recognises the number of times a published article is referenced by others. A journal becomes increasingly sought after by potential authors because the likelihood that an accepted work will be read by a large number of individuals increases. However, the more important consideration is that readers remain a critical, professionally responsible review body rather than an adoring audience. The literature is replete with examples of statistical flaws or other concerns in landmark articles or the recognition that some widely held opinions are supported by little evidence other than passing a "credibility" test. In anaesthesiology, the debate continues about whether a Sellick manoeuvre (backward pressure on the cricoid cartilage) is a necessary component of a rapid-sequence intubation. The question for an author assigned the task of writing the airway chapter in a new edition of a standard textbook is different from that of an investigator interested in revisiting the question of whether or not the technique is beneficial. For one, it is a matter of adjudicating the technique's inclusion; for the other, it is a question of hypothesis and result. For the student, the standard text becomes the gold standard; for the experienced practitioner, the hypothesis-driven study may become the foundation of a new reality. The tension is clear and the discriminatory responsibility of author–reader relationship is highlighted.

Another difficulty for the author is the necessity of catering to multiple reader types in a single manuscript or chapter. It is apparent that readers vary in their attention span and the manner in which they obtain and process information. For some, the text itself is the key; for others, the graphics, figures and tables are the most important area and primary focus. Although most authors perceive their articles to be a consistent whole, the most discerning provide each reader a content and style with a unique experience, ensuring that graphs, figures, tables and text tell the story independently yet collaboratively. Figures and tables are felt to be the most effective way to present results, but much of the standard textbook relies on a complete, easily understood explanation of technique or process. All graphic material should be presented in a manner that is easy to interpret, and the captions or titles should be understandable independently of the accompanying text. It is dangerous to suppose that the reader will follow the author's detailed logic to gain an independent interpretation of the data; rather, the author must sell the message in all locations. This is a difficult task and one that becomes increasingly complex as the subject matter broadens and the available information is more expert opinion than objective data. In this setting, the experienced context expert is able to present a balanced assessment of available information in a manner that is both useful and intellectually and practically challenging. "Can I think what I read"? in this context becomes a generally acceptable manner in which to engage in the subject while providing the discerning student the ability to generate important questions that may stimulate hypothesis-generated experiments that shape future advances.

There are general rules that authors must consider: The manuscript must establish the subject and context clearly. It should be concise and accurate. The reader should not be confused about the article's purpose or become confused by a poorly constructed argument. The peer reviewers and editor have a responsibility to the author and reader to help refine the manuscript and to make it relevant while avoiding hyperbole. The author must understand that reviewers are likely authors themselves and that personal opinion and experience, linguistic and stylistic preferences and writing mannerisms are prevalent. Therefore, any criticism or suggestion should not be taken as a personal attack. Rather, the

experienced author is able to ascertain the substance of peer review and adapt the ideas to the work in preparation, ultimately creating a publication that is personal while representative, individual while a unification of collective wisdom and unique while incorporating universally accepted methodology and process.

In summary, “Can I think what I read”? becomes a question for exploring new truths and revisiting behaviours established in current practice and belief. The responsibility for appropriate and ethical publication rests with the author and editor; the responsibility for disseminating the information rests with the publisher; the responsibility for appropriate utilisation of the information rests with the reader. Wherein lies the greater responsibility? All participants in the process are responsible. The partnership is becoming increasingly important, and the reader must take increasing responsibility for discriminatory consumption. Electronic systems and open publishing platforms reduce the ability of peer and editorial review to refine the final submission, and the reader must undertake many of these responsibilities personally. The learning–reading cycle comes full circle: from uncritical acceptance of the information presented to scepticism. Ultimately, the reader is responsible for performing not only a critical review of information presented but also for placing the relevant pieces into an appropriate context. It is only in this manner that the question posed can be answered in the affirmative.

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Part II
Clinical Pharmacology

Pharmacological Manipulation in ICU

2

D. De Backer, K. Donadello and S. Scolletta

Multiple organ failure is a common feature in critically ill patients, and the severity of organ dysfunction is associated with outcome. Multiple mechanisms can be implicated in the development of multiple organ failure, including global and regional haemodynamic alterations and microcirculatory and cellular alterations. Microcirculation may play a crucial role in the pathophysiology of multiple organ failure. Indeed, it is the primary site for gas and nutrient exchange with tissues. In addition, the microcirculatory bed represents the largest endothelial surface of the body and takes an important place in the initiation and amplification of inflammatory processes and of the coagulation cascade. It is also implicated in permeability alterations. Accordingly, even though the importance of global and regional vascular alterations should not be minimised, many events implicated in impairment in tissue oxygenation and inflammatory processes occur at the microcirculatory level.

Microvascular alterations have been observed in various experimental conditions, including severe haemorrhage [1], ischaemia–reperfusion injury [2] and sepsis [3–7]. These alterations are characterised by a decrease in capillary density and the presence of stopped-flow capillaries in close vicinity of well-perfused capillaries (blood flow heterogeneity) [1, 3, 5]. Similar alterations have been observed in patients with severe sepsis [8, 9] or severe heart failure, as well as in patients submitted to high-risk surgery [10, 11]. The severity and persistence of these alterations is associated with development of organ failure and results in poor outcome [12].

How can microvascular blood flow be manipulated? As rarefaction of capillaries and heterogeneity are characterising these microvascular alterations, microvascular recruitment is more likely to improve tissue perfusion than simply increasing microvascular blood flow in already perfused capillaries. In this chapter, we describe the impact on microvascular perfusion of various interventions typically used in haemodynamic resuscitation, as well as those of other therapies used in critically ill patients.

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2.1 Effects of Fluids

Animal experiments have shown that colloid solutions can improve microcirculatory blood flow, whereas crystalloids have a more limited impact [13–15]. Until recently, data were lacking in humans. In a series of 60 patients in septic shock, Ospina-Tascon et al. [16] demonstrated that fluids improve sublingual microvascular perfusion by a combined increase in capillary density and improvement in proportion of perfused capillaries. The improvement in microvascular perfusion was associated with a decrease in lactate levels. The authors failed to notice differences in microcirculatory effects with administration of albumin 4% compared with crystalloids. More interestingly, the authors evaluated the effects of fluids at two different phases of sepsis: 37 patients were investigated within 24 h of diagnosis of sepsis and 23 patients after more than 48 h. Microvascular perfusion improved in all patients investigated early after diagnosis of sepsis, whereas it was unchanged in patients investigated later (Fig. 2.1).

Importantly, whatever the time at which fluids were administered, the microvascular effects of fluids were dissociated from the impact on global haemodynamics, as patients who had improved cardiac output in response to fluids sometimes failed to show improved microcirculation, whereas patients who failed to show increased cardiac output sometimes demonstrated improvement in microvascular perfusion in response to fluids. These results were confirmed by Pottecher et al. [17], who restricted fluid administration to patients who were predicted to be fluid responsive by a passive leg-raising test. In all patients, microcirculation improved in response to initial fluid administration, but a second fluid bolus, which further increased cardiac output, failed to further improve microvascular perfusion.

Hence, fluids may have a place in microvascular resuscitation at early stages of sepsis but fail to affect the microcirculation at later stages, independent of their global haemodynamic effects.

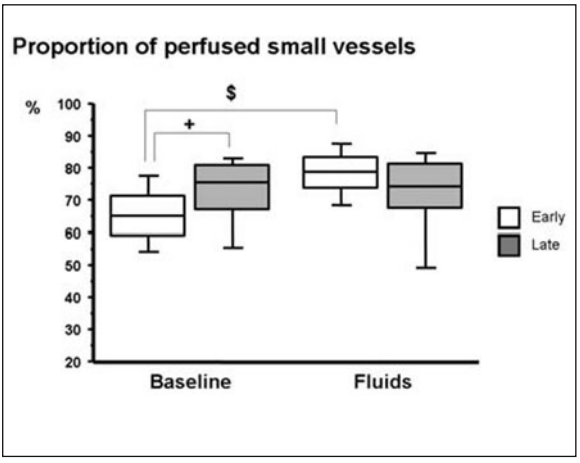

Fig. 2.1 Effects of fluids on sublingual microcirculation in patients with septic shock. Patients investigated within 24 h of diagnosis of severe sepsis (n = 37) are represented by white rectangles; patients investigated after 48 h of diagnosis (n = 23) by grey rectangles. + $p < 0.01$ between the two groups; *$* $p < 0.01$ fluids vs baseline. Reprinted from [16], with permission

2.2 Effects of Red Blood Cell Transfusions

The effects of packed red blood cells are quite controversial, with some data suggesting that red blood cell transfusion can improve microcirculation perfusion [18] and others showing the opposite effect [19]. Even if severe anaemia may weaken microcirculatory oxygenation [20], less severe haemodilution may be beneficial so that the effects of red blood cell transfusions should be analysed according to baseline haematocrit. The effect of storage time and the presence or absence of residual leucocytes in the transfused products can represent important factors affecting the microvascular response to red blood cell transfusions.

In 35 patients with severe sepsis, Sakr et al. [21] evaluated the effects of transfusions of 1–2 U of red blood cells. Transfusion failed to affect microvascular perfusion, as both capillary density and proportion of perfused vessels remained unchanged. However, this apparent absence of change masked a dichotomous response: patients with markedly altered microcirculation at baseline demonstrated improved microcirculation, whereas patients with relatively normal microcirculation showed deteriorated microcirculation during red blood cell transfusions. There was no relationship between microcirculatory changes and age of red blood cells. Hence, red blood cell transfusions can either be beneficial or detrimental for microcirculation.

2.3 Effects of Inotropic Agents

The role of adrenergic agents is unexpectedly less well defined. Some data are available regarding the role of beta adrenergic stimulation. Several experimental studies reported that dobutamine improves microcirculatory blood flow [22, 23], probably via a vasodilatory effect on arterioles or a decrease in leukocyte adhesion to the endothelium. In patients with septic shock, dobutamine moderately improved sublingual microcirculation, but these effects were quite variable and independent from its systemic effects [24]. In experimental animal models, phosphodiesterase inhibitors [25] and levosimendan [26] were shown to have similar effects on microcirculation, but human data are lacking.

2.4 Effects of Vasopressor Agents

Even though the various alpha adrenergic agents have now been tested in large-scale, randomised trials [27], their effects on microcirculation are less well defined. These may depend on site, dose and setting. In normal conditions, the topical application of norepinephrine induces arteriolar vasoconstriction, whereas intravenous administration of norepinephrine did not affect the rat proximal (A2) arterioles [28]. However, microvascular diameter and perfusion decreased in distal arterioles and capillaries, which was associated with decreased intravascular partial pressure of oxygen (PO_2) [29]. However, correction of severe hypoten-

sion with norepinephrine was associated with a non-significant improvement in microvascular perfusion [30]. Human data are lacking regarding the effects of alpha adrenergic drugs on microcirculation. Ledoux et al. [31] reported, using the laser Doppler technique, that increasing mean arterial pressure with norepinephrine from 65 to 85 mmHg did not affect skin microcirculatory blood flow. Similar results were later observed by other groups [32, 33]. Interestingly, one of those studies looked at individual responses and identified baseline microvascular perfusion as a key determinant for the response to norepinephrine: microvascular perfusion improved in patients with markedly altered microvascular perfusion at baseline, whereas it deteriorated it in patients with less abnormal microcirculation.

The effects of vasopressin are not well defined. Albert et al. demonstrated that vasopressin preserved renal blood flow in endotoxaemic rabbits [34], whereas a major decline in gut perfusion occurred in rats submitted to coecal ligation [35]. In another animal model of experimental endotoxic shock, vasopressin slightly but non-significantly increased gut mucosal perfusion, but this effect was similar to that of norepinephrine [30]. Differences in the arteriolar vasoconstrictive response between vasopressin and norepinephrine have been shown in the dorsal skinfold of hamsters [29]. Reduction of arteriolar diameter and arteriolar blood flow in large (A0) arterioles was significantly more pronounced in animals treated with vasopressin. Data in humans are actually restricted to case descriptions. Dubois et al. [36] reported no deterioration in sublingual microcirculation in patients with severe vasodilatory shock treated with low doses of vasopressin. Larger series are clearly required to better define microcirculatory effects of vasopressin in humans with circulatory failure.

2.5 A Place for Vasodilatory Agents?

Other strategies, and especially vasodilatory agents, can be used to manipulate microcirculation in sepsis [37]. Among them, nitric oxide (NO) donors may appear promising. Animal data suggest that NO deficiency accentuates microcirculatory alterations [38]. We [8, 9] observed that microvascular alterations were fully reversible after topical application of a high dose of acetylcholine, suggesting that vasodilators may be of value. This was further corroborated by Spronk et al. [39], who reported that nitroglycerin improved sublingual microcirculation. Unfortunately, it also induced marked hypotension. In addition, the potential cytotoxic effects of NO donors should not be neglected. In patients with cardiogenic shock, nitroglycerin improved sublingual microcirculation in a dose-dependent manner, and these effects occurred independently of changes in global haemodynamics [40]. In a randomised trial of 70 patients with septic shock, Boerma et al. [41] observed that nitroglycerin and placebo similarly affected microcirculation. Of note, the microcirculation was already close to normal at baseline in these patients, and the chances of affecting it were hence quite minimal. At this stage, the beneficial effects of nitroglycerin on diseased microcirculation remain hypothetical, and further studies are clearly needed before this intervention can be recommended at bedside.

2.6 Effects of Agents with Anticoagulant Properties

Among therapies with anticoagulant properties, activated protein C is particularly promising. Several experimental studies have shown that activated protein C improves microcirculation of various organs [42–44]. These effects may be mediated by inhibition of rolling/adhesion leucocytes to endothelium [42–44], perhaps by preserving endothelial glycocalyx [44]. Similar effects were found in patients with septic shock receiving activated protein C [45].

2.7 Conclusions

Microvascular alterations are frequent in critically ill patients, especially in patients with septic shock, and their severity has been shown to be associated with outcome. These alterations can be improved by topical application of acetylcholine or intravenous administration of nitrates. Microcirculatory effects of other interventions more classically used to improve global oxygen delivery are less well defined. Fluids, especially colloids, and dobutamine have been shown to improve microcirculation, whereas red blood cell transfusions have more variable effects. Experimental studies suggest that activated protein C may improve the septic microcirculation.

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Part III
Kidney

Renal Injury

3

V. Gašparović, I. Gornik

3.1 Introduction

Renal injury is a clinical syndrome characterised by progressive deterioration of renal function. In acute renal injury, the deterioration of kidney function occurs rapidly, over a period of days or weeks. It is often precipitated by a wide range of disorders affecting multiple organ systems. Conversely, renal dysfunction may develop gradually and is then termed chronic renal failure (CRF). Abrupt decline in renal function results in a potentially lethal condition if not promptly addressed. The disturbance in the internal milieu is manifested by azotaemia and multiple electrolyte imbalances. The development of CRF is far more insidious. The initial, barely noticeable, laboratory disarray will over time progress to major disturbances, warranting a variety of supportive treatments. Acute renal injury is a reversible event. Its resolution depends upon successful management of the underlying condition leading up to it. CRF, in contrast, is an irreversible condition. Whereas its exacerbations may be resolved upon recovery from the event that led to it, the underlying level of renal dysfunction will never recover. It should be mentioned that renal failure may at times be termed as subacute. It occurs gradually, over a period of several weeks, and results in high levels of azotaemia with a potentially poor outcome. The classification of renal injury into acute, subacute and chronic form is pivotal for the understanding and management of these pathologic entities.

3.2 Definition

The defining attribute of acute kidney injury (AKI) is rapid decrease of glomerular filtration rate (GFR) coupled with impaired excretion of uraemic toxins. Multiple conditions can provoke AKI. Most commonly, AKI is characterised by either oliguria (<500 ml of urine produced over 24 h) or anuria (<100 ml of urine produced over 24 h). Patients suffering from the nonoliguric form of acute renal injury (ARI) produce more than 500 ml of urine over 24 h.

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3.3 Epidemiology

AKI affects 2–5% of patients admitted to hospital wards and as many as 10–30% of patients in surgical or medical intensive care units.

3.4 Aetiology

The aetiology of AKI is multifactorial, and in many cases, more than one predisposing condition can be identified. The classification of AKI differentiates between prerenal, intrinsic renal and postrenal azotaemia. Approximately 75% of AKI cases is caused by prerenal problems, i.e. insufficient blood flow to the kidneys leading up to functional disturbances. Most of these patients will show no evidence of end-organ damage once the underlying condition has been corrected. Intrinsic azotaemia accounts for approximately 20% of AKI cases. Injury to the kidney may be predominantly vascular, glomerular or tubular. Postrenal azotaemia is the least frequent form of AKI. It develops secondary to urinary tract obstructions (Table 3.1).

3.5 Differences Between Acute and Chronic Kidney Injury

Differentiating between AKI and chronic kidney injury may not, at times, be a simple task. It is vital to identify AKI to promptly discover and treat its underlying cause. The finding of normal serum creatinine values prior to the development of renal failure is definitive proof of an acute nature of kidney dysfunction. Patients suffering from CRF are more susceptible

Table 3.1 Aetiology of acute kidney injury (AKI)

Prerenal AKI	Intrinsic renal AKI	Postrenal AKI
Hypovolaemia (vomiting, diarrhoea, burns, fluid loss via fistulae)	Acute renal parenchymal diseases (glomerulonephritis, vasculitis, interstitial nephritis, acute tubular necrosis, malignant nephroangiosclerosis)	Obstruction of both ureters (intraluminal, extraluminal)
Worsening cardiac performance		Impaired urinary bladder emptying (prostatic hyperplasia, urinary bladder cancer, neuropathic bladder)
Peripheral vasodilatation		Obstruction of urethra
Renal vasoconstriction		
Renal artery stenosis/ obstruction		

to various noxious factors that may provoke renal failure, even in healthy individuals. Longer duration of symptoms, frequent nocturnal urination, long-standing hypertension, chronic anaemia and pruritus all point to the diagnosis of CRF. Anaemia, hypocalcaemia and hyperphosphataemia may develop quickly in AKI and are, therefore, not very useful in differentiating between AKI and CRF. Conversely, normal complete blood count in the setting of azotaemia typically indicates AKI. The notable exception to this rule is polycystic renal disease with azotaemia. Renal osteodystrophy develops after long-standing and severe chronic renal insufficiency. Smaller kidney dimension is a manifestation of chronic renal disease, whereas normal or even enlarged kidneys are usually seen in AKI. Unfortunately, kidney size is fairly non-specific, as CRF may be accompanied by normal kidney dimensions in conditions such as multiple myeloma, diabetic nephropathy and amyloidosis. Renal size may best be evaluated by ultrasound. Normal values are between 10 and 12 cm. An estimation of kidney size may also be obtained from plain abdominal radiographs.

3.6 Prerenal Acute Kidney Injury

3.6.1 Aetiology of Prerenal AKI

Prerenal AKI may be caused by any of the following:

- lack of intravascular volume: vomiting, diarrhoea, haemorrhage, insufficient fluid replacement;
- decreased effective circulating volume: cardiogenic shock; congestive heart failure; pericardial tamponade; massive pulmonary embolism; vasodilatation in septic, anaphylactic or posttraumatic shock;
- occlusion of renal blood vessels;
- intrarenal vasoconstriction (endotoxin, radiopaque contrast);
- disturbed renal autoregulation (medications, with marginal hypovolaemia).

3.6.2 Pathophysiology of Prerenal AKI

Hypovolaemia (true or functional lack of circulating volume) leads to hypotension and secondary activation of cardiovascular baroreceptors, the sympathetic and renin-angiotensin-aldosterone systems, as well as to the release of various vasopressors, including vasopressin. During episodes of hypotension, glomerular filtration rate (GFR) is maintained via vasodilatation of preglomerular arterioles and vasoconstriction of efferent arterioles. Failure of autoregulation in the setting of hypovolaemia will lead to prerenal kidney dysfunction. The net result of the imbalance between vasoconstrictors (catecholamines, angiotensin II, vasopressin, endothelin) and vasodilators (nitric oxide, atrial natriuretic peptide) is a decrease in GFR. The higher concentration of intracellular calcium leads to an

increased susceptibility of smooth muscle cells of afferent arterioles to vasoconstrictors.

Decreased renal perfusion due to vasoconstriction may also be the result of bacterial endotoxins, hypercalcaemia, non-steroidal anti-inflammatory drugs (NSAIDs) and immunosuppressant drugs. NSAIDs decrease the synthesis of vasodilatory prostaglandins PGE2 and PGI2 and therefore contribute to impaired renal perfusion. In the event of reduced renal perfusion, GFR may be maintained by increasing the vascular tone of the efferent arteriole as a result of increased availability of angiotensin II. Medications that block the renin-angiotensin system will counteract this effect and may thus provoke azotaemia. Prerenal azotaemia is reversible with prompt restitution of adequate kidney perfusion. Long-lasting hypoperfusion, however, will lead to irreversible acute tubular necrosis (ATN) and thus intrinsic renal failure. Elderly individuals, diabetics and patients with a known reduction of renal function are more susceptible to the deleterious effects of hypovolaemia and will, therefore, develop renal failure sooner.

3.7 Intrinsic Acute Kidney Injury

3.7.1 Aetiology

Intrinsic AKI can be caused by the following:

- long-lasting renal hypoperfusion: evolution of functional prerenal AKI into acute tubular necrosis;
- kidney infection or reaction to systemic infection: septic conditions caused by aerobic and anaerobic bacteria, leptospirosis, viral haemorrhagic fever etc.;
- kidney diseases: acute glomerulonephritis, non-bacterial interstitial nephritis, systemic diseases that affect kidneys (disseminated intravascular coagulation, microangiopathies and malignant nephroangiosclerosis);
- exogenous toxins: nephrotoxic drugs, iodine contrast agents, intoxications (ethylene glycol, organic solvents, heavy metals);
- endogenous toxins: pregnancy toxicosis, liver insufficiency, acute pancreatitis, haemolysis, rhabdomyolysis;
- metabolic disorders: hypercalcaemia, hyperuricaemia;
- physical and chemical agents: burns, frostbites, electrical injury.

The underlying cause of intrinsic AKI is a haemodynamic disturbance in more than 50% of cases (systemic vasodilatation, renal vasoconstriction). This is most often related to sepsis. Exogenous nephrotoxins (i.e. drugs) cause AKI in 25% of cases in this population and are responsible for an additional 20%, whereas primary renal diseases cause 5% of intrinsic AKI.

3.8 Pathogenesis of Acute Intrinsic Kidney Injury

The three major mechanisms of induction of intrinsic AKI are:

1. disturbed haemodynamics: vasoconstriction of the afferent arteriole reduces glomerular blood flow and therefore GFR. Blood flow is also reduced in the peritubular capillary network, which leads to tubular hypoxia and destruction of cellular structure;
2. glomerular problem: changes at the level of the glomerular endothelium and filtration membrane may reduce permeability of the glomerular filter and thus a reduction in GFR ensues;
3. tubular problem: sublethal injury to tubular cells by hypoxia or nephrotoxins renders them incapable of preventing fluid return from the tubules into the peritubular capillary network, thus annihilating the effects of glomerular filtration. This results in azotaemia. Necrotic tubular cells, haemoglobin and myoglobin cylinders, sulphonamides, urate and oxalate crystals may all be found within the tubular lumen, all of which lead to impairment in urine flow.

3.9 Postrenal Acute Kidney Injury

Obstruction of urinary pathways is an important cause of AKI and is usually easily manageable. It is mostly associated with prostatic hyperplasia but may be seen in patients with a single kidney and those suffering from pelvic malignant disease. In order for AKI to develop, the obstruction must either affect both kidneys or the patient's only kidney. The sites of obstruction vary and may include any location from the renal pelvis to the urethra. The causes include local changes in the lumen or the wall of urinary pathways but may also be extraluminal. The most common cause of lower urinary tract obstruction is prostatic hyperplasia, which may be either benign or malignant in origin. In women, the predominant reason for lower urinary tract obstruction is pelvic malignancy (cervical cancer) or radiotherapy.

One should have a high index of suspicion for obstructive postrenal AKI in the event of abrupt anuria, significant variations in urine quantity, history of nephrolithiasis or bladder emptying disorders and progressive renal insufficiency with normal urine analysis.

3.10 Clinical Presentation of Acute Kidney Injury

The initial stages of the presentation are dominated by symptoms of the underlying disease that provoked AKI. This is followed by oliguria, with a qualitative change in urine that becomes darker due to the presence of blood elements and necrotic by-products. There is an in increase in the serum concentration of blood urea nitrogen (BUN). Urine osmolality becomes similar to serum osmolality due to the incapability of the kidneys to concentrate urine. In approximately 20% of patients, urine output is maintained despite the occurrence

of AKI as evidenced by an increase in BUN and a drop in urine osmolality. Total anuria is a rare occurrence in AKI and indicates a likely postrenal obstruction.

Should the fluid intake surpass the urine output by a significant enough volume, this will result in peripheral or pulmonary oedema. This may be accompanied by transudation of fluid and hypertension. Nausea and fatigue are symptoms commonly seen at this stage of clinical presentation. Hydrogen ions are not adequately removed by the kidneys, and they may be produced at an increased rate. Their accumulation will lead to metabolic acidosis and Kussmaul breathing. Hyperkalaemia leads to muscular weakness, arrhythmogenesis and an increased risk of diastolic cardiac arrest. Hyperkalaemia may induce typical electrocardiographic (EKG) changes, but their absence is not infrequent. Multiple symptoms are exacerbated with worsening degrees of azotaemia. These include nausea, vomiting, stupor and muscle twitching.

Some of the most common effects of renal failure on various organ systems are the following:

1. cardiopulmonary manifestations: pulmonary congestion with transudation of fluid into the alveoli with resultant pulmonary oedema and pleural effusions. Diastolic hypertension is evident in 25% of patients. Arrhythmias may be present, as may be pericarditis accompanied by chest pain. The potential for cardiac tamponade also exists;
2. neurological manifestations: advanced renal insufficiency may present with diminished levels of consciousness. Muscle spasms may be present, and in severe cases, convulsions have been described. The underlying causes are cell oedema, acidosis and electrolyte imbalances;
3. gastrointestinal (GI) manifestations: worsening renal function is followed by increased vascular fragility, oedema and injury to the gastrointestinal (GI) mucosa due to retention of urea and excess fluid. Erosive gastritis is often seen, as are gastric and duodenal ulcerations. Additional symptoms include vomiting, diarrhoea and GI bleeding;
4. haematological manifestations: accumulation of uraemic toxins leads to the depression of erythropoiesis, reduced levels of erythropoietin and haemolysis.

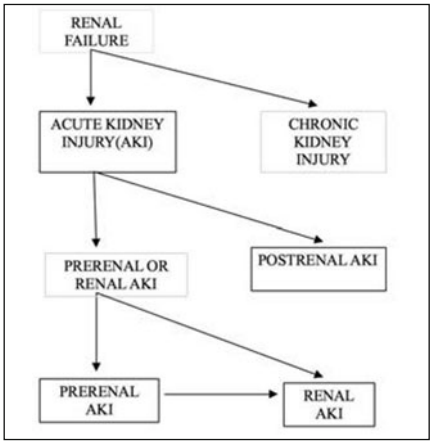

Fig. 3.1 Diagnostic algorithm for acute kidney injury

This leads to normochromic normocytic anaemia. Endothelial dysfunction may provoke disseminated intravascular coagulation, with secondary derangements in the local microcirculation. In some cases, thrombocytopoenia is also present;

5. infection: infections remain one of the most common manifestations of renal injury. Predisposing factors include artificial ventilation, impaired consciousness, decreased cough reflex, aspiration, invasive vascular access, urinary catheterisation and various invasive urinary tract procedures. Infections are responsible for two thirds of deaths in patients with AKI and are mostly caused by hospital-acquired bacteria.

3.11 Diagnostic Algorithm and Differential Diagnosis

The diagnosis of kidney injury cannot be conclusively established based only upon clinical signs and symptoms. Laboratory findings of increased serum creatinine and BUN are necessary. It is very important to follow these laboratory tests longitudinally to continuously assess the dynamics of renal failure. The diagnostic procedure is presented in tabular form below (Fig. 3.1).

3.11.1 Postrenal AKI

The presence of urinary tract obstruction must be ruled out in every patient suffering from AKI. Re-establishment of urinary flow will treat the kidney dysfunction, whereas unrecognised long-standing urinary tract obstruction will eventually lead to irreversible kidney damage. A distended bladder in patients suffering from lower urinary tract obstruction can be palpated. Often, urinary bladder catheterisation is all that is required, although in certain cases, one must resort to suprapubic bladder drainage. Obstruction leads to proximal dilatation of urinary pathways, which may be documented by ultrasound, computed tomography and antegrade or retrograde ureteropyelography. Antegrade ureteropyelography is performed by inserting a catheter into the renal pelvis, whereas retrograde ureteropyelography is performed by inserting a catheter into the bladder cystoscopically and injecting contrast into the ureteral orifices.

3.11.2 Prerenal or Intrinsic Renal AKI?

It is paramount to rule out hypovolaemia as the cause of AKI. A detailed medical history must be taken and special attention paid to fluid losses, such as vomiting, diarrhoea, sweating, bleeding, through a nasogastric tube, biliary fistula, etc. The clinical examination may reveal dehydration, dry mucosal membranes, tachycardia, orthostatic hypotension and poor filling of jugular veins in a recumbent position. Invasive monitoring may reveal a central venous pressure lower than the expected 8–12 cm water (H_2O) (0.78–1.2 kPa). In such a scenario, fluid replenishment is vital. This simple manoeuvre will restore diuresis if the azotaemia is truly prerenal. If this does not occur, intrinsic renal failure has developed.

3.12 Treatment of Acute Kidney Injury

It is very important to identify and treat the underlying disease that led to renal failure. Furthermore, one must monitor and treat some clinical parameters.

3.12.1 Fluid Balance

Fluid deprivation will be indicated by dry mucosal membranes, dry skin, hypotension, tachycardia and low central venous pressure (CVP). The intravascular volume should be supplemented by isotonic fluid, with the exception of bleeding, when volume should be replaced by packed red blood cells. Fluid loss may be precipitated by vomiting, diarrhoea, sweating and through various fistulae. Excess nasogastric tube output leads to excess chloride loss. Biliary loss will be accompanied by a bicarbonate (HCO_3) deficit. This emphasises the fact that volume replenishment must be supplemented by various electrolytes and additives, depending upon the aetiology of fluid loss. The daily net fluid deficit is about 400 ml and is the result of endogenous water formation in the amount of 400 ml and insensible fluid losses in the amount of approximately 800 ml. This daily net fluid deficit must be incorporated into calculations regarding daily fluid supplementation. Every effort should be made to alter the oliguric form of AKI into non-oliguric AKI, as this greatly facilitates fluid management, which is constantly affected by i.v. fluid supplementation as well as enteral and parenteral nutrition.

3.12.2 Hyperkalaemia

Excess serum potassium is a potentially lethal electrolyte imbalance, as it may lead to cardiac arrest. Hyperkalaemia may be urgently treated by 10–30 ml of 20% solution of calcium gluconate due to the rapidity of is action. Calcium antagonises the effects of hyperkalaemia on cardiac myocyte polarisation. Insulin will stimulate the sodium-potassium-adenosine triphosphatase (Na-K-ATPase) interaction, which promotes entry of potassium ions into the cell and hence reduces the serum concentration of potassium. Simultaneous administration of glucose will prevent hypoglycaemia. One of these strategies is to infuse 200–500 ml of 10–20% glucose solution with 1 U of insulin per 3 g of glucose. $NaHCO_3$ may also reduce the serum content of potassium by stimulating its transfer from the extracellular into the intracellular space. This effect is the result of the buffering capability on hydrogen ions exerted by $NaHCO_3$. The effects of insulin and HCO_3 take about an hour to become appreciable and last for about 6 h. Ion exchange resins will lead to increased potassium loss by exchanging it for sodium, calcium or aluminium ions in the GI tract. They are administered two to three times per day by mouth or as an enema. The serum potassium levels will begin to decline 2–3 h afterwards.

3.12.3 Metabolic Acidosis

Metabolic acidosis should be treated with an 8.4% solution of $NaHCO_3$. The volume of $NaHCO_3$ needed for the pH to be increased by 0.1 is calculated from the following formula: $6 \times 0.3 \times$ body weight (kg).

3.12.4 Diet

In patients with AKI, it is important to closely monitor the oral and i.v. intake of sodium, potassium and water. In patients already enrolled in a renal replacement therapy (RRT) programme the dietary regime may be less strict. The modern management dogma no longer includes protein restriction, as the increased rate of catabolism may lead to degradation of enzymatic proteins that are critical to cell function. The energy requirement of patients with AKI ranges from normal values (146.3 kJ/kg or 35 kcal/kg) to increased ones (200–282 kJ/kg or 50–70 kcal/kg), as is seen in the setting of extreme catabolism. In patients who are unable to meet their needs by oral intake or by a feeding nasogastric tube, parenteral nutrition must be instituted. It has to meet the patient's calorie requirements, which are increased due to the aforementioned catabolism.

3.12.5 Indications for Haemodialysis

In patients suffering from oliguric AKI, there is nothing to gain by postponing RRT. Instead of restricting fluid intake and awaiting the development of uremic symptoms, one should commence dialysis early and provide simultaneous hyperalimentation. Dialysis is necessary if more conservative methods of treating hyperkalaemia, hypervolaemia or metabolic acidosis fail. Once serum creatinine reaches 400 μmol/L or the potassium concentration exceeds 6 mmol/L in a patient with oliguric renal failure, haemodialysis should be promptly instituted to prevent the development of uraemic syndrome with its associated complications. RRT facilitates regulation of electrolyte and fluid balances, as well as the acid-base status, and eliminates toxic nitrogen products. Dialysis may be performed intermittently for several hours on a daily basis or continuously over a 24-h period. Continuous methods of haemodialysis should be used in haemodynamically unstable patients suffering from AKI. The most commonly used modality is continuous venovenous haemofiltration (CVVH), which is based on convective clearance. Continuous methods of RRT allow for hyperalimentation with large volumes of infusions. Various modifications of RRT may be implemented depending upon the degree of catabolism, volume overload or haemodynamic stability. The dosing of haemofiltration is influenced by choosing the volume of filtration and its simultaneous replacement. Procedures characterised by high efficacy (with large volumes of filtration) improve patient outcomes. In the event of substantial catabolism coupled with inadequate management of small molecules (potassium, urea, creatinine)

with haemofiltration alone, the procedure may be expanded to include a dialysate flow. The ensuing diffusion (haemodialysis) will improve the elimination of small molecules. Such a combined procedure is termed continuous venovenous haemodiafiltration (CVVHD). It is important to ensure that dialysis duration is adequate for both metabolic and volume control. Larger doses of dialysis improve survival in this subset of patients. There is no conclusive evidence supporting the benefit of continuous methods of dialysis over intermittent ones. Peritoneal dialysis was once the most commonly used method of RRT in patients with AKI. It has been substituted by extracorporeal dialysis procedures due to their efficacy and reduced complications. Adult patients with AKI complicated by catabolism are poor candidates for peritoneal dialysis, as adequate metabolic control is unlikely to be achieved. It should also be avoided in patients who have had prior abdominal surgery.

3.13 Prognosis

Despite adequate replacement of kidney function, the mortality rate in AKI may be as high as 50%. The outcome is greatly influenced by the underlying condition that led to renal failure. AKI occurring as a complication of pregnancy has an approximate mortality of 15%. In contrast, death will occur in as many as 60% of patients developing AKI as a consequence of major trauma or surgery. Advanced age further compromises outcome, especially if AKI occurs as part of multiple organ failure. In the majority of survivors, renal function will recover, but in as many as 50% of those survivors, a subclinical impairment will persist. Only about 5% of patients will remain permanently dependent upon dialysis. Sometimes, temporary improvement in renal function is seen only to be followed by progressive deterioration.

3.14 Prevention

AKI is a life-threatening disorder that requires supportive management. Despite the advances in medical management, it is still associated with a high mortality rate. The cost of care and duration of treatment make it a substantial burden on healthcare resources. This emphasises the importance of measures aimed at preventing the development of AKI.

All patients admitted to a hospital due to any acute illness should have their BUN and serum creatinine determined. This should be complemented by the evaluation of serum electrolyte concentrations as well as the acid-base status. During the course of patient management, every effort should be made to diagnose AKI early and institute treatment as soon as it is discovered. Fluid input and output should be closely monitored. Patients more prone to developing AKI are those known to have underlying renal disease, elderly patients, diabetics and those suffering from congestive heart failure. The administration of iodine-based contrast agents may precipitate AKI in susceptible patients. Up to 10% of patients with preterminal renal insufficiency will require RRT following coronary angiography. The overall incidence of dialysis after left heart catheterisation is 1%. Contrast nephropathy may be prevented by maintaining adequate intravascular fluid status, minimising the volume of the appropriate contrast agent and discontinuing nephrotoxic drugs, such as NSAIDs, aminoglycosides etc.

Further Reading

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Part IV
Ventilation: Adult and Paediatric

Respiratory Mechanics: Principles, Utility and Advances

4

A.R. Carvalho, W.A. Zin

4.1 Introduction

Pulmonary gas exchange requires a continuous flow of fresh gas and blood through the alveoli and alveolar capillaries. Air flows from a region of higher pressure to one of lower pressure. At end expiration, the alveolar pressure is equal to atmospheric pressure, and during inspiration, the alveolar pressure must be less than atmospheric pressure. As the movements of the lungs are entirely passive, forces must be applied in order to expand the lungs, and as a consequence, alveolar pressure is decreased from its resting pressure at the end of expiration. In the case of spontaneous breathing, the respiratory muscles provide the external forces, whereas artificial ventilation moves the relaxed respiratory system [1]. During inspiration, the external forces must overcome the impedance of the lung and chest wall, the two components of the respiratory system. This impedance stems mainly from the force to overcome elastic recoil, the frictional resistance during the movement of the tissues of the lungs and thorax, and the force to overcome the frictional resistance to airflow through the tracheobronchial tree. The inertial component of gas and tissue is usually negligible during conventional ventilation [2].

At end inspiration, the potential energy accumulated in the elastic tissues of the lungs and thorax throughout inspiration is used to generate the pressure gradient that will favour exhalation. During spontaneous ventilation, the beginning of expiration is determined by the progressive and gradual inactivation of the inspiratory muscles [1]. On the other hand, a release exhalation valve avoids expiration during artificial ventilation. If non-elastic tissue and airway resistances are negligible, the elastic recoil causes the lung and thorax to return very rapidly to the resting expiratory level in a completely passive expiration. If expiratory resistances opposing elastic recoil are abnormally large, active contraction is necessary unless the expiratory time increases.

In this chapter, we present the pressures and resistances that determine the continuous flow of gas in and out of the lungs. For this purpose, we consider basic aspects of respiratory system mechanics, its utility in the clinical scenario and the most recent techniques applied at the bedside for patient monitoring and, most often, for optimising ventilatory support. Excellent review articles can be consulted if further details are desired [2–11].

APICE 23. Antonino Gullo (Ed.)

4.2 Principles

Both the lungs and the chest wall can be approximated to elastic structures, with transmural pressure gradient corresponding to stress and lung volume to strain. Over a certain range of volumes and pressures, lung and chest-wall structures obey Hooke's law. Thus, the change in lung and chest-wall volumes divided by the changes in the elastic pressure required to produce them yields compliance (C). Elastance (E) is the reciprocal of compliance, i.e. ΔPel/ΔV, and is usually expressed in centimetres of water per litre (cmH_2O/L).

$$\Delta Pel = Ers \cdot \Delta V \quad \text{or} \quad \Delta Pel = \frac{1}{Crs} \cdot \Delta V \qquad \text{(Eq. 4.1)}$$

Stiff structures present high elastance. Respiratory system elastance equals the sum of lung plus chest wall elastance (Ers = EL + Ew, respectively), whereas compliances are more difficult to be added: 1/Crs = 1/CL + 1/Cw.

4.2.1 Pleural Pressure

Because the variations in lung and chest wall volumes are virtually identical, compliances of the respiratory system, lung and chest wall vary according to the change in the transmural pressure (i.e. inside minus outside pressures) across these structures. Under static conditions the respiratory system (Prs), lung (PL) and chest wall (Pw) distending pressure are displayed in Figure 4.1:

PL is commonly referred to as transpulmonary pressure and can be calculated as:

$$PL = Palv - Ppl \qquad \text{(Eq. 4.2)}$$

where Palv represents alveolar pressure that equals airway pressure (Paw) or pressure

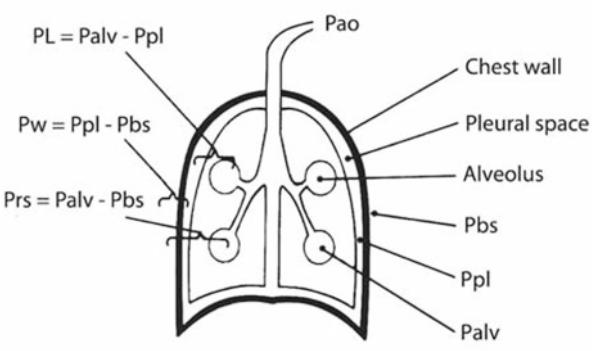

Fig. 4.1 Overview of respiratory system (Prs), lung (PL) and chest-wall (Pw) distending pressures under static conditions. *Pbs,* barometric pressure, *Ppl,* pleural pressure, *Palv,* alveolar pressure. Adapted from [12]

at the airway opening (Pao) under static conditions (zero flow) and in the face of an open glottis, and Ppl stands for intrapleural pressure. The chest wall or transthoracic distending pressure can be calculated as follows:

$$Pw = Ppl - Pbs \quad \text{(Eq. 4.3)}$$

where Pbs corresponds to the pressure at the body surface (usually barometric pressure). Considering that the transmural pressure of the respiratory system is the pressure across the lung and chest wall, we can write that:

$$Prs = PL + Pw \quad \text{(Eq. 4.4)}$$

and by substituting Eqs. 4.1 and 4.2 into Eq. 4.3, it follows that:

$$Prs = Palv - Ppl + Ppl - Pbs \quad \text{(Eq. 4.5)}$$

or:

$$Prs = Palv - Pbs \quad \text{(Eq. 4.6)}$$

As can be understood, the precise determination of swings in Ppl is of paramount importance when one needs to split respiratory-system mechanics into its lung and chest-wall components. However, in clinical practice, pleural pressure is not often measured because of all the risks involved in the procedure. Instead, one determines the variations in oesophageal pressure (Poes) that reflect quite accurately the changes in pleural pressure. Usually, a latex balloon or a liquid-filled catheter is placed in the lower third of the oesophagus; its correct positioning must be accomplished to achieve a perfect reading of the changes in intrathoracic pressure [13]. Complete descriptions of the techniques used to measure Poes can be found in the literature [14–16].

4.2.2 Elastic Recoil of the Lungs

The elastic recoil of the lungs tends to bring them all the way down to their minimum volume. In this manner, the elastic component (Pel,rs) of the total pressure applied to the respiratory system during inspiration is restored during expiration to promote expiration. In other words, the potential energy stored during inspiration returns to the system as kinetic energy. The passive volume–pressure (V-P) curve of the lung is almost linear (constant compliance) up to volumes around 80% of the total lung volume. Beyond this point, the curve flattens down (compliance decreases) mainly because the elastic limit of the lung is being reached and the structures stiffen. If transpulmonary pressure rises above 30 cmH_2O, the danger of tissue rupture may ensue.

4.2.2.1 Tissue Recoil

Two components account for the elastic recoil of the lungs [16]. One is represented by the elastic elements of lung tissue (mainly collagenous and elastic fibres). It is believed that the elastic behaviour of the lung does not depend strongly on the elongation of these fibres but mainly on their geometric arrangement. The network of pulmonary connective tissue interconnects all pulmonary structures (vessels, bronchioles, alveoli and so forth) and, as a result, they dilate during inspiration. This phenomenon is known as interdependence and contributes to keep the alveoli open, because if some of them collapse, their neighbours would tether their walls, tending to reopen them. In addition to the elastic properties of their tissues, the lungs present another component that contributes importantly to their elastic characteristics: the surface tension of the liquid lining the alveoli and distal air spaces.

4.2.2.2 Surface Tension

The air–liquid interface of the thin film of liquid that covers the surface of terminal respiratory units and probably also lines the luminal surface of terminal bronchioles displays surface tension, i.e. the molecules in the film attract each other along the surface. This component must also be overcome during inspiration: energy is stored throughout inspiration and returned during expiration. Pure liquids and solutions present a constant surface tension and obey Laplace's law:

$$P = K \cdot T/R \qquad \text{(Eq. 4.7)}$$

where P corresponds to the pressure inside a sphere, T represents the tension on its wall and R equals its radius. K corresponds to a constant. Thus, if two soap (constant T) bubbles with

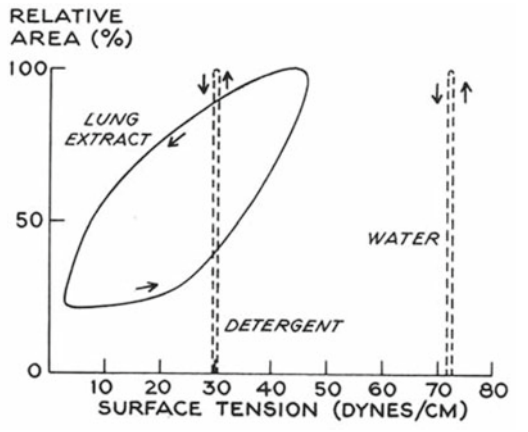

Fig. 4.2 Relationship between relative area and surface tension in water, detergent and lung extract. Pulmonary hysteresis results from the surfactant lining the alveoli; i.e. if the lung is slowly inflated from its degassed volume up to total lung capacity and subsequently deflated, two diverse limbs will result: an inspiratory limb, lower and to the right of the expiratory one. Adapted from [20]

different radii are connected, that with the shorter radius (and higher internal pressure) will empty into the bigger one (with a smaller internal pressure) until the two pressures become equal. If the same behaviour were found in the lung, one would expect that a great deal of its 300 million alveoli would discharge their gas content into the larger ones, yielding a massive atelectasis.

The liquid lining the terminal air spaces, however, is not a simple saline solution (constant T). Type II pneumocytes constantly secrete into this liquid layer a mixture of lipids (90%) and proteins (10%). As a result, the surface tension decreases well below that of a simple saline solution both in large and small alveoli [17, 18], as shown in Figure 4.2. Furthermore, the surface tension varies remarkably as the area of the surface layer changes, so that T and R in Laplace's equation vary proportionately and P remains equal in all alveoli. Larger alveoli present higher surface tension than their smaller neighbours, and the danger of atelectasis is avoided [19], as inferred from Figure 4.2. Pulmonary hysteresis constitutes the third phenomenon resulting from the existence of the surfactant lining the alveoli, i.e. if the lung is slowly inflated from its degassed volume up to total lung capacity and subsequently deflated, two diverse limbs will result: an inspiratory limb, lower and to the right of the expiratory one (Fig. 4.2).

The lung is known to be active in the synthesis of fatty acids, lipid esterification, lipid–ester bond hydrolysis and fatty acid oxidation [21]. Type II pneumocytes represent the main site of release of a surfactant, which they store in their lamellar bodies. The surfactant undergoes a constant turnover. Some molecules leave the surface film, whereas recently synthesised ones are added to it. The role of the surfactant can be easily appreciated by means of a simple experiment. Excised and degassed lungs are stepwise inflated with known gas volumes. At each step, airway pressure is also measured. After the total lung capacity is reached, known gas volumes are removed while the pressures continue to be determined. In the end, the V-P curve 2 in Figure 4.3 results. Note that the inspiratory and expiratory limbs are not superimposed, thus being characterised by pulmonary hysteresis. After this experiment, the lungs are filled with warm (37°C) saline solution [0.9% sodium chloride (NaCl)], and the aforementioned inflation and deflation manoeuvres are repeated. In this case, hysteresis is practically negligible. Furthermore, a smaller pressure is required to totally inflate the lung (Fig. 4.3, curve 1). One should keep in mind that when the lungs are inflated with a liquid, surface tension disappears as a consequence of the absence of the air–liquid interface. Some conclusions can be drawn from these experiments:

1. in the absence of surface tension, lung compliance results are higher than in the aerated normal lung;
2. pulmonary hysteresis occurs almost exclusively due to the surface tension of the air–liquid interface;
3. the pressure required to overcome tissue tension at any lung volume corresponds to the horizontal distance between the ordinate and curve 1;
4. at any lung volume, additional energy is required to overcome surface tension (distance between curves 1 and 2).

In order to stress the importance of the surfactant, curve 3 (Fig. 4.3) represents a condition in which the lung is filled with air but no surfactant lines the alveoli. It can be seen that the end-inspiratory lung volume in this case lies well below that obtained in the normal lung because of the presence of a large amount of atelectatic alveoli.

In summary, the lung component of the elastic pressure (part of the total applied pressure)

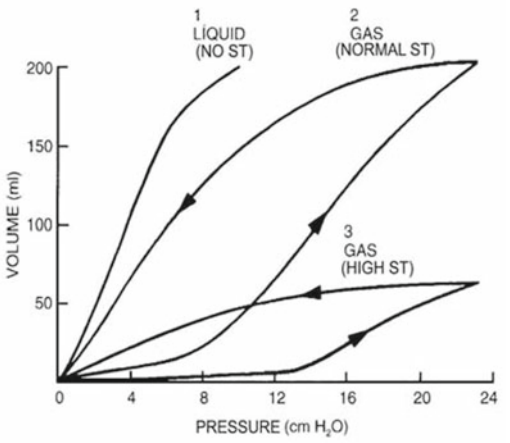

Fig. 4.3 Volume–pressure curves of excised and degassed lungs. Curve 2 represents lungs inflated stepwise with known gas volumes up to total lung capacity. Note that the inspiratory and expiratory limbs are not superimposed, thus displaying pulmonary hysteresis. Curve 1 represents lungs filled with warm (37ºC) saline solution [0.9% sodium chloride (NaCl)]. In this case, hysteresis is practically negligible. Furthermore, a smaller pressure is required to totally inflate the lung. Curve 3 represents a condition in which the lung is filled with air, but no surfactant lines the alveoli. It can be seen that the end-inspiratory lung volume in this case lies well below that obtained in the normal lung because of the presence of a large amount of atelectatic alveoli. Adapted from [22]

developed by the respiratory muscles or by a ventilator during inspiration overcomes two pulmonary elastic components: tissue forces and surface forces.

4.2.3 Elastic Recoil of the Chest Wall

Under the pathophysiological prism, the chest wall comprises all the structures that move during the breathing cycle, except the lungs. Thus, it also includes the diaphragm, the abdominal wall and the mediastinum, besides the thorax. A simple experiment can clarify this assertion: a person lies in the supine position, and to inspire, his/her diaphragm must produce some force (work) to push caudally the abdominal content and outwards the abdominal wall. If a 10-kg weight is placed on the top of his/her abdominal wall, the neuromuscular drive to the diaphragm will increase to cope with the added elastic load. Hence, any change in the abdominal wall will induce mechanical modifications in the respiratory system.

Naturally, the chest wall also exhibits elastic properties. It can be depicted for schematic purposes as a compressible and distensible structure that contains an appreciable volume in its resting state [23]. Whereas the lung always tends to retract to its minimum volume over the entire lung-volume range, the chest-wall elastic properties expand it from the residual volume up to about 75% of the vital capacity. From this point onwards, the chest-wall elastic forces change direction and favour its closure [23]. To calculate chest-wall elastance (Ew), transthoracic pressure (= Ppl – Pbs) is used in the numerator and divided

by the change in lung volume. As in the case of lung compliance, there is an elastic limit to the chest wall. From total lung capacity down to approximately 20% of the vital capacity, chest-wall compliance (Cw) is fairly constant. Below this point, it decreases progressively with the fall in lung volume.

Determination of the chest-wall elastance/compliance conveys important clinical information, as its elastic behaviour can be affected by a series of conditions, e.g. ascites, obesity, extremely voluminous breasts, vertebral ankylosis or severe kyphoscoliosis.

4.2.4 Elastic Recoil of the Respiratory System

For didactic purposes, it is useful to describe the recoil characteristics of the lungs and chest wall separately, but obviously they have to be appraised together. The two structures are in series with each other, and therefore, the elastic pressure of the total respiratory system (Pel,rs) constitutes the sum of the lung and chest-wall elastic pressures (Pel,L and Pel,w, respectively). Thus, the respiratory system V-P curve presents an S-shaped profile: limited at high lung volumes by the fall in lung compliance and at low lung volumes by the chest wall's smaller compliance. In a normal adult person, the expanding tendency of the chest wall exactly counterbalances the lung recoil at a lung volume approximating 35% of its vital capacity. This point on the V-P curve of the respiratory system represents the functional residual capacity and the system is said to be at its elastic equilibrium point. In other words, to inflate it from functional residual capacity (FRC), an inspiratory force must be applied, whereas exhalation below FRC demands an expiratory force.

As the lungs and chest wall recoil in opposite directions, forces tend to separate the visceral from the parietal pleura. Considering the pleural surface as a continuum, a virtual closed space (pleural space) is formed. A small amount of liquid exists in this space, which allows not only the coupling of visceral and parietal pleurae, thus yielding the transmission of forces between the two structures, but also generates a lubricated system that allows free and rapid movement of the lung in relation to the chest wall. Measurement of the Ppl at the elastic equilibrium point of the respiratory system (FRC) discloses a subatmospheric value, normally around –4 cmH_2O. This "negative" pressure reflects the net result of the forces acting on the pleurae (lung recoil and chest-wall expansion). During spontaneous inspiration, muscle contraction expands the chest wall and the parietal pleura pulls out the visceral leaflet. As a result, Ppl becomes more negative, reaching values around –7 or –8 cmH_2O during resting tidal breathing. Naturally, during expiration, it returns to its resting value. Ppl may become positive, though. For instance, it may increase during augmented ventilation as a result of physical exertion or during cough. Under these conditions, muscle force is directed to quickly diminish lung volume, and the parietal pleura compress the visceral ones. Ppl can also increase and become positive during artificial ventilation because now the positive pressure in the airways pushes the visceral pleura against the parietal leaflet.

Ppl should not be confounded with Palv. During spontaneous tidal breathing, Palv can reach –2 cmH_2O at midinspiration and rise to +2 cmH_2O at midexpiration. When airflow is null (end inspiration and end expiration), Palv equals Pbs. Palv is generated during inspiration as a result of the inspiratory muscle contraction and ensuing dilation of air spaces.

However, there is a resistance opposing the fast inlet of gas, and hence, Palv decreases. During expiration, the process is inverted.

4.3 Resistive Properties

So far, we have dealt with pressures related solely to the elastic properties of the respiratory system, which depends on gas volume and elastance of each component of the system, i.e. lung and chest wall. Pressure gradients generated by pure elastic forces are static and thus independent of the existence of airflow. When the respiratory system moves, an additional mechanical element must be overcome by the driving force of the system: resistance (R) or resistive pressure (Pres). Respiratory system resistance (Rrs) can be measured by dividing Pres,rs by airflow, where Pres,rs represents the respiratory system resistive pressure, or, in other words, the pressure used to overcome its resistive elements. Airway resistance and the resistance offered by the lung and chest-wall tissues contribute to Rrs. Rrs can be divided into RL (pulmonary resistance) and Rw (chest-wall resistance).

4.3.1 Pulmonary Resistance

Pulmonary resistance can be subdivided into airway resistance and lung-tissue resistance.

4.3.1.1 Airway Resistance

Airway resistance (Raw) depends on airflow in the lungs. As air is a fluid, the concepts of fluid dynamics can be directly applied to Raw. Thus, Raw can be defined as the ratio between the pressure gradient necessary to move gas from room air to the alveoli and airflow. If air flows in a tube, there is a pressure difference (ΔP) between the two extremities of the tube. This pressure gradient will depend on the airflow ($\dot{V}$) and its characteristics. In the face of low airflows, the gas molecules move smoothly along the entire length of the tube with different velocities. This constitutes the laminar flow. Under these circumstances, one can imagine a series of parallel ring-like sheets of fluid sliding past each other. The more external one has a longer perimeter (and surface) and, as a consequence, a higher shear force; its velocity will be small. The central lamina presents a minute area and thus a higher fluid velocity. In the face of laminar flow, resistance equals $\Delta Pres/\Delta \dot{V}$.

According to Hagen-Poiseuille's law:

$$\Delta Pres = \frac{(8 \cdot \eta \cdot L)}{\pi \cdot r^4} \cdot \Delta \dot{V} \qquad \text{(Eq. 4.8)}$$

thus,

$$R = \frac{(8 \cdot \eta \cdot L)}{\pi \cdot r^4} \quad \text{(Eq. 4.9)}$$

where η represents the gas viscosity, L is the length of the tube and r corresponds to the tube radius. One can quickly appreciate that the radius of the airways represents the main component of airway resistance, as it is raised to the power of 4. In this line, if the radius of the tube is halved, ΔP should be multiplied by 16 (= 2^4) if the same airflow were to be maintained.

If airflow increases, the gas molecules lose their laminar arrangement and turbulence ensues. This random movement of the gas molecules is called turbulent flow. The pressure required to keep this flow is substantially larger than that necessary to maintain a laminar flow. Under these conditions, the driving pressure is proportional to the squared flow:

$$\Delta Pres = K_2 \cdot \dot{V}^2 \quad \text{(Eq. 4.10)}$$

where K_2 is a constant. Turbulent flow depends on the density of the gas but not on its viscosity.

The tracheobronchial tree represents a complicated system of tubes with many branching points, changes in diameter and irregular surfaces. In a system such as the lung that branches out quite rapidly, laminar flow occurs solely in the small airways. Over the major portion of the tree, flow is transitional, and Rohrer's equation, where resistive pressure is determined by flow and also by its square, should be employed:

$$\Delta Pres = K_1 \cdot \dot{V} + K_2 \cdot \dot{V}^2 \quad \text{(Eq. 4.11)}$$

where K_1 relates to the laminar flow and K_2 to the turbulent component. Thus, for the same driving pressure, if no turbulence occurs, the second component of the equation becomes null, and all the pressure produces airflow. On the other hand, in the presence of turbulence, the same pressure must be split between the two components, and less energy is available to generate airflow, as part of it will be spent as heat by the turbulent flow [24].

As the radius constitutes the most important factor determining resistance through a tube, a thorough measurement of the cross-sectional area of each branching generation of the tracheobronchial tree was done. Interestingly, the narrower segment of the tree occurs in the central airways, somewhere around the segmental/subsegmental bronchi [25]. As a result, Raw is much higher in the central bronchi than at the lung periphery, which characterises the difficulty to measure peripheral airway resistance.

4.3.1.2 Pulmonary Tissue Resistance

Pulmonary tissue resistance results from energy loss generated by the viscosity pertaining to the movement of lung tissue itself. In other words, the molecules that constitute the tissue burn energy as heat as they move past each other. Formerly, tissue resistance was

regarded as negligible, but now it is known to be highly dependent on inspiratory duration [26], volume and flow [27–29].

4.3.2 Chest-wall Resistance

The shear forces developed during movement of the chest-wall tissues determines chest-wall resistance. Similarly to the pulmonary tissue resistance, chest-wall tissue resistance depends on volume and airflow [29–31]. Chest-wall resistance is not negligible in healthy individuals and may account for a substantial amount of energy expenditure in certain pathological conditions, compromising the unhindered movement of the chest wall.

4.3.3 Respiratory System Resistance

Respiratory system resistance is the net result of pulmonary plus chest-wall resistance. It thus follows that the simple measurement of Rrs may blunt the diagnosis of an important condition that could be localised in the abdomen, for instance.

4.4 Utility and Advances

During mechanical ventilation, inappropriate values for end-inspiratory and end-expiratory pressure likely increase the risk of lung-tissue damage and predispose to ventilator-associated lung injury [32]. For decades, static airway pressures (plateau pressure [33, 34]), respiratory system or lung compliance [35–38], the shape of the inflation as well as the deflation limb of the airway V-P curve and its derived parameters (inflection points [39] or airway-pressure-curve profile [39–41]) have been suggested to guide ventilatory life support adjustment in patients with acute lung injury (ALI). Assuming the constitutive properties of the respiratory system previously shown in Equations 4.1 and 4.8, one can write:

$$Paw(t) = Pres(t) + Pel(t) + P_0 \quad \text{(Eq. 4.12)}$$

where Pres and Pel are the resistive and elastic pressure, respectively, and P_0 is the end-expiratory pressure. Thus, Equation 4.12 can be rewritten as:

$$Paw(t) = Rrs \cdot \dot{V}(t) + Ers \cdot V(t) + P_0 \quad \text{(Eq. 4.13)}$$

This is the equation of motion of the single-compartment linear model. The variables of the model are Paw, $\dot{V}$ and V, and its parameters are Rrs and Ers. This model is linear because Rrs and Ers will not change with $\dot{V}$ and V, respectively. Historically, this equation

of motion of the respiratory system is often applied to the monitoring of respiratory system mechanical properties.

Despite being attractive, mostly because Paw, $\dot{V}$ and V are easily measured at bedside, the use of the airway pressure as a surrogate to overall lung impedance is quite limited. First, we must consider the chest wall, also taking into account the abdominal compartment, as an important component of respiratory system impedance [42]. Accordingly, to eliminate the thoracic component, Equation 4.12 must be slightly modified with the use of transpulmonary pressure (Eq. 4.2). Therefore, oesophageal pressure, an indicator of changes in pleural pressure adjacent to the oesophagus, must be measured. Second, the single-compartment model (Eq. 4.13) assumes that Rrs and Ers are linear and that the only forces opposing lung inflation are the resistive and elastic pressures, thus neglecting viscoelastic and inert properties, as well as ventilatory non-homogeneities [43]. Third, respiratory muscle tone must be suppressed or at least decreased for estimation of passive Rrs and Ers by Equation 4.13 [38].

Another important aspect related to the utility of monitoring respiratory system mechanical properties at bedside is the fact that airway pressure and flow are usually measured using the mouth as a window to the lung. Thus, the estimated Ers, Rrs or even indices derived from the airway pressure contours, such as stress index (an index associated with the rate of change in Ers throughout inspiration), may only be representative if the lung regional mechanical properties are uniformly distributed and well characterised by their mean value. It is important to bear in mind that all parameters derived from respiratory system mechanical properties are averages of thousands of interconnected structures. Accordingly, the estimated Ers is just a surrogate of the mean (most prevalent) elastic recoil of several alveoli disposed in parallel and interconnected. Thus, it is possible that in the absence of a prevalent behaviour, such as alveolar overdistension or recruitment, Ers may not change along a broad range of end-expiratory pressures, as normally occurs in experimental models and patients with ALI.

As recent advances in the monitoring of respiratory system mechanical properties, the use of the forced oscillation technique, in both spontaneously breathing and mechanically ventilated patients, seems to be quite attractive, as no sedation or muscle paralysis is required [44–46]. Additionally, the nonlinearities related to the volume dependence of the Ers and flow dependencies of the Rrs are quite low, as the amplitude and frequency of the oscillatory wave are small compared with the regular airway pressure and flow patterns [47].
Another attractive approach rests on the possibility of adjusting tidal volume to the actual size of the aerated lung compartment. For this purpose, the absolute lung volume at end expiration at a given end-expiratory pressure must be measured. Considering that the specific compliance of the normally aerated areas in ALI seems to be similar to that of healthy lungs, the reduction of tidal volume to levels proportional to the actual aerated volume seems to be in line with lung protection [48].

In summary, monitoring respiratory system mechanical properties represents an important tool at bedside for the institution of a more protective ventilatory approach in critically ill patients or in identifying respiratory functional disorders associated with chronic diseases. However, careful interpretation of each estimated variable should be always carried out considering the limitations of the used models and parameters in identifying the overall mechanical properties.

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Capnometry/capnography in Prehospital Cardiopulmonary Resuscitation

5

Š. Grmec, K. Lah and Š. Mally

5.1 Introduction

Capnometry is a measurement of end-tidal carbon dioxide ($etCO_2$). $EtCO_2$ represents a partial pressure or maximal concentration of CO_2 at the end of exhalation. Capnography is a measurement and a graphic display of the characteristic waveform against time or volume, known as the capnogram. CO_2 reflects cellular metabolism. There are four main stages of normal CO_2 physiology: production, transport, buffering and elimination. The principal determinants of $etCO_2$ are alveolar ventilation, pulmonary perfusion (cardiac output) and CO_2 production. Capnography is most commonly used during endotracheal intubation to identify correct placement of an endotracheal tube. During acutely low cardiac output, as in cardiac arrest, decreased pulmonary blood flow becomes the primary determinant resulting in abrupt decrease of partial pressure of $etCO_2$ ($petCO_2$). If ventilation and chest compressions are constant – with the assumption that CO_2 production is uniform – then the change in $petCO_2$ reflects the changes in systemic and pulmonary blood flow. Ultimately, it can be used as a quantitative index of evaluating adequacy of ventilation and pulmonary flow during cardiopulmonary resuscitation (CPR) [1, 2].

5.2 Physiology and Clinical Applications of Capnography

CO_2 is produced in tissues by aerobic and/or anaerobic cellular metabolism and is eliminated primarily through exhalation of gases via the lungs [minute ventilation (VE)]. CO_2 is transported in blood to the lungs by venous return, which is essentially equal to cardiac output [3]. It then diffuses from pulmonary capillaries into pulmonary alveoli. CO_2 storage and transport can also be represented in a hydraulic model in the form of a large peripheral tissue compartment and a small pulmonary compartment. VE is determined by tidal volume and respiratory rate per minute. Tidal volume is a volume of air movement during each breath and is composed of a dead-space ventilation (VD) + alveolar ventilation (AV).

APICE 23. Antonino Gullo (Ed.)

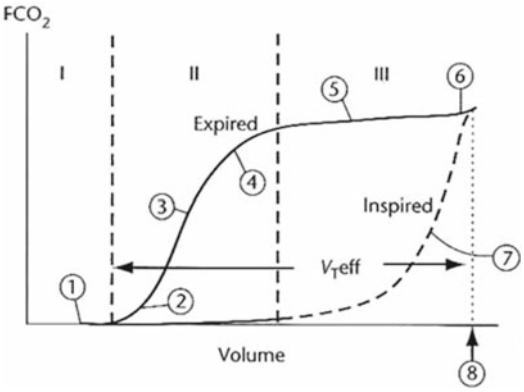

Fig. 5.1 Normal capnogram (adapted from [4]) PCO_2, partial pressure of carbon dioxide

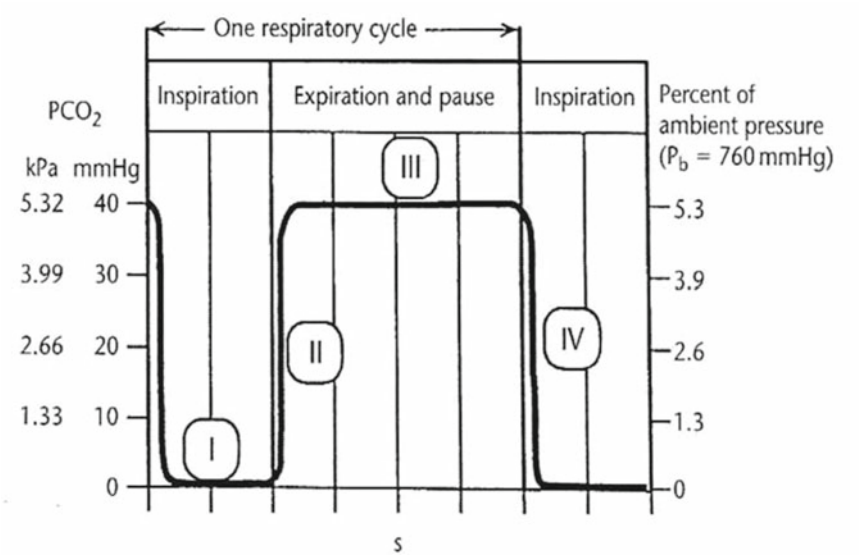

Fig. 5.2 Normal volume-based capnogram (adapted from [4]). *FCO_2*, fractional concentration of carbon dioxide; *VTeff*, effective tidal volume

Physiologic dead space includes anatomic and alveolar dead space. Alveolar dead space is directly related to the relationship between alveolar ventilation and perfusion (V/Q ratio). Assessment of $petCO_2$ may be misleading if not considered in the context of changing haemodynamics and ventilatory patterns. During normal V/Q ratio, partial pressure of arterial CO_2 ($PaCO_2$) and $petCO_2$ will be held within 1–5 mmHg of each other [p (a-e) CO_2 gradient; $PaCO_2 > petCO_2$] because not all areas of the lungs are perfused. In capnography, we look for: (a) presence of exhaled CO_2; (b) typical pattern of the capnogram. Characteristic parameters derived from capnogram are $petCO_2$, CO_2 production, pa-etCO_2 and dead spaces). If the end-expiratory CO_2 is not present, the reason for failure to ventilate the patient's lungs must be assumed (oesophageal intubation, accidental extubation, disconnection of breathing circuit,

cardiac arrest, apnoeic spells, complete obstruction of endotracheal tube, disconnection of CO_2 sample tube, water condensation or secretions in the sampling tube and capnograph failure). Independent of whether time- or volume-based capnography is used, the shape of the capnogram must be compared with the typical pattern (Fig. 5.1). In phase I, or inspiratory CO_2 baseline phase, the waveform is at zero (CO_2 in rebreathing is an exception). The capnogram demonstrates an increase in CO_2 pressure at expiration onset. During expiration (phase II), the first amount of gas comes from the CO_2 free anatomic dead space. After this initial exhalation, $petCO_2$ increases, reflecting CO_2 from the gas exchange regions of the lung. The capnogram plateau during this period of alveolar emptying (phase III) indicates that alveolar gas was sampled. The end portion of CO_2 elimination represents emptying of the distal alveoli and is the value associated with the end-tidal pressure measurement ($petCO_2$). After expiration, the fresh gas from breathing circuit (inspiration) rinses out the CO_2 from the previous exhalation, and there should be a decrease in CO_2.

Volume-based capnography (Fig. 5.2): a volumetric capnogram, unlike time capnography, plots partial pressure of CO_2 (pCO_2) as a function of expired volume during a single breath. Volumetric capnography measures variations in CO_2 concentration and tidal volume simultaneously during the respiratory cycle. The new "combined" monitoring device, which can measure CO_2 partial pressure of expired gas and airflow at the same time, makes it possible to plot CO_2 concentration against expired volume (achieved by the integration of flow signal), thus obtaining the volumetric capnogram.

Whereas changes in the amplitude of the capnographic curve suggest haemodynamic impairments, changes in the morphology are the expression of V/Q disturbances. In order to quantify these disturbances, several indices based on geometrical analysis of the curve have been developed, and among them, the slope of phase III is one of the most frequently used. Volumetric capnography also gives the opportunity to determine physiological dead space and its components with the equal area method. This method consists of tracing two lines: one is the back extrapolation of the phase III slope; the second is a vertical line passing through phase II, positioned so that the two areas p and q are equal (evaluation of the volumetric capnogram by Fletcher's method). The area Y corresponds to the exhaled amount of CO_2 and the areas Z + Y to the unexhaled CO_2 as a consequence of the anatomic (X) and alveolar (Y) dead space. Thus, for the physiological dead space, it holds that VD physiologic = ventricular tachycardia (VT) × (Y + Z) / (X + Y + Z). Carbon dioxide elimination (VCO_2) can also be calculated from volume capnogram and corresponds to the sum of the areas X and p. This information can easily be obtained with a combined CO_2/flow sensor. By plotting VCO_2 as a function of tidal volume, the alveolar ejection volume fraction can be calculated [1, 5, 6].

Alveolar dead space is directly related to the relationship between alveolar ventilation and perfusion. Conditions that increase alveolar dead space and potentially widen the p (a-et) CO_2 gradient are pulmonary emboli, shock (cardiogenic, hypovolaemic), left ventricular failure, cardiac arrest and chronic obstructive pulmonary disease (COPD) (Table 5.1). When perfusion is less than ventilation, less CO_2 is added to the alveolar emptying pattern. The result is a decrease in exhaled CO_2 from this alveolar unit. Pulmonary embolism can be distinguished from lung diseases such as COPD by exploiting differences in the shape of volumetric capnogram, specifically the slope of phase III (pulmonary embolism will decrease the slope of phase III towards the horizontal line, and COPD will generally result in an increased slope of phase III) [7, 8].

Current clinical applications of capnography are shown in Table 5.2.

Table 5.1 Factors that influence partial pressure of end-tidal carbon dioxide ($petCO_2$) values

Increase in $petCO_2$ values	Decrease in $petCO_2$ values
Metabolism	
Fever, tyrotoxicosis, malignant hyperthermia, $NaHCO_3$, venous CO_2 embolism, convulsions, shivering, yielding of muscular relaxation, infusion of carbohydrates, yielding of general anaesthesia, alkalosis	Hypothermia, sedation, muscular relaxation
Ventilation	
Decreased ventilation, bronchial intubation, partial airway obstruction, re-breathing, nontension pneumothorax	Hyperventilation, apnoea, complete airway obstruction, accidental extubation
Circulation	
Increased minute volume, high blood pressure, inotropic drugs, peripheral vasodilatation, replacement of blood volume	Decreased minute volume, peripheral vasoconstriction, hypovolaemia, peripheral shunts, cardiac arrest, pulmonary embolism
Technical errors	
Dry CO_2 absorber, incorrectly working valve and/or ventilator, inappropriate fresh air flow	Disconnection of breathing circuit, ventilator error, errors in capnometer/capnograph collection unit

$NaHCO_3$, sodium bicarbonate

5.3 Research of Capnometry/capnography in the Centre for Emergency Medicine, Maribor

5.3.1 Capnography/capnometry and Verification of Endotracheal Tube Placement

In our department, we realised two prospective clinical studies on the use of capnography in verification of endotracheal tube placement. In a prospective study in the prehospital setting, Grmec [9] observed all adult patients (>18 years) who were intubated by an emergency physician in the field. The position of the endotracheal tube was initially evaluated by auscultation. Capnometry and capnography were then performed with the infrared method. The physicians searched for the characteristic CO_2 waveform and at the same time determined the value of $petCO_2$. Over a 4-year period, 345 patients requiring emergency intubation were studied. Indications for intubation included cardiac arrest (246; 71%) and nonarrest (99; 29%) conditions. Capnography had 100% sensitivity and specificity in both arrest and nonarrest patients compared with capnometry, which had 88% sensitivity and 100% specificity in the arrest population. This study showed that if capnographic waveform during cardiac arrest and resuscitation is present, regardless

Table 5.2 Current applications of capnography

Clinical use	Clinical application
Endotracheal intubation	Quick detection of exhaled CO_2; verification of endotracheal tube placement
Detection of mechanical ventilation disconnection	Continuous monitoring of $petCO_2$ with endotracheal and tracheostomy tubes quickly alert the clinician of tube displacement if the capnogram is lost
Nasogastric tube placement	During insertion, capnography can be measured to assess presence of CO_2 to prevent tracheal placement of a nasogastric tube
Predictive prognosis of cardiopulmonary arrest	$PetCO_2$ measurements that do not increase in response to CPR represent a low chance of survival
Assessment of resuscitation efforts	Use of capnometry/capnography throughout a resuscitative effort will provide information regarding ROSC and response to resuscitation
Detection of alveolar dead space changes	$PaCO_2$ to $petCO_2$ gradients can be assessed for changes in alveolar dead space
Identification of alveolar emptying patterns	Capnogram waveforms can be analysed to assess expiratory pattern

CO_2, carbon dioxide; *$petCO_2$*, partial pressure of end-tidal CO_2;
ROSC, return of spontaneous circulation; *$PaCO_2$*, partial pressure of arterial CO_2

of its amplitude, the tube can be confidently judged to be correctly placed. Grmec and Mally [10] compared three different methods for immediate confirmation of tube placement in patients with severe head injury in a prospective study in the prehospital setting. Eighty-one patients were enrolled. The initial capnometry (sensitivity 100%, specificity 100%), capnometry after sixth breath (sensitivity 100%, specificity 100%) and capnography after sixth breath (sensitivity 100%, specificity 100%) were significantly better indicators for tracheal tube placement than was auscultation (sensitivity 94%, specificity 66%, $p < 0.01$). We concluded that auscultation alone is not a reliable method to confirm endotracheal tube placement in patients with severe head injury in the prehospital setting. It is necessary to combine auscultation with other methods, such as capnometry or capnography.

Our studies confirmed that the capnographic waveform monitor is the most reliable technique for identifying correct tube placement in both arrest and nonarrest endotracheal intubations. Based on the results presented, we made a suggested integral algorithm for tracheal tube confirmation and prevention of dislodgement in emergency intubation [11]. Verification methods should include a combination of clinical signs and the use of adjunctive devices, such as the presence of exhaled CO_2 and oesophageal detection devices. Once

correct placement has been confirmed, the endotracheal tube should be secured. Confirmation of tube placement is a dynamic process requiring ongoing patient assessment.

5.4 Capnography in Cardiac Arrest and Cardiopulmonary Resuscitation

There has been increased interest in the use of capnometry in recent years. During CPR, $petCO_2$ correlates with cardiac output and, consequently, has a prognostic value in CPR. In a prospective study, Grmec and Klemen [12] analysed the utility of $etCO_2$ as a prognostic indicator of initial outcome of resuscitation in adult victims of out-of-hospital, nontraumatic cardiac arrest. We prospectively analysed 139 adult patients. The initial, final, average, minimal and maximal $etCO_2$ was significantly higher in resuscitated patients than in nonresuscitated patients. Using an initial, average and final $etCO_2$ value of 10 mmHg correctly identified 100% of patients who were subsequently resuscitated, with an acceptable specificity (74.1%; 90%; 81.4%). Important observation from this study is that none of the patients with an average, initial and final $etCO_2$ level of <10 mmHg were resuscitated. Data from this prospective clinical trial indicate that initial, average and final $etCO_2$ monitoring during CPR correlates with resuscitation efforts. $EtCO_2$ monitoring has potential as a noninvasive indicator of cardiac output during resuscitation and a prognostic indicator for resuscitation. A similar study [13] was published by Grmec and Kupnik in which capnography was added to the Mainz Emergency Evaluation Scoring (MEES) system. In this prospective clinical study, we observed 246 adult patients who were found in nontraumatic normothermic cardiac arrest. We included all data collected from February 1998 to February 2001. Initial and final (post-CPR) values of $petCO_2$ were significantly higher in the group of patients with return of spontaneous circulation (ROSC) and in those who survived than in the group of patients without ROSC and those who died. All patients with ROSC and those who survived had initial values of $petCO_2$ >1.33 kPa (10 mmHg). The mean of all initial values of $petCO_2$ in patients without ROSC was 2.12 kPa ± 0.68, and the mean of all final values in patients with ROSC was 3.11 kPa ± 0.55. Our study showed that initial and final values of $petCO_2$ <2.13 kPa correlate with higher mortality rate and that values <1.33 kPa are incompatible with survival in normothermic nontraumatic cardiac arrest. The study confirmed that the MEES combined with capnometry in a new scoring system – MEESc – compared with MEES is significantly better and has greater value in predicting survival after CPR in patients with normothermic nontraumatic cardiac arrest.

Grmec, Lah and Tušek-Bunc [14] compared the initial $petCO_2$ with $petCO_2$ after 1 min during CPR in the prospective observational study and included two groups of patients: cardiac arrest due to asphyxia with asystole or pulseless electrical activity (PEA) as the initial rhythm, and cardiac arrest due to acute myocardial infarction or malignant arrhythmia ventricular fibrillation (VF) with VF or pulseless VT as the initial rhythm. $PetCO_2$ was measured for both groups immediately after intubation and then repeatedly every minute, both for patients with and without ROSC. We analysed 44 patients with asphyxial cardiac arrest and 141 with primary cardiac arrest. The first group showed no significant difference in the initial $petCO_2$ value, even when we compared those with and without ROSC. There was a significant difference in $petCO_2$ after 1 min of CPR between patients with and without ROSC. The mean value for all patients was significantly higher in the group with

asphyxial arrest. In the group with VF/VT arrest, there was a significant difference in the initial $petCO_2$ between patients without and with ROSC. In all patients with ROSC, initial $petCO_2$ was >10 mmHg.

Initial $petCO_2$ is significantly higher in asphyxial arrest than in VT/VF cardiac arrest. Regarding asphyxial arrest, there is also no difference in values of initial $petCO_2$ between patients with and without ROSC. On the contrary, there is a significant difference in values of initial $petCO_2$ in VF/VT cardiac arrest between patients with and without ROSC. This difference could prove to be useful as one of the methods in prehospital diagnostic procedures and attendance of cardiac arrest. For this reason, we should always include other clinical and laboratory tests.

Grmec et al. [15] analysed the outcome of patients with out-of-hospital cardiac arrest (OHCA) in a prospective cohort study in Maribor over a 4-year period using a modified Utstein style. We analysed the effects of various factors on outcome in OHCA, especially $petCO_2$, efficacy of bystander CPR and their elementary knowledge of basic life support (BLS). We also examined motivation among potential bystanders and possible implementation for BLS education in our community. After treating OHCA by a physician-based prehospital medical team, ROSC was obtained in 61%, ROSC on admission was 50% and overall survival to discharge was 21%. Initial $petCO_2$ [odds ratio (OR) 22.04; 95% confidence interval (CI) 11.41–42.55], VF or pulseless VT as initial rhythm (OR 2.13; 95% CI 1.17–4.22), bystander CPR (OR 2.55; 95% CI 1.13–5.73), female sex (OR 3.08; 95% CI 1.49–6.38) and arrival time (OR 1.29; 95% CI 1.11–1.82) were associated with improved ROSC when using multivariate analysis. Using the same method, we found that bystander CPR (OR 5.05; 95% CI 2.24–11.39), witnessed arrest (OR 9.98; 95% CI 2.89–34.44), final $petCO_2$ (OR 2.37; 95% CI 1.67–3.37), initial $petCO_2$ (OR 1.61; 95% CI 1.28–2.64) and arrival time (OR 1.39; 95% CI 1.33–1.60) were associated with improved survival. A questionnaire completed by potential bystanders revealed disappointing knowledge about BLS fundamentals. However, there was a welcomed willingness of potential bystanders to take BLS training and to follow dispatchers' instructions by telephone on how to perform CPR.

After OHCA in a physician-based prehospital setting in our region, overall survival to discharge was 21%. The potential bystander in our community is generally poorly educated in performing CPR but is willing to gain knowledge and skills in BLS and to follow dispatchers' instructions. Arrival time, witnessed arrest, bystander CPR, initial $petCO_2$ and final $petCO_2$ were significantly positively related with ROSC on admission and with survival. Prehospital data from this and previous studies provide strong support for a $petCO_2$ of 1.33 kPa to be a resuscitation threshold in the field. In our opinion, the initial value of $petCO_2$ should be included in every Utstein style analysis.

In other studies [16, 17], we analysed how changes in $petCO_2$ levels during CPR could predict successful resuscitation and serve as a tool to help determine when to cease CPR efforts. $petCO_2$ values after 20 min of advanced life support (ALS) were 6.9 ± 2.2 mmHg in patients without ROSC and 32.8 ± 9.1 mmHg in patients with ROSC ($p < 0.001$). When a 20-min $petCO_2$ value of 14.3 mmHg was used as a screening test to predict ROSC, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were all 100%.

In our prospective pilot study [18, 19] we evaluated the ability of focused echocardiography (FE) and capnography to differentiate between PEA (true cardiac standstill) and pseudo-PEA (FE signs of spontaneous mechanical myocardial activity and valvular

motion) in OHCA and the potential survival benefits with modified treatment. In patients with a stable $petCO_2$ value during the compression pause and FE showing cardiac kinetic activity, the compression pause was prolonged for 15 s, and an additional 20 IU of vasopressin were administered. If pulselessness persisted, compressions were continued. Amongst the 16 patients in the study, 15 (94%) achieved ROSC, with eight (50%) attaining a good neurological outcome (Cerebral Performance Category 1 or 2). In a historic PEA group with stable $petCO_2$ values (n = 48), ROSC was achieved in 26 (54%), and only four (8%) attained Cerebral Performance Category 1 or 2. Echocardiographic verification of pseudo-PEA enabled additional vasopressor treatment and cessation of chest compressions and was associated with significantly higher rates of ROSC, survival to discharge and good neurological outcomes.

In our recent prospective observational study [20], we investigated the effect of pO_2 and pCO_2 and $petCO_2$ on the occurrence of near-death experiences (NDEs) in OHCA survivors. Fifty-two consecutive patients (median age 53.1 years, 42 males) were studied. Patients with higher initial $petCO_2$ had significantly more NDEs ($p < 0.01$). Patients with higher $PaCO_2$ had significantly more NDEs ($p = 0.041$). Scores on a NDE scale were positively correlated with pCO_2 ($p = 0.017$) and serum levels of potassium ($p = 0.026$). The logistic regression model for the presence of NDEs ($p = 0.002$) revealed higher pCO_2 to be an independent predictor of NDEs. The higher pCO_2 indicates better cardiac output and perfusion pressure, which would reduce the amnesia that is usually seen in cardiac arrest, so that patients would be more likely to remember what happened during the arrest. The association between NDEs and hypercapnia may thus indicate that patients who are able to recall more of their cardiac arrest also report more NDEs. In light of patient-oriented care, it is important to take into account the existence of NDEs in cardiac arrest patients and to develop protocols of care for such patients.

5.5 Conclusions

The use of capnometry and capnography in the prehospital setting is increasing. With extended use come new studies, which expand their applications even further. They are now used to verify endotracheal tube placement and assess resuscitation efforts, and they have a prognostic value for CPR outcome. In the Centre for Emergency Medicine Maribor, we find capnometry and capnography very useful tools, especially in combination with ultrasound, which help us monitor patients and sometimes make important decisions on the feasibility of CPR. With our research work, we hope to contribute to further widening the applications for capnometry and capnography.

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Weaning from Mechanical Ventilation

6

I. Cortés Puch, A. Esteban

6.1 Introduction

Weaning describes the process of liberating the patient from mechanical ventilation. It is a withdrawal or discontinuation process that covers the transition from mechanical support to spontaneous breathing. In most patients, this transition is quick and uneventful once we realise that the respiratory failure has improved and the patient is ready for spontaneous breathing. However, a minority of mechanically ventilated patients (one of every four or five patients) will need a more gradual approach to weaning.

Mechanical ventilation is a lifesaving intervention used in approximately 33% of patients admitted to intensive care units (ICUs) [1]. Approximately 40% of the total ventilator time is devoted to liberating the patient from mechanical ventilation [2]. Therefore, given the large amount of time that weaning takes, one goal is to achieve a safe and early discontinuation from ventilatory support, avoiding unnecessary delay. Delays are associated with increased mortality and morbidity rates as well as costs [3]. However, an aggressive discontinuation of mechanical ventilation is unsafe and premature, leading frequently to reintubation and its secondary complications. In light of the recommendation of an international consensus conference [4], mechanically ventilated patients can be classified into three groups according to the difficulty of their weaning process:

1. simple weaning: the patient is successfully weaned after tolerating an initial spontaneous breathing trial (SBT);
2. difficult weaning: successful weaning requires up to three SBTs or as long as 7 days from the first trial;
3. prolonged weaning: the patient fails at least three weaning attempts or needs more than seven days to be successfully weaned.

Approximately 20–30% of mechanically ventilated patients fall into the second and third groups. Studies performed to validate this classification have observed that patients with a prolonged weaning (>7 days) incur a higher mortality rate [5].

The benefits of shortening the weaning process, and therefore the length of mechanical ventilation, led many physicians to develop different strategies to liberate their patients

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from ventilatory support. Nevertheless, 20 years ago, this process was far from being standardised, and weaning was managed quite empirically. In the 1990s, several studies attempted to clarify many questions raised around this topic. Two large randomised controlled trials (RCTs) [6, 7] were conducted to compare different strategies for withdrawal from mechanical ventilation to throw light on this issue. Since then, and bearing in mind that mortality rates and costs increase with weaning delays, efforts have been made to increase and disseminate evidence-based practices.

Weaning can be considered a continuum or series of stages that cover the process from intubation until successful extubation [4]. This transition involves many steps: from recognising respiratory improvement through realising that the patient is ready to breathe spontaneously then testing tolerance to an SBT until the patient can be successfully liberated from ventilator support. These stages are reviewed in this chapter.

6.2 Assessing Readiness for Weaning

Weaning begins with the recognition of an adequate recovery from acute respiratory failure. Bearing in mind that prolonged mechanical ventilation is associated with significant morbidity and mortality, it is important that this step is not delayed. Therefore, we must be aware of the signs indicating that ventilatory support is no longer necessary. Clinical assessments will help determine whether the patient is ready for weaning and then to be successfully extubated.

Most studies consider that patients who meet certain clinical parameters are ready to wean (Table 6.1). Nevertheless, these criteria have been set arbitrarily and have not been properly validated in clinical trials. It seems reasonable that ventilatory support should be

Table 6.1 Criteria with which to consider the patient ready to start withdrawal from mechanical ventilation

Criteria	
Adequate oxygenation	PaO_2 ≥60 mmHg on FiO_2 ≤0.4 and PEEP ≤5–10 cmH_2O; PaO_2/FiO_2 >150–300
Stable cardiovascular function	Absence of significant hypotension; no (or minimal) pressors
Temperature	<38ºC
Adequate mental status	Easily arousable
Haemoglobin	≥8–10 g/dl
Resolution of the acute phase of the diseases	

PaO_2 , partial pressure of arterial oxygen; *FiO_2* , fraction of inspired oxygen; *PEEP* , positive and expiratory pressure; *H_2O* , water

continued until there is sufficient improvement of the underlying cause that required its initiation. Nevertheless, many patients who do not meet all of these readiness criteria can be successfully weaned. Ely and colleagues observed that 30% of patients who do not satisfy these objective criteria are able to be liberated and breathe spontaneously [8]. During the last two decades, several questions have been raised about the adequacy of these criteria. The appropriateness of using the same oxygenation threshold for patients with chronic hypoxaemia or the mental status required are two of the arguable topics around these readiness criteria.

Evidence supports that protocol-driven weaning, guided by intensive care nurses or respiratory therapists, is probably the best way to assess the readiness of patients for spontaneous breathing. Saura et al. [9] conducted a study in which 51 patients weaned according to a fixed protocol were compared with 50 historical controls. The duration of mechanical ventilation was shorter in the protocol group than in the control group (10.4 ± 11.6 vs. 14.4 ± 10.3 days, $p < 0.05$). As a consequence, the ICU stay was reduced (16.7 ± 16.5 days vs. 20.3 ± 13.2 days, $p < 0.05$), with no differences in the reintubation rate. Ely et al. [10] conducted a randomised, controlled trial involving 300 mechanically ventilated patients who were randomly assigned to receive standard care or an intervention strategy. In both groups, patients underwent daily screening of respiratory function by physicians, respiratory therapists and nurses to identify those possibly capable of breathing spontaneously. In the intervention group, successful tests were followed by 2-h trials of spontaneous breathing in those who met the criteria, and physicians were notified when their patients successfully completed these trials. The results showed a reduction of weaning time (1 vs. 3 days, $p < 0.001$), duration of mechanical ventilation (median 4.5 vs. 6 days, $p = 0.003$), complications and costs. There were no significant differences in ICU stay and mortality rates.

6.2.1 Predictors of Adequate Spontaneous Breathing

Many efforts have been made to identify some simple and objective parameters that could help discriminate which patients will tolerate a trial of spontaneous breathing. Assessing the likelihood of tolerance to an SBT will avoid performing these trials in patients with a high risk of failing it. Several parameters have been evaluated for this purpose: minute ventilation, negative inspiratory pressure, airway occlusive pressure at 0.1 s, rapid shallow breathing index, etc. Nevertheless, the predictive value of these parameters is low in clinical practice. Among these parameters, the most commonly used is the rapid shallow breathing index (RSBI), or Yang-Tobin index, which is a ratio between respiratory frequency (fR) and tidal volume (VT). In the original prospective study performed by Yang and Tobin [11], with the threshold set at 105 breaths/min/l, the reported sensitivity to predict a successful SBT was 0.97 and the specificity was 0.65. Tanios et al. [12] observed that including this index for deciding whether or not to perform an SBT increased weaning duration, with no difference in the rate of extubation failure. Many other weaning predictors have been evaluated with poor results. In clinical practice, the use of these parameters is limited by their low predictive value, the fact that they do not confer a clear benefit in patient survival and that they can even prolong duration of the weaning process.

6.3 Spontaneous Breathing Trials

A trial of spontaneous breathing is necessary once the patient satisfies the readiness criteria. Multiple studies have investigated how to correctly perform an SBT. Traditionally, these trials were conducted with a T tube. However, low-level pressure support ventilation (PSV) would have the advantage of counterbalancing the endotracheal tube resistance and, therefore, a work overload that could be responsible of some patient's failing the SBT. The level of pressure support needed to overcome this resistive load appears to be different in each patient. According to a study performed by Nathan et al. [13], the mean level of pressure support is 7 cm water (H_2O) (range 4–10 cmH_2O). Different techniques [PSV, continuous positive airways pressure (CPAP) and automatic tube compensation] have been proposed to overcome the resistive load of the endotracheal tube. Nevertheless, studies have failed to demonstrate any difference when comparing T tube and PSV for an SBT. The Spanish Lung Failure Collaborative Group compared extubation outcome after an SBT with T tube or PSV [14]. The study failed to account for differences in the percentage of patients who remained extubated after 48 h (63% vs. 70%, $p = 0.14$), although more patients in the T-tube group failed the trial (22% vs. 14%, $p = 0.03$). Ezingeard et al. [15] conducted a prospective, nonrandomised trial in which patients who failed a 30-min T-tube SBT were then given a 30-min trial with pressure support of 7 cmH_2O. Although the extubation failure rate after 48 h did not differ significantly between both groups (13% vs. 19%, $p = 0.39$), 18% of patients were successfully extubated after a PSV trial despite having previously failed a T-tube trial. Regarding patients with chronic obstructive pulmonary disease (COPD): a higher percentage of them were extubated when PSV rather than a T tube was used (38% of extubation after PSV trial vs. 13% after T-tube trial, $p = 0.003$). Due to the presence of dynamic hyperinflation and auto-positive end-expiratory pressure (auto-PEEP), patients may benefit from a CPAP trial [16]. This topic needs to be further investigated.

6.3.1 Duration of the Spontaneous Breathing Trial

Although, traditionally, SBTs were performed over a 2–h period, several studies have demonstrated that the failure of an SBT usually takes place within the first 20 to 30 min. Two studies investigated the optimal duration of an SBT. The Spanish Lung Failure Collaborative Group performed a multicentre, prospective study [17] comparing 30-min and 120-min T-tube SBTs in 526 mechanically ventilated patients. There were no differences between groups in the percentage of patients who remained extubated after 48 h (75.9% in 30-min vs. 73% in 120-min trials, $p = 0.43$). Similar results were reached in a study conducted by Perren et al. [18] in which 30-min and 120-min trials using a pressure support level of 7 cmH_2O were compared.

Table 6.2 Most commonly used criteria to describe tolerance or success of a spontaneous breathing trial (SBT)

Criteria	
Objective parameters	
Acceptable oxygenation	SpO_2 ≥85–90% or PaO_2 ≥50–60 mmHg on FiO_2 ≤0.5
Acceptable ventilation	Increase in $PaCO_2$ ≤10 mmHg or decrease in pH <0.10
Stable ventilatory pattern	Respiratory rate <35 breaths/min or increased from baseline <50%
Haemodynamic stability	Heart rate <140 beats/min or increased from baseline <20%, systolic blood pressure 80–160 mmHg
Subjective assessments	Absence of signs of increased work of breathing No diaphoresis, agitation or discomfort

SpO_2, pulse oximeter oxygen saturation; *PaO_2*, partial pressure of arterial oxygen; *FiO_2*, fraction of inspired oxygen; *$PaCO_2$*, partial pressure of arterial carbon dioxide

6.3.2 Criteria to Define SBT Tolerance/Success

Criteria used to describe the success or failure of an SBT are similar to those of the readiness criteria previously reviewed. They include several physiological parameters as well as subjective, clinical factors (Table 6.2). These criteria have not been validated but have been used in several large trials. Their negative predictive value (NPV) has not been formally assessed. Therefore, we cannot know how many patients who fail an SBT would be able to tolerate liberation using these criteria. To date, there is no evidence of benefit from performing arterial blood gas measurements at the end of an SBT, although further research is needed to determine whether there is a subgroup of patients who could benefit from this simple procedure.

6.4 Failure of the Spontaneous Breathing Trial

6.4.1 Causes of Weaning Failure

There are several reversible causes that we should evaluate when a patient fails an SBT. The most common aetiologies of weaning failure are listed in Table 6.3 and are generally related to an imbalance between load and capacity.

Table 6.3 Causes of weaning failure

Causes	
Respiratory factors	
Increased respiratory load	Increased resistance: auto PEEP during the spontaneous breathing trial Increased secretions
	Decreased compliance: reduced lung compliance (pneumonia, infiltrates, oedema, fibrosis
	Abdominal compression
	Increased ventilatory requirements: increased CO_2 production; increased dead space
Reduced respiratory capacity	Depressed central drive Peripheral nervous dysfunction Reduced muscular capacity: critical illness polyneuropathy, malnutrition, diaphragmatic fatigue
Cardiovascular factors	Increased cardiac load: sepsis, increased metabolic demands Decreased cardiac load: ischaemia, arrhythmias
Metabolic and endocrine disturbance	Thyroid gland dysfunction, adrenal insufficiency, obesity, malnutrition
Psychological factors	Anxiety, delirium
Anaemia	

PEEP, positive end-expiratory pressure; CO2, carbon dioxide

6.4.2 Management of Patients who Fail Spontaneous Breathing Tests

When a patient fails an SBT, and after correcting all reversible factors that may have contributed to this failure, several questions must be dealt with. For example: When should the SBT be repeated? Which type of ventilatory support is more appropriate in the meanwhile? The basis of our practice is demonstrated in our algorithm (Fig. 6.1).

As to when to attempt a new SBT, several studies recommend waiting 24 h. This advice is based on the fact that respiratory muscle fatigue can be triggered by a failed SBT and is unlikely to recover in less than 24 h. In a study performed by Laghi et al. [19] to evaluate the rate of recovery from diaphragmatic fatigue, 12 healthy individuals underwent a protocol of inspiratory resistive loading. Using the measurements of baseline transdiaphragmatic twitch pressure and how it changed after diaphragmatic fatigue

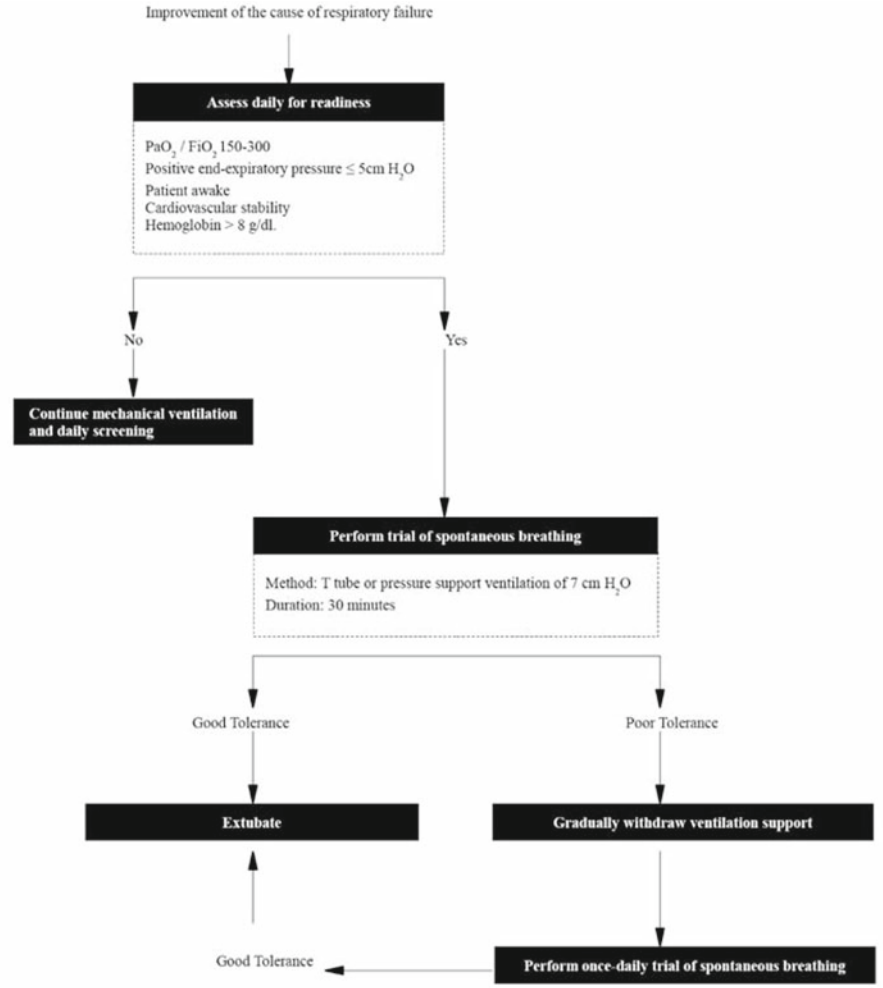

Fig. 6.1 Evidence-based algorithm for the withdrawal of mechanical ventilation. PaO_2 , partial pressure of arterial oxygen; FiO_2 , fraction of inspired oxygen; H_2O , water

occurred, the researchers found that recovery probably took longer than 24 h. The study conducted by the Spanish Lung Failure Collaborative Group [7] comparing four methods of patient weaning failed to demonstrate any benefit of multiple daily trials over a single, once-daily SBT.

6.4.3 Withdrawal of Ventilatory Support

In the guidelines for weaning by the American College of Chest Physicians, the American

Association for Respiratory Care and the American College of Critical Care Medicine [20], the recommendation for patients failing an SBT is that they should receive a "stable, non-fatiguing, comfortable form of ventilatory support".

Approximately 25% of mechanically ventilated patients will not tolerate the initial SBT. Different techniques have been proposed to ease the transition from mechanical ventilation to spontaneous breathing. In the 1990s, three techniques were the most commonly used for this purpose: T-tube, synchronised intermittent mandatory ventilation (SIMV) and pressure support ventilation (PSV). In this context, two large RCTs were conducted comparing the different weaning methods to determine whether one of these shortened weaning time.

Esteban et al. [7] performed a prospective randomised multicentre study in 546 mixed medical–surgical patients mechanically ventilated who were considered ready to wean. The 130 patients who failed the initial 2-h SBT were randomly assigned to four groups: SIMV, decreasing two to four breaths per minute at least twice a day (29 patients), once-daily T-tube SBT (31 patients), T-tube SBT twice or more times a day (33 patients) or PSV decreasing 2–4 cmH_2O at least twice a day (37 patients). In this study, four factors were found in a cox proportional hazards regression analysis that predicted the time for successful weaning (off ventilator for >48 h at 14 days): age ($p < 0.02$), duration of ventilatory support before starting weaning ($p < 0.005$), time to failure of the first SBT ($p < 0.001$) and the weaning technique. Once adjusted, the rate of successful weaning was higher with a single, once-daily T-tube trial than either with SIMV [rate ratio 2.83; 95% confidence interval (CI) 1.36–5.89; $p < 0.006$) or with PSV (rate ratio 2.05; 95% CI 1.04–4.04; $p < 0.04$).

In a randomised multicenter study, Brochard et al. [6] compared three modalities of weaning among 456 mixed medical–surgical patients. Of these,109 (24%) failed the first SBT and were randomly assigned to three groups: trials with T tube until a 2-h trial was tolerated (35 patients); SIMV, decreasing two to four breaths per minute twice a day (43 patients); or PSV, decreasing 2–4 cmH_2O of pressure support twice daily until 8 cmH_2O was tolerated (31 patients). A lower number of failures (patients in ventilatory support at day 21 and patients who required reintubation in a 48-h period following extubation) was found with PSV than with the other two modes together (23% for PSV, 43% for T tube and 42% for SIMV, $p = 0.05$). This result is limited by the fact that the comparison was made between one mode and another (T tube with SIMV). The weaning time, or time required for successful weaning, was shorter with PSV than with the other two methods.

A systematic review was published in 1999 [21], including these two large randomised trials [6, 7] and two other trials in which at least two of the three previously described methods of weaning were compared in mechanically ventilated patients who failed initial SBT [22, 23]. The review was unable to demonstrate the superiority of any of these methods, although SIMV does result in a longer weaning time than the two others. Due to the differences between the studies – which affected the population, the intervention application, the outcomes assessed and the extubation criteria – there was insufficient evidence to identify a clearly superior mode of weaning. These studies offer no evidence of superiority of gradual support methods rather than using stable support between SBTs. Nevertheless, an aggressive support reduction is potentially harmful for the patient as it increases respiratory load and does not allow recovery of muscle fatigue. Maintaining stable ventilatory support between SBTs reduces this risk, only requires once-daily evaluation of the patient's ability to breathe spontaneously, and allows recovery of muscle fatigue. Gradual but unaggressive

reduction of support, coupled with daily SBTs, could be useful and harmless.

Our recommendation is to perform a single daily SBT, bearing in mind that in the only study in which this option was compared [7], this method was superior. Moreover, it allows respiratory muscles to rest during the next 24 h, with a possible benefit according to the study performed by Laghi [19], and requires less work load than any other strategy.

6.5 Extubation

Once the patient is capable of breathing spontaneously, it must be decided whether to extubate or not, bearing in mind that 8–24% of patients who tolerate an SBT will be reintubated in the ensuing hours, which causes a higher mortality rate and hospital and ICU stay [24]. However, both extubation failure (defined as the need for reintubation within the first 48–72 h) and the delay of extubation are linked to unfavourable outcomes. Hence, many efforts have been made to identify objective parameters that could help predict successful extubation. However, the variables we use to define the tolerance to an SBT are less useful for predicting extubation success following a tolerated and successful SBT. In a study performed in an heterogeneous large cohort of mechanically ventilated patients [25], reintubation within 72 h was associated with an RSBI >57 breaths/min per litre, a positive fluid balance in the 24 h before extubation and pneumonia as the cause for initiating mechanical ventilation. Nevertheless, the predictive capacity of these parameters was weak. In a subsequent prospective study [26] evaluating the predictive ability of serial measurements of the RSBI during 120 min of SBT, these measurements were unable to predict extubation failure in patients following a successful SBT with initial fR/VT <105. Other approaches to this topic have evaluated several parameters and their capacity to predict the success of extubation. Measuring the airway occlusion pressure at 0.1 s (P0.1) [27] and expiratory flow limitation [28] have also been assessed as possible predictors of extubation failure, with variable results. Despite all of these approaches, it is still challenging to predict extubation outcome.

Regarding the decision to extubate a patient after a successful SBT, it must be borne in mind that extubation failure is often a consequence of the patient's inability to protect adequately the airway and to manage respiratory secretions [29]. Therefore, it is important to assess that ability, as well as cough strength and capacity to deal with respiratory secretions. Poor cough strength and a higher amount of secretions and the inability to manage them correctly make the patient more likely to fail after extubation and to require reintubation [30]. Mental status was, traditionally, considered highly important at this point, and a Glasgow Coma Scale (GCS) score >11 was thought to be necessary to safely extubate a patient. Nevertheless, this issue has been recently questioned, and it is no more considered as a compulsory criterion for extubation. Studies with opposite results have been published in the last decade. According to a study conducted by Coplin et al. [31] in 136 neurological patients, there is no need to delay extubation when neurologic impairment is the only concern prolonging mechanical ventilation. In that study, 80% of patients with GCS ≤8 and 91% of patients with GCS ≤4 were successfully extubated. However, in a study by Namen et al. [32], GCS score was associated with extubation success in a multivariate analysis ($p < 0.0001$).

Another cause of extubation failure is related to upper airway obstruction, with an incidence of nearly 7%. Patients especially at risk of upper airway obstruction are those with longer duration of mechanical ventilation, when the cause of intubation is upper airway obstruction or trauma, female gender and reintubated patients. The cuff-leak test, based on identifying an air leak when the endotracheal tube balloon is deflated (a positive test is the absence of leak) can help indicate the possibility of an upper airway obstruction. A leak of >110 ml during volume control ventilation should indicate that the diameter of the airway is adequate. False-positive tests can occur, for example, when secretions adhere to the external surface of the tube. Several studies have evaluated the accuracy of this observation as a predictor of laryngeal oedema and the need for reintubation. Recently, a meta-analysis and systematic review was published [33], although the 11 studies included were quite heterogeneous and the leak cutoff value was different in each one. The overall incidence of upper airway obstruction was 6.9% (range 0.6–36.8%). Regarding the value of the test for predicting upper airway obstruction secondary to laryngeal oedema, even with the high heterogeneity of the statistical operative parameters (sensitivity, specificity, positive and negative likelihood ratio), the positive likelihood ratios were always >3, indicating that a positive test (absence of leak) is related to an increased risk of upper airway obstruction. However, a negative test had less clinical relevance (pooled negative likelihood ratio 0.46). Regarding the value of the cuff-leak test for predicting reintubation, only three of the 11 studies evaluated this variable. According to the results, this test has low accuracy to predict reintubation secondary to upper airway obstruction.

6.5.1 Risks Related to Reintubation

Reintubation is associated with an increased mortality rate. According to the different published series, mortality in reintubated patients ranges between 10% and 43% (compared with a rate of 2.6–12% among patients who require a single intubation). Many studies have tried to elucidate whether this increased mortality rate is secondary to reintubation per se or to the underlying cause of reintubation. Two studies [17, 34] demonstrated that cause and timing of reintubation are associated with mortality rate. Therefore, patients who develop upper airway obstruction and require reintubation have a lower mortality rate than patients who are reintubated for other causes. Several studies evaluated the influence of reintubation in the incidence of ventilator-associated pneumonia (VAP). Torres et al. [35] conducted a multivariate analysis involving 322 mechanically ventilated patients. There were 78 episodes of nosocomial pneumonia. One variable significantly associated with a higher risk of VAP was having more than one intubation ($p = 0.000012$). This association was further proven by the same group [36] in a case–control study.

6.6 The Role of Noninvasive Positive Pressure Ventilation

The use of noninvasive positive pressure ventilation (NPPV) in withdrawing the patient from mechanical ventilation has three possible scenarios:

- as an alternative weaning technique in patients who do not tolerate an initial SBT;
- as a treatment for postextubation acute respiratory failure;
- as a prophylactic strategy in patients at high risk of reintubation.

6.6.1 Noninvasive Positive Pressure Ventilation as a Weaning Method

In the last two decades, there has been increasing interest in the use of noninvasive ventilation as an alternative to conventional weaning methods in order to avoid the complications and mortality rates associated with prolonged intubation. The use of NPPV has been evaluated in several RCTs, although with small sample sizes. In these studies, patients who failed to tolerate SBTs are usually randomised into two groups: an intervention group, in which patients are extubated and NPPV is administered; and a control group, in which conventional, invasive weaning is performed. A recent meta-analysis and systematic review has also evaluated this issue.

The first RCT was performed by Nava et al. [37] and involved 50 COPD patients with hypercapnic respiratory failure. Mechanically ventilated patients who failed an SBT with T tube were randomly assigned into two groups. In the intervention group, patients were extubated and supported with NPPV, whereas patients in the control group remained intubated and were gradually weaned with a conventional approach. At 60 days, more patients from the NPPV group were successfully weaned (88% vs. 68%). The mean duration of mechanical ventilation was shortened (10.2 ± 6.8 vs. 16.6 ± 11.8 days, $p = 0.021$) and survival rates at 60 days higher in the NPPV group (92% vs. 72%, $p = 0.009$). Nevertheless, it seems obvious that mechanical ventilation will be shorter in the NPPV group, bearing in mind that patients in this group were extubation to receive noninvasive ventilation. A decrease in the incidence of nosocomial pneumonia was also observed.

A subsequent study, conducted by Girault et al. [38] included 33 patients with acute-on-chronic respiratory failure receiving mechanical ventilation and who failed a 2-h T-tube SBT. In the intervention group, extubation was performed and NPPV applied. The duration of invasive mechanical ventilation was reduced in these patients (4.56 ± 1.85 vs. 7.69 ± 3.79 days, $p = 0.004$), although the duration of total ventilatory support related to weaning was increased (11.54 ± 5.24 vs. 3.46 ± 1.42, $p = 0.0001$). Length of ICU and hospital stay and 3-month survival rate was similar between groups.

In a study performed by Ferrer et al. [39], 43 mechanically ventilated patients who had failed three consecutive SBT were randomly assigned to extubation and NPPV application or to remain intubated with a conventional weaning strategy. The intervention group had shorter duration of invasive ventilation (9.5 ± 8.3 vs. 20.1 ± 13.1 days, $p = 0.003$) as well as decreased ICU and 90-day survival. Length of ICU and hospital stay was also reduced, as was the incidence of nosocomial pneumonia and septic shock. In their study, 33 of the 43 patients participating had underlying chronic respiratory diseases, and it was only in those patients that the significant differences were observed. The small sample size makes it difficult to extrapolate the results of this study.

Trevisan et al. conducted a study in 2008 in which they randomly assigned 65 patients who failed T-tube SBT to be extubated and receive NPPV or to stay intubated and be weaned conventionally [40]. The incidence of ventilator-associated pneumonia and the need for tracheotomy were reduced in the NPPV group.

In a Cochrane meta-analysis [41] in 2008, a consistent decrease in mortality and length of hospital and ICU stay was found, predominantly in COPD patients. Nevertheless, the evidence is insufficient, and the review involved only 171 patients.

A recent meta-analysis and systematic review [42] from the same group, including 12 trials (530 patients), reported reduced mortality (30 days, 60 days or 90 days) with NPPV weaning [relative risk (RR) 0.55, 95% CI 0.38–0.79, p = 0.001]. A decrease in the incidence of ventilator-associated pneumonia was also found, as well as a trend to shorter both mechanical and invasive ventilation and decreased length of ICU and hospital stays, although with significant heterogeneity. Most studies in this review included patients with COPD, and subgroup analysis suggested a higher benefit of NPPV weaning in these patients. However, the small number of patients in each study and the fact that there was no adequately powered RCT limits inference of these results. Moreover, the protocols used in each trial differed in the way NPPV was applied, time of randomisation and screening for readiness for spontaneous breathing. In some of these studies, a daily assessment of readiness and SBT were not included after randomisation, and, therefore, some of these invasively ventilated patients may have remained intubated longer than needed. Another potential bias is that mortality rates of the control groups were considerably higher in comparison with other mechanical ventilation studies. Hence, more trials with a higher power are needed to evaluate net clinical benefits. Regardless, when considering the use of NPPV as a weaning method, it should be used in COPD patients.

6.6.2 Noninvasive Ventilation for Respiratory Failure after Extubation

Given the higher morbidity and mortality rates associated with reintubation, researchers have evaluated the potential of using noninvasive ventilation to manage patients who develop respiratory failure after extubation. The results raised by two randomised clinical trials [43, 44] were quite disappointing, showing no benefits for avoiding reintubation.

Keenan et al. [43] conducted a study in 81 patients who developed respiratory failure during the first 48 h after a planned extubation. The use of NPPV showed no benefit in the rate of reintubation (72% vs. 69%, RR 1.04, 95% CI 0.78–1.38), duration of mechanical ventilation, hospital mortality rates and length of ICU and hospital stay.

In a multicenter international trial by Esteban et al. [44], 221 patients with respiratory failure after elective extubation were randomly assigned to either NPPV or standard therapy. No significant differences in reintubation rate and length of hospital stay were found. Moreover, the results showed a higher mortality rate in ICUs in the NPPV group (25% vs. 14%, RR 1.78, 95% CI 1.03–3.2), which might be explained by a delay in reintubation.

Hence, NPPV is not effective for managing respiratory failure after elective extubation. Both trials were performed, however, in populations with a relatively low percentage of COPD patients. Nevertheless, this is actually the usual percentage of such patients in a mixed medical–surgical ICU population [1]. It is important to emphasise that the application of NPPV protocols is probably limited also by the type of ICU, and the benefit on patient outcomes may differ when NPPV is performed in the setting of a specialised unit rather than in a standard one.

6.6.3 Noninvasive Positive-Pressure Ventilation for Preventing Respiratory Failure after Extubation

As noninvasive ventilation has no benefit in managing postextubation respiratory failure, efforts have switched lately to evaluating the use of this technique for its prevention, specifically in patients at high risk of developing this complication.

Jiang et al. [45] conducted a randomised controlled trial in 93 extubated patients (56 after elective and 37 after unplanned/accidental extubation). The patients were randomly assigned to receive either standard oxygen-based therapy or noninvasive bilevel positive pressure ventilation. The study failed to show any benefit of NPPV, with no significant difference in the rate of reintubation (28% in NPPV group vs. 15% in the control group).

Nava and colleagues [46] performed a multicentre, randomised controlled trial in 97 patients electively extubated and considered at risk of developing postextubation respiratory failure: patients with hypercapnia, congestive heart failure, ineffective cough and excessive secretions, more than one failed weaning trial, more than one comorbid condition or upper-airway obstruction. The NPPV group had a lower reintubation rate (4.8% vs. 12.24%, $p = 0.027$). This reduced need for reintubation resulted in a lower risk of ICU mortality, with no difference in overall mortality.

Ferrer et al. [47] conducted an RCT involving 162 patients ventilated for 48 h or more and who were extubated after a successful SBT. Patients were considered at risk of developing respiratory failure with at least one of the following: age >65 years, congestive heart failure or Acute Physiology and Chronic Health Evaluation II (APACHE II) score >12 (on extubation day). Patients were randomly assigned to receive either noninvasive ventilation or standard oxygen over the next 24 h. Respiratory failure after extubation was less frequent among patients in the NPPV group (13.16 vs. 27.33%, $p = 0.029$). No survival differences were found at 90 days, although in a subgroup analysis, there was an improved 90-day survival among patients with hypercapnia during SBT. In 2009, a new RCT conducted by the same group [48] enrolled 106 patients from three ICUs, all with chronic respiratory disorders and hypercapnia after a successful SBT. After extubation, patients were randomly assigned to receive either NPPV or standard therapy for 24 h. A lower frequency of postextubation respiratory failure and a significantly lower 90-day mortality rate was found in the NPPV group, although the use of this outcome rather than ICU/hospital/overall mortality is controversial. Nevertheless, the characteristics of the control group were quite different to what was expected in terms of mortality rates, tracheotomies, etc.

Hence, applying an NPPV strategy after extubation of COPD patients with hypercapnia must be considered, as it has the potential benefit of preventing the development of postextubation respiratory failure. Nevertheless, in these studies, the criteria to consider a patient at high risk of reintubation are chosen by the researchers and have not been properly validated, nor has their sensitivity to predict reintubation been assessed. More studies need to be performed to evaluate this indication of NPPV in this selected population.

6.7 Management of Sedation and Weaning

The use of sedatives and analgesics to alleviate pain, agitation and discomfort is a common practice in the ICU, particularly in mechanically ventilated patients. However, recent research suggests that prolonged and excessive use of sedative medications may prolong the duration of mechanical ventilation and the length of ICU stay. Therefore, over the past 10 years, many efforts have been made to reduce the use of these medications in order to improve patients' outcomes.

Kollef and colleagues [49] performed a prospective observational study to evaluate the influence of analgesics and sedatives on the overall outcomes of critically ill patients. The study involved 242 mechanically ventilated patients, of whom some received continuous sedation i.v. (38.4%) and the rest (61.6%) received either bolus i.v. administration of sedatives or no sedatives at all. The duration of mechanical ventilation was longer among patients with continuous i.v. sedatives (185 ± 190 h vs. 55.6 ± 75.6 h, $p < 0.001$). Moreover, lengths of ICU and hospital stay were significantly longer in those patients compared with patients who were not receiving continuous i.v. sedation. In a multiple linear regression analysis adjusted for potential confounders, the adjusted duration of mechanical ventilation was longer in patients sedated with continuous i.v. infusions (148 h, 95% CI 121–175 h vs. 78.7, 95% CI 68.9–88.6 h, $p < 0.001$).

In the light of these results, during the last decade, efforts have been made to evaluate and implement strategies characterised by reducing sedation or not using these agents at all in an attempt to shorten the duration of mechanical ventilation. In this context, many alternative sedation methods have been developed to achieve safe management of the patients' pain and anxiety, as well as to reduce the deleterious effects of oversedation, particularly a slower withdrawal from mechanical ventilation. These strategies include intermittent therapy, protocols or algorithms with defined endpoints to titrate sedatives, use of medications with a shorter half-life or even no sedation at all.

Kress et al. [50] performed a randomised controlled trial involving 128 mechanically ventilated patients who received continuous sedative and analgesics infusions. In the intervention group, sedation was interrupted each morning until the patient was capable of following three to four simple commands or until he or she became agitated. Then infusions were restarted. In the control group, infusions were only interrupted at the discretion of the clinician. There was a significantly reduced duration of mechanical ventilation (4.9 days vs. 7.3 days, $p = 0.004$) and length of ICU stay (6.4 days vs. 9.9 days, $p = 0.02$) in the intervention group, and there was no increase in the rate of adverse events. In a follow-up study [51], the researchers evaluated the possible adverse psychological effects attributable to daily sedation interruption and found it actually reduced symptoms of post-traumatic stress disorder and had no adverse psychological effects.

Thus, a new concept, daily interruption of sedation, appeared. In recent years, the term "spontaneous awakening trials" (SATs) has emerged to describe this concept, in allusion to SBTs. Furthermore, in 2008, Girard et al. [52] conducted an RCT to assess a protocol that paired SATs with SBTs: the awakening and breathing controlled trial. In that trial, 336 mechanically ventilated patients were randomly assigned to perform a daily SAT followed by an SBT (wake up and breathe protocol) or to a standard sedation management with

daily SBTs. Patients in the intervention group had significantly higher ventilator-free days (14.7 vs. 11.6 days, mean difference 3.1 days, 95% CI 0.7–5.6, p = 0.02) and earlier ICU and hospital discharge. The study confirmed the benefit of the strategy raised previously by Kress and colleagues [43].

Recently, Strøm et al. [53] performed a randomised trial to assess a protocol of no sedation in 140 mechanically ventilated patients. Patients were assigned to receive no sedation or sedation with daily SATs. In both groups, i.v. boluses of morphine were allowed. Patients in the intervention group had more ventilator-free days, with a mean difference after correcting for baseline variables of 4.2 days (95% CI 0.3–8.1). Length of ICU and hospital stay was significantly shorter in the intervention group. No difference in the occurrence of complications was recorded.

Another approach to manage sedation in order to improve overall outcomes of mechanically ventilated patients is the establishment of patient-targeted sedation protocols. Several trials have evaluated the effect of using these protocols/algorithms, some of which are nurse driven [54–57], showing a benefit in weaning outcomes.

6.8 Weaning in Special Populations

In many patients, withdrawal from mechanical ventilation is influenced by their underlying conditions, and weaning will entail several particularities. Therefore, we include a few words about the process of weaning in these special groups.

6.8.1 Critical-Illness Polyneuropathy (CIP) and Weaning

Several studies have compared the duration of mechanical ventilation among patients who develop critical-illness neuromuscular dysfunction and those who do not, observing a prolonged time of ventilatory support in the former group [58–62]. CIP may prolong the need of mechanical ventilation because the phrenic nerve and the diaphragm can be affected. Actually; difficulties in withdrawal from mechanical ventilation are often the first clue for diagnosing CIP, even before observing the presence of limb weakness. Nevertheless, determining whether CIP per se is a risk factor for prolonged weaning is somewhat controversial.

In a prospective cohort of 64 patients, Garnacho-Montero et al. [58] observed a longer duration of mechanical ventilation among patients with CIP (median 34 vs. 14 days). Moreover, the weaning process took longer in those patients and, in the multiple logistic regression analysis, CIP was the only risk factor independently associated with weaning failure (odds ratio 15.4; 95% CI, 4.55–52.3; $p < 0.001$). These findings were confirmed in a study conducted by De Jonghe and colleagues [59] in a prospective cohort of 95 patients. Those who developed CIP took longer to wean, and in a multivariate analysis, both CIP and COPD were independent risk factors associated with prolonged weaning.

However, the possible association of CIP and other conditions that prolong the weaning process have been poorly evaluated. Some risk factors for developing CIP are also risk factors for a difficult weaning. Therefore, prolonged duration of mechanical ventilation could

represent the effect of the underlying conditions rather than the presence of CIP.

Thus, given this relationship between CIP and prolonged weaning, it is important to insist upon implementing preventive measures to avoid CIP and the consequences such implementation regarding important outcomes for mechanically ventilated patients, as treatment is solely based on rehabilitation.

6.8.2 Neurological and Neurosurgical Patients

We have already emphasised that adequate mentation is needed to consider the patient ready to wean. Nevertheless, controversy has been raised around the threshold of mental status actually required for successful weaning. As we previously described, the study performed by Coplin et al. [31] does not support delaying weaning when impaired neurologic status is the only reason for keeping the patient intubated. The absence of adequate mental status actually prolongs mechanical ventilation among this population. Nevertheless, in the study in which Namen et al. [32] assessed the predictors of successful weaning in neurosurgical patients, the GCS score was actually associated with extubation success in a multivariate analysis. Several studies have assessed whether a systematic approach to weaning in these patients is better than using physician judgment alone. In a study by Navalesi et al. [63], 318 neurologic or neurosurgical patients receiving mechanical ventilation were randomly assigned into two groups. In the intervention group, a systematic approach to weaning and extubation was used, whereas in the control group, physician's judgment only was considered. Reintubation rate was lower among patients of the intervention group (5% vs. 12.5%, $p = 0.047$). Other features that must be considered when weaning these patients are the role of performing an early tracheotomy, and carefully assessing adequate cough and secretion amount. Several studies have demonstrated the importance of evaluating cough strength, amount of secretions and mental status to successfully wean a patient [30, 64].

6.8.3 Chronic Obstructive Pulmonary Disease

A large percentage of COPD patients admitted to an ICU will need ventilatory support. In some of these patients, weaning from mechanical ventilation is particularly difficult [64]. In this chapter, many questions have been raised and features considered regarding weaning such patients: do they benefit from an SBT with a positive end-expiratory pressure (PSV or CPAP modes)? Is there a role for blood gas measurement at the end of the SBT? In which scenarios of the weaning process can they benefit from NPPV? Do the risk factors for extubation failure differ from those in a pooled mixed population? Is weaning different in patients with chronic hypercapnia compared with normocapnic patients? Should the same oxygenation threshold be used to assess readiness to start weaning among patients with chronic hypoxia? Several studies that try to solve these issues have been reviewed here; nevertheless, further evidence is necessary to answer many of these questions, and studies performed solely involving these subgroup of patients would probably be useful for this purpose.

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Ventilatory Strategies in Acute Lung Injury

7

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7.1 Introduction

Acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) are devastating disorders characterised by pulmonary inflammation leading to hypoxaemia and respiratory failure and are some of the most important causes of admission to the paediatric intensive care unit (PICU) [1, 2]. The American European Consensus Conference (AECC) criteria define ALI and ARDS in adults and children using four clinical parameters [3]:

1. acute onset;
2. severe arterial hypoxaemia resistant to oxygen therapy alone [partial pressure of oxygen in arterial blood (PaO_2):(fraction of inspired oxygen (FiO_2) ratio ≤200 Torricelli (torr) for ARDS and PaO_2:FiO_2 ratio ≤300 for ALI);
3. diffuse pulmonary inflammation (bilateral infiltrates on chest radiograph);
4. no evidence of left atrial hypertension.

Although ALI/ARDS occur with less frequency in children than in adults, the risk factors and pathophysiology are similar [4]. The most common trigger is infection of the lower respiratory tract as pneumonia, followed by sepsis and bronchiolitis [5]. Irrespective of age, ALI is characterised by an initial insult that triggers cell-mediated mechanisms, releasing a cascade of a variety of mediators that disturb the integrity and function of the cellular linings of the alveolar–capillary unit. Hyaline membranes, flooded alveoli with protein-rich oedema fluid, infiltrates of polymorphonuclear neutrophils (PMN), macrophages and erythrocytes are the leading histological hallmarks of ALI [6]. Proinflammatory mediators are expressed in lung alveolar and endothelial cells and are associated with ALI onset, severity and course, whereas the degree of inflammation depends on the biologic activity and the imbalance between pro- and anti-inflammatory cytokines [7]. The dynamic interaction between inflammation, coagulation, restoration of water transport and cell function need to be rebalanced and surfactant production restarted [8]. Clearance of pulmonary oedema fluid and transcapillary water transport is crucial, and apoptosis should be rebalanced, providing the clearance of inflammatory cells [9]. This pathophysiological overview explains the impending respiratory failure that develops and that subsequently

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necessitates supplementary oxygen and respiratory support while appropriate aetiologic therapy is administered (i.e. antibiotic, surfactant, corticosteroids, etc.).

In this chapter, we discuss the indications, contraindications, uses and difficulties of what has come out in recent years regarding invasive and noninvasive ventilation and strategies in children with ALI and ARDS.

7.2 Ventilatory Support

The mainstay of respiratory support in children is providing adequate oxygenation and ventilation while minimising lung damage. The National Institutes of Health ARDS Clinical Trials Network (ARDSNet; http://www.ardsnet.org/) ventilator management protocol for adults uses a PaO_2 target of 55–80 torr [saturation of peripheral oxygen (SpO_2) target 88–95%]. The effect of tolerating lower levels of oxygenation for prolonged periods on the developing brain is unknown; long-term follow-up studies in paediatric ALI/ARDS to evaluate neurologic function have not been performed. Maintaining a PaO_2 of 60–80 torr (or SpO_2 ≤90%) is usually considered safe in children with ALI/ARDS; however, there are no studies supporting the safety of this therapeutic target. Lower pH and higher $PaCO_2$ levels should be tolerated if respiratory support strategies are potentially damaging to the lung [1, 10]. It is believed that very high $PaCO_2$ levels are not damaging to the brain, but rigorous long-term outcome studies in children with ALI/ARDS have not been performed. Optimally, the target arterial pH levels in children with ALI/ARDS are the same as in adults (7.30–7.45) [9, 10]. Although some children survive ALI/ARDS requiring only supplemental FiO_2, most require assisted ventilatory support [11]. Infants and small children present peculiar features compared with larger children and adults: smaller airways with increased resistance, less rigid chest walls and lower functional residual capacity leading to a higher risk of respiratory failure and more rapid development of sustained hypoxia.

There are no clear guidelines about time of endotracheal intubation and starting ventilatory support in children with ALI/ARDS, with the exception of children with loss of consciousness and inability to protect the airway. Personal skill in intubating paediatric airways and use of appropriately sized equipment and endotracheal tubes are important factors. Cuffed endotracheal tubes can be used safely in infants and young children, and may even be optimal to ensure adequate positive end-expiratory pressure delivery in the face of low pulmonary compliance [2]. Although mechanical ventilatory support is life-saving, low lung compliance and high ventilatory pressures can lead to ventilator-induced lung injury caused by alveolar overdistention (volutrauma), repeated alveolar collapse and reexpansion (atelectrauma) and oxygen toxicity [12].

7.2.1 Ventilator-induced Lung Injury

Ventilator-induced lung injury (VILI) is considered to initiate and sustain lung injury following a similar histological and inflammatory pattern to that of original ALI [13]. VILI also contributes to multiorgan failure and death. Barotrauma is characterised by the fact

that mechanical forces (high-pressure inflation) during artificial inflation cause pressure-related ''shear forces'' on inhomogeneous (partly aerated and partly consolidated) lung tissues [14]. On microscopy, lungs show disruption of the alveolar capillary sheets with air leaks. Atelectrauma is defined as repetitive opening and closing of alveolar units during mechanical ventilation, with alveolar–capillary stress failure. Volutrauma comes when large tidal volumes (Vt) cause disruption of alveolar–capillary sheets, pulmonary oedema, increased alveolar–capillary permeability, alveolar–capillary stress failure and structural abnormalities on electron microscopy [15, 16]. Ranieri et al. developed the "biotrauma" hypothesis, which addressed the question of why mechanically ventilated patients with ALI die [17, 18]. VILI shows biochemical characteristics similar to those of original ALI [19]. Invasion of PMN and the presence of proinflammatory cytokines [e.g. tumour necrosis factor alpha, interleukin (IL)-6, IL-10] play a major role. Additionally, mechanical stretch activates many signal transduction pathways (e.g. mitogen-activated pathway), which in turn activate inflammatory mediators. However, the exact relationship between pro- and anti-inflammatory mediators and their balance are still under debate: they might differ in children and may occur in healthy as well as in preinjured lungs (e.g. sepsis-induced ALI) [14, 15, 20]. Finally, these proinflammatory mediators may spill over from the pulmonary compartment to the systemic circulation and trigger a generalised inflammatory response in major organs, leading to multiorgan failure and death [13]. Protective ventilation strategies, in order to prevent VILI, should aim at preventing atelectasis, reopen atelectatic regions and keep the lung open. Furthermore, overdistention should be prevented and high-pressure ventilation avoided. It has been shown that atelectrauma (alveolar collapse) could be prevented by sufficient positive end-expiratory pressure (PEEP) above the lower inflection point in combination with recruitment manoeuvres [21–23]. Optimal PEEP has been shown to reduce biotrauma by preventing translocation of cytokines (or even bacteria) from the alveolar compartment to the systemic circulation. Without PEEP, however, this compartmentalisation is lost, and inflammatory mediators as well as pathogenic microbes are distributed to other organs and cells, contributing to secondary sepsis, multiorgan failure and death [19, 24]. Despite the experimental evidence for applying sufficient PEEP, clinical results question the benefits concerning final outcome. In a randomised controlled trial (RCT) of low versus high PEEP, the high PEEP group (13 cmH_2O) disappointingly did not demonstrate a significant mortality reduction [25]. The effect of PEEP on mortality could be hidden by the low overall mortality rate (<26%) produced in the two groups of patients by the "lung-protective" basic ventilator settings: Vt <6 ml/kg and positive inspiratory pressure (PIP) <30 cmH_2O. Therefore, additional benefits from a single parameter such as PEEP might have been difficult to demonstrate. Second, a PEEP level of 13 cmH_2O might not have been high enough. It has been demonstrated that PEEP levels >15 cmH_2O are necessary to keep alveoli open and prevent lung injury [26, 27]. Third, when optimal PEEP was combined with small Vt of <6 ml/kg and recruitment manoeuvres, patient outcome improved [28, 29]. Despite some limitations in study design, the ARDS Network study set a new ventilation strategy as a gold standard: sufficient PEEP (titrated on FiO_2 or respiratory function measurements), lung recruitment, avoiding PIP >30 cmH_2O and Vt not exceeding 6 ml/kg of ideal body weight [22, 23, 30]. Furthermore, Gattinoni et al. recommended calculating the Vt not in relation to ideal body weight but in relation to the actual (i.e. smaller) lung volume, which can be measured by computed tomography [31]. Using this approach, the levels of inflammatory markers as well as mor-

tality rates in adult patients have been reduced [17, 18, 28]. However, reliable data from children with ALI are lacking, and it is questionable whether or not evidence from adult patients can be applied to children. Unfortunately, conducting a well-designed trial in the paediatric age group is difficult due to the smaller number of children with ALI. In the meantime, the evidence and practice derived from adult patients have already entered and are being applied in the PICU.

7.2.2 Prone Positioning

In the prone position, dependent lung regions are recruited under the influence of gravity. Promising clinical observations in adult ALI/ARDS patients demonstrated that the prone position improves oxygenation by 70–80% [32–34]. A trend towards lower mortality rates was observed when patients with severe ARDS were put in the prone position within 48 h after onset of ALI/ARDS for at least 17 h per day for 7 days [35]. In paediatric patients, Numa et al. demonstrated that the prone position increases functional residual capacity, improving lung compliance and oxygenation [36]. Many clinical case series have shown that oxygenation improved in children when placed in the prone position [36–46]. Oxygenation improves within a short period (1–2 h) after position change and can be sustained. For example, Casado-Flores et al. showed in a prospective case study that repetitive changes of positioning every 8 h improved oxygenation in 18 of 23 children with ARDS; however, mortality rate was not affected [41]. The largest prospective multicentre RCT found no differences between both groups on important outcome variables, such as ventilator-free days and mortality rate [39]. Despite these disappointing findings, it has been shown that regular prone position is able to ameliorate the degree of VILI [47–49]. In summary, at this time, there is not enough evidence to recommend prone positioning for routine use. However, "turning the child around" should not be definitely disregarded [38, 50].

7.2.3 Noninvasive Respiratory Support

Noninvasive respiratory support (NRS) is the delivery of ventilatory support without the need of an invasive airway, such as endotracheal intubation or tracheostomy. Two types of NRS are commonly used: (1) noninvasive continuous positive airway pressure (nCPAP); and (2) noninvasive positive pressure ventilation (nPPV). NCPAP applies a constant distending airway pressure throughout the entire respiratory cycle while the patient is spontaneously breathing. It exerts its effects by: (1) increasing oxygenation and carbon dioxide (CO_2) washout by inflating collapsed alveoli and recruiting lung volume; (2) reducing the effort to breathe; (3) preventing apnoea by stabilising upper airways and chest wall, particularly in ex-preterm babies. During nPPV, the patient's spontaneous inspiratory effort triggers the ventilator to provide a variable flow of gas that increases until airway pressure reaches a selected level. Thus, during each spontaneous inspiration, the patient receives a pressure-supported breath that theoretically allows better respira-

tory system muscle unloading, alveolar recruitment, oxygenation and CO_2 washout. Unfortunately, patient–ventilator asynchrony may become a major issue, leading to nPPV treatment failure. Two physiological studies by Essouri at al. [51] and Stucki et al. [52] demonstrated the effectiveness of nPPV in reducing inspiratory effort evaluated by oesophageal and transdiaphragmatic pressure time product and oesophageal tidal swings in children with acute respiratory failure (ARF). The application of nPPV by nasal and/or facial mask was associated with a significant improvement in breathing pattern and gas exchange.

7.2.3.1 NRS as Prophylactic or Curative Treatment

NRS has been proposed in two different contexts: (1) as a preventive, or prophylactic, application in postoperative patients at risk; and (2) as a curative application to improve respiratory function and avoid endotracheal intubation. Contrary to adults, to now, no published papers are present in the paediatric literature on the use of NRS in the postoperative period. As a curative application, NRS should be initiated according to: (1) clinical signs – moderate to severe dyspnoea and/or tachypnoea (defined as respiratory rate >75th percentile according to age); and (2) gas-exchange derangement – hypoxaemia [defined as an oxygen inspired fraction >0.5 to obtain peripheral oxygen saturation ($SpaO_2$) >94%] and/or respiratory acidosis (defined as pHa <7.35). Possible contraindications for NRS are: life threatening hypoxaemia; obstruction of the upper airways; vomiting; cough or gag reflex impairment; surgery, trauma or deformity of the face; Glasgow Coma Scale <10; haemodynamic instability requiring inotropes/vasopressors or cardiac arrhythmia; cyanotic congenital heart disease.

NRS should not be started in more severe ARF in the presence of: (1) clinical signs of exhaustion (active contraction of accessory muscles of respiration with paradoxical abdominal and thoracic motion); (2) PaO_2:FiO_2 ratio <150 mmHg and/or $PaCO_2$ >55 mmHg; (3) pHa <7.30. Mayordomo-Colunga et al. [53], in a prospective observational study, demonstrated that pneumonia as primary cause of ARF, Paediatric Risk of Mortality (PRISM) score and slow RR decrease during NRS initial period were independent factors for noninvasive treatment failure. These results confirmed previous data by Essouri et al. [54] and Bernet et al. [55].

7.2.3.2 Settings of NRS

There are practically no data on how to initiate NRS in children. Knowledge is based on the direct experience of clinicians working in the field, and a variety of routines are applied. In nCPAP, PEEP pressures between 4 and 8 cm H_2O are safe and not associated with adverse haemodynamic effects. Of note, when nCPAP is delivered by helmet, a high-flow system should be used to prevent CO_2 rebreathing (minimum flow rate 40 L/min). A ventilator should thus never be connected to a helmet in the nCPAP mode.

7.2.3.3 Ventilators

Three methods can be used to administer nCPAP in infants and children: (1) the high-flow system, which incorporates a blender, a flow meter and an underwater PEEP valve (bubble CPAP); (2) the fluidic logic system, in which the pressure is generated by a high gas flow through a tube with increased resistance; (3) the ventilator CPAP system, in which resistance is applied to the expiratory valve. No compelling evidence supports the use of one system over the other. NPPV can be administered by both intensive care unit (ICU) and portable ventilators, although important differences exist among ventilators [56]. The sensitivity of inspiratory and expiratory triggers is of great importance in children, in particular in case of air leaks through the interface. In adults, ineffective inspiratory efforts and double triggering are the most common types of asynchrony leading to patient discomfort [57], whereas in children, autotriggering has been shown to be the primary cause of difficult patient–ventilator interaction [51]. To minimise asynchrony, the following options can be considered: (1) setting an inspiratory trigger that is as sensitive as possible but avoiding autotriggering; (2) preventing prolonged inspiratory time using a preset limited inspiratory time or an appropriate flow threshold of the expiratory trigger; (3) using ventilators with leak-compensation software [58].

7.2.3.4 Interfaces

Comparative data on noninvasive interfaces in the paediatric population are virtually absent despite the crucial role this piece of equipment plays, both with respect to successful ventilation and to adverse effects. An interface that fits properly is crucial to minimise air leaks and maximise noninvasive respiratory support treatment efficiency and success. The interfaces have included facial masks, moulded masks and modified nasal cannulae, and in some cases full-face masks, but nasal masks seem to be preferred, particularly in younger children. The transparent paediatric helmets, made of polyvinyl chloride have been proposed as a possible alternative to masks, with potential advantages: (1) good tolerability; (2) no air leakage; (3) more stable fixation system; (4) speaking and coughing is facilitated; (5) application regardless of facial contour, facial trauma or edentulism; (6) lower risk of pressure sores, resulting in better comfort and prolonged time of use [59]. In a recent paper [60], a group of 20 infants with moderate hypoxaemic ARF treated with CPAP delivered by helmet was compared with a matched control group who received CPAP by facial mask. The authors demonstrated the use of the helmet was better tolerated, required less patient sedation, allowed a more prolonged application time and avoided facial skin irritation when compared with a facial mask. In a very recent paper by Milési et al. [61] the feasibility of helmet use in infants between 1 and 12 months (median 5 months) of age with ARF was analysed in 23 infants. Helmet CPAP failed in two (9%) patients. Stability or improvement occurred in 16 (70%) patients. Pain and discomfort score was stable or improved in 22 (96%). Pressure sores were found in three (13%). Humidity was 98% (98–99%) and fell to 40% (39–43%) after the humidifier was stopped. The noise level in the helmet was

81 (77–94) dB–sound pressure level (SPL). The helmet was thus judged a satisfactory interface for CPAP delivery in young infants in more than two thirds of cases.

7.2.3.5 Noninvasive Respiratory Support in Specific Settings

At this point we focus on three recent issues related to the application of NRS in children with ARF: (1) the use of nCPAP combined with helium–oxygen gas mixture; (2) the use of NRS to reduce the rate of endotracheal intubation; (3) the use of nPPV in immunocompromised oncologic patients.

1. NCPAP combined with heliox: NCPAP has been shown to be effective in the early treatment of acute severe bronchiolitis [62]. A preliminary uncontrolled study suggests that the effectiveness of nCPAP could be further increased if a mixture of helium and oxygen (heliox) is added to the gas mixture [63]. The benefit of heliox has been attributed to its lower density, leading to reduction of the respiratory muscle work of breathing [64]. Martinon-Torres et al. [65] carried out a single-centre, prospective, randomised, crossover study using nasal CPAP with and without heliox in 12 infants with severe bronchiolitis. End points were reduction in Clinical Asthma Score and improved gas exchange. Nasal CPAP with either gas mixture (air–oxygen or heliox) was safe and effective in ameliorating gas exchange and respiratory pattern. Furthermore, when heliox was used in place of an air–oxygen mixture, clinical scores and transcutaneous $PaCO_2$ improved almost twofold. As heliox is effective when used at a concentration >60%, benefits cannot be expected for patients with oxygen requirements >40%. Moreover, heliox produces hypothermia and is quite expensive;
2. NRS and intubation rate: a Cochrane Collaboration review concluded that there is a lack of well-designed, controlled experiments of nPPV in children with acute hypoxaemic respiratory failure [66]. Since that review, the efficacy of nPPV in reducing the intubation rate was evaluated by two studies: Javouhey et al. [67] conducted a retrospective study comparing infants with severe bronchiolitis admitted to the PICU during two different winter epidemics. In the first epidemic, invasive ventilation by tracheal intubation was the sole ventilatory support strategy available (invasive ventilation period). During the following winter epidemic, the attending physician was encouraged to use nPPV by nasal mask as the primary ventilation technique (nPPV period). The authors demonstrated a significantly lower rate of intubation and ventilator-associated pneumonias in the nPPV period compared with the invasive ventilation period. Yanez et al. [68] carried out a prospective, randomised, controlled study on the same topic. Fifty children with ARF, mainly due to pneumonia and bronchiolitis, were randomly assigned to either nPPV by facial mask or standard medical therapy. NPPV diminished respiratory rate and heart rate within 1 h and reduced tracheal intubation by 47% compared with standard therapy. It is noteworthy that the higher intubation rate was reported in the youngest patients, and one could speculate the facial mask is not the recommended device in that age group. Actually, most papers suggest the use of nasal masks in infants with respiratory disorders [52, 62, 63]. Moreover, infants with ARF are severely tachypnoeic, with respiratory rates

as high as 100 bpm. Patient–ventilator asynchrony frequently occurs when nPPV is used, and nCPAP by helmet could represent a valid alternative in nonhypercapnic patients, as proposed by Codazzi et al. [59] and Chidini et al. [60];

3. NRS in immunocompromised oncologic children: immunosuppressed children have been regarded as having a poor outcome, especially when tracheal intubation and conventional mechanical ventilation for respiratory failure is required. Two nonrandomised studies explored the feasibility of nPPV in this subgroup: Pancera et al. [69] retrospectively analysed 239 children admitted to PICU for ARF and treated by either invasive or noninvasive ventilation. In their study, nPPV reduced the need for endotracheal intubation, and haemodynamic impairment was identified as an independent factor for intubation. Piastra et al. [70] evaluated nPPV by mask or helmet in 23 consecutive immunocompromised children with ARDS. The authors showed treatment effectiveness, and intubation was avoided in >50% of children. Moreover, early improvement in PaO_2:FiO_2 ratio was able to predict nPPV success.

7.3 Conclusions

NRS in the paediatric population is now an option and is being increasingly applied. Evidence supporting its use in infants and children with ARF is limited, and identifying the appropriate patient, application time and setting are yet to be determined. However, the most recent physiological and randomised studies indicate that early application of NRS ameliorates breathing pattern, gas exchange and respiratory-muscle unloading. The effects of NRS concerning complex outcomes require further investigations. CPAP by nasal mask or helmet could be considered as the first-line noninvasive respiratory treatment in infants and children with mild to moderate ARF. NPPV by facial mask probably represents the technique of choice in moderate to severe acute respiratory disorders. Furthermore, it is most important to rely on well-trained medical and nursing staff at all times and that NRS is applied only in the setting of an ICU with appropriate cardiorespiratory monitoring.

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Mechanical Ventilation Beyond the PICU

8

G. Ottonello, A. Franceschi

8.1 Introduction

Long-term ventilation is referred to any child who, when medically stable, requires mechanical aid for breathing after an acknowledged failure to wean, or a slow wean 3 months after ventilation initiation [1]. The number of children with chronic respiratory failure requiring long-term ventilation support, even 24 h a day, is constantly increasing as a consequence of better medical treatment and technological advances that have contributed to longer survival of critical patients and to the development of suitable home medical equipment [2–4]. However, the hospital – and especially the intensive care unit (ICU) – is definitely an inadequate environment in which to assist these patients, particularly in regard to their physical and psychological development [5, 6]. Furthermore, in these cases long-term hospitalisation represents inappropriate exploitation of resources [7]. Therefore, for children who are medically stable, home care is an appropriate alternative despite the resulting radical change in family life.

Home ventilation can be provided by positive pressure in the form of either invasive or noninvasive ventilation (NIV). Invasive ventilation refers to the delivery of mechanical ventilation to the lungs using an endotracheal tube; NIV refers to the delivery of mechanical ventilation to the lungs using techniques that do not require an endotracheal device. However, some children are treated with negative pressure ventilation, with phrenic pacing and for hours, during the day, some patients with neuromuscular disorders use glossopharyngeal breathing. This technique consists of swallowing air into the lungs, thus bypassing the need for respiratory-muscle strength.

8.2 The Extent of the Problem

The number of children treated at home with mechanical ventilation has increased for several reasons:

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1. improved survival of children affected by chronic respiratory diseases;
2. availability of portable devices suitable for home use, such as mechanical ventilators, suction devices, monitors;
3. increased expectation of life, even for patients with severe and life-threatening diseases;
4. physician attitude to offer all available options for the patient to attain an improved quality of life at home despite shifting the care from the hospital.

A national survey in Italy in 2007 investigated long-term ventilation in children. Data assess all patients <17 years of age who were on mechanical ventilation, including continuous positive airway pressure (CPAP) at home. A questionnaire was sent to all facilities that dealt with home ventilatory programmes. Investigators obtained answers regarding 535 patients, with an estimated prevalence of long-term mechanical ventilation of 5.4/100,000 population, which is similar to other surveys from other countries (Canada, Chile, Germany, France, Italy, Japan, New Zealand, Switzerland, The Netherlands, Turkey, the UK, and USA [8–25]). Median age was 8 (interquartile range 4–14) years; median age at starting mechanical ventilation was 4 (1–11) years, and 56% were boys. The most frequent diagnostic category was neuromuscular disorders (49%), followed by lung and upper respiratory diseases (18%), hypoxic (ischaemic) encephalopathy (13%) and abnormal ventilation control (12%). Noninvasive ventilation is used in 60% of Italian patients, with the remainder being ventilated through a tracheostomy. No patients in Italy are on negative-pressure ventilation; at the time of the survey, five patients were using phrenic nerve pacing, and four patients with neuromuscular disorders were using glossopharyngeal breathing. There was 56% receiving ventilation only while asleep, 24% received ventilation for >20 h/day; 21% were ventilated for 12–20 h/day. Only nine (2%) patients were still living in the hospital at the time of the survey, the vast majority (98%) living at home.

8.3 Patient Care: A Multisystemic Approach

8.3.1 Mechanical Ventilation

The first step in a programme of home ventilation is to obtain normal pulmonary ventilation parameters. The gold standard for mechanical ventilation is for haemoglobin saturation values >95%. The end tidal carbon dioxide range may be broad, with limits of 30–45 mmHg, allowing for variation with sleep position. Ventilation mode will depend on several other aspects:

1. noninvasive ventilation: this technique is usually preferred by patients [26] and their families. Advantages are avoidance of surgery and its possible related complications [27]; reduced risk of respiratory-tract infections and interference with swallowing and speaking, even if swallowing can be preserved and speech can be obtained during both inspiration and expiration [28]; and the psychologically relevant impact of the tracheostomy for the growing child;

2. invasive ventilation: tracheostomy is reserved for patients with totally impaired bulbar function who present continuous inhalation of saliva or gastric content with consequences on pulmonary function. Other possible indications for tracheostomy ventilation are the need for 24-h/day mechanical ventilation and diagnosis of congenital central hypoventilation syndrome [29].

8.3.1.1 Noninvasive Ventilation

Mask Ventilation

Interfaces for NIV are crucial for patient acceptance of the technique and for good ventilation. Different manufacturers have created different types of equipment to connect the mechanical ventilator to the patient that minimise air leak, improve comfort and allow patient synchrony with the ventilator [30]. Unlike results in adult studies, paediatric studies show that nasal masks seem to be preferred for noninvasive positive-pressure ventilation (NIPPV), both in the chronic and acute settings, despite the fact that children enrolled in these studies were often past the age of obligatory nose breathing [31, 32]. In the clinical setting, it is recommended to have different models and types of masks available in order to find the best fit for each patient [33]. None of the NIPP ventilators available are ideal and able to adequately ventilate every patient type. Sensitivity triggering inspiration of most ventilators is insufficient for infants breathing through the mask in the presence of leaks [34]. For NIPPV, the mechanical ventilator must have:

- a very sensitive inspiratory trigger;
- the ability to compensate for large air leaks;
- a high maximal inspiratory flow;
- the possibility to silence alarms indicating apnoea, low exhaled tidal volume, high inspiratory volume – in infants the presence of air leaks often causes zeroing of expired tidal volume;
- the availability of different modes of ventilation, including time-cycled and pressure-limited.

NIPPV with unidirectional flow increases the need for humidification due to the high flow of fresh air used by the ventilator. The nasal mucosa loses water delivered to the inspiratory gas, leading to an increase in nasal airway resistance, which in adults has been shown to increase up to six times the baseline value [35]. Because the older child is no longer an obligatory nose breather, this could lead to mouth breathing and associated air leaks [36]. Only heated humidifiers can be used during NIPPV. One must consider that the presence of a humidifier will increase the resistance of the circuit and interfere with triggering and pressure delivery.

Side effects of NIV in the chronic setting are mainly related to the consequences of the pressure of the mask on the skin and facial bones. Skin injuries are more common during the acute setting, but often, children on chronic NIV experience episodes of respiratory tract infections that cause continuous application of NIV for some days, with possible skin damage. Lesions are usually seen on the nose and forehead. They can manifest even after a few hours if the mask is not properly dressed and can be so severe as to create perma-

nent skin scars. Facial flattening with midface hypoplasia is a problem of great concern. The continuous pressure of the nasal mask on the maxilla causes a lack of bone growth, with dental type III malocclusion [37]. Consequences are both aesthetic and functional. A preventive approach is needed and will consist in continuous monitoring provided by an expert maxillofacial surgeon and a strategy of rotating different types of masks avoid applying pressure at the same points.

8.3.1.2 Invasive Ventilation

Ventilation with Tracheostomy

Tracheostomy for home mechanical ventilation is used by 40% of patients in Italy, primarily for those with neurological impairment and the need or 24 h/day mechanical ventilation. The tracheostomy allows more reproducible parameters of mechanical ventilation with measurable volumes and settable alarms. If the cannula is not cuffed, as is usually the case in children, and if leaks are consistent, ventilation through the cannula may present similar difficulties as those experienced with the mask. Caregivers must be aware of the two most severe and common complication that can occur during tracheal ventilation in children: dislocation; and cannula plugging. Caregivers must be trained to recognise and solve these problems; moreover, it must be made very clear that children with tracheostomy can only be with people who are able to treat these events, which if not promptly and effectively treated, may cause severe complications and even death [38]. Pressure-limited ventilation with volume guarantee is available with several portable mechanical ventilators. This offers the possibility of compensating for the leaks that occur when using uncuffed cannula, together with the availability of increasing ventilation pressure to guarantee a minimum preset tidal volume in the presence of obstruction, for example, for tracheal secretions. Such ventilators offer two different modes by which to deliver a target volume during pressure-limited ventilation: dual control mode within a breath; and dual-control mode, breath to breath.

Nonrespiratory Problems

Feeding

Children affected by chronic respiratory failure needing home mechanical ventilation often suffer feeding problems too: many need enteral feeding, as problems of swallowing are often present. This is the situation with children affected by severe neuromuscular diseases (MD) such as spinal muscular atrophy type 1 (SMA1) and some with type 2 (SMA2), other congenital myopathies, and severe cerebral palsy due to hypoxic ischaemia or congenital metabolic diseases [39]. Children affected by sever pulmonary diseases such as bronchopulmonary dysplasia, manifest continuous dyspnoea with increased intrathoracic depression. This condition predisposes the child to gastroesophageal reflux disease (GERD), which itself worsens respiratory function [40]. Even children unable to maintain the sitting

position, as with SMA1 children, are predisposed to GERD, even as a consequence of the frequent need for cough-assisting manoeuvres. Such patients need some intervention for treating and avoiding GERD. They can be treated with medical support, such as antacid and prokinetic drugs, but frequently they need even more invasive manoeuvres, such as duodenal jejunal feeding or antireflux surgery (gastrooesophageal Nissen fundoplication, etc.) [41].

Swallowing

Neurological compromise is often associated with swallowing diseases. Failure to swallow requires accurate diagnosis and appropriate treatment, as it represents severe impairment for the child's social integration within the family and at school. Early rehabilitation must be instituted to prevent swallowing diseases. Children on long-term ventilation and, in particular, children with tracheostomies, may spend weeks without ingesting anything per os. This limitation must be counteracted, and a quick oral feeding, even with a small amount of food, will avoid future impairment. In the presence of already established disease, prompt intervention by the logopaedist will be needed to try to rehabilitate the lacking function. A narrow tracheal cannula will facilitate the use of the speaking valve, which allows phonation and permits better movement of the air through the vocal cord and a more prompt reflex of swallowing [42].

Movement

Physicians taking care of patients with severe respiratory system compromise must frequently deal with patients affected by NMD. The mode of respiratory support needed will probably influence the patient's capacity to move. Those patients with 24-h/day support will need a mechanical ventilator in their wheelchair; moreover, if they are on NIV, the system will need special regulation: the ventilator will be volume-limited, pressure-cycled, have a battery power supply and a flow-restrictive mouthpiece to create resistance high enough to prevent autocycling [43]. Children affected by SMA1 will tolerate only few hours with their head and shoulders elevated above the level of their torso if they are on mask ventilation because of the lack of good swallowing ability and saliva inhalation. This point will be crucial for their quality of life: some may be better supported with tracheal ventilation if bulbar weakness is severe.

Comprehensive treatment directed to care of movement and position is of great concern: children with lengthy hospitalisation, often from birth, will probably experience lack of stimulation. Hopefully in such cases, a preventive approach is initiated consisting in 24-h/day free access to the unit for the parent. They can help the baby by touching and talking. Moreover, a rehabilitation specialist will be involved early with the baby, identifying possible deficits and working with and teaching parents how to interact with their child. For neuromuscular patients, the experience of being in the water is exciting. They have the sensation of less gravity and experience some movements that they are commonly unable to perform. This is also an important benefit for joints and spine. Thanks to the technological development, NMD children can be offered new electronic wheelchairs, which they can manoeuvre thanks to very sensible controls, such as joystick and soft-touch controls, and also controls operated with the eyes, head, and even the pacifier. Special technologies are Micro Light, Egg Switch, Zero Touch Switch, Infrared Switch [44].

The Spine: Prevention and Treatment of Scoliosis

NMD patients must be cared for appropriately to prevent or reduce the severity of scoliosis. The spine is inevitably exposed to the risk of developing scoliosis, and in some categories of patients, such as those affected by SMA2, a surgical procedure must be taken into consideration at a certain time. Prevention of scoliosis is achieved with postural hygiene and proper building and use of the corset. Close attention must be paid to the development of the spine, in particular during school age and adolescence. In the presence of an increase of the Cobb angle >30°, the surgical approach must be considered. Patients will need to be trained in the use of NIV and cough assist. This will facilitate extubation after surgery and a quicker recovery. This is particularly true for SMA2 patients and in all those affected by NMD, whose forced vital capacity will be <50% of predicted value [45].

8.4 Prescribing Home Ventilation: Certification and Documentation

8.4.1 Attribution of Disability

For attribution of Italian state rights regarding "Disability", the following criteria are necessary: Permanent impairment in accomplishing activities and skills for age (that peers without disabilities are able to perform). Only for the children >15 years will the percentage of civil disability be reported, and that exclusively for the purpose of being placed on a special employment list (law 68/99); When applying for disability benefits, the steps can be performed according to a specific section (Invalidità Civile 2010; InvCiv2010) on the official National Public Health Institute (INPS) Web site www.inps.it.

8.4.2 Handicapped Certification

In the evaluation of a handicap, the commission can even define even the degree of severity of that condition according to the impairment that decreases personal independence and leads to the need for permanent or continuous assistance (art. 3, comma III, law 104/1992).

8.4.3 Rare Disease Certification

The carrier of a rare disease is exempt from participating (sharing) in the paying expenses for medical care and associated investigations.

8.4.4 School Attendance

The family can request a medical certificate be sent to the school describing the child's special needs: (1) schools must accept the child and arrange for the special needs with an individual teacher and a nurse, if needed; (2) the working group who will take care for the pupil will prepare a dynamic functional profile (PDF), and individual educational plan (PEI.) and a so-called personalised educational plan (PEP).

8.4.5 Worker Benefits

Some workers who care for people with disabilities can apply for "exceptional biannual leave," which is a 2-year period during which they continue to be paid. Also, art 53 of legislative decree 151/2001 states that individuals who care for an individual with a disability, as per law 104/1992, do not need to work nights, and therefore can apply for a "nights on call exemption".

8.5 Caregiver Training

Required parental/caregiver preparedness consists of the following:

1. complete knowledge of the complexity of the patient's disease through in-depth discussion with clinicians, simulation of emergency situations, videotapes and contact with associations for families with disabled children;
2. training on how to move the infant and hold him or her in their arms;
3. instruction on how to feed the child per os and when it is appropriate to switch to nasogastric tube feeding. Parents can modify quantity and timing of nutrition according to periods of sleep, respiratory fatigue and increased need of cough assist;
4. learning how to use the suction machine and oximeter;
5. training in basic paediatric life support: parents' skills are first evaluated on a dummy and they are then asked to demonstrate efficacious bag-and-mask ventilation on their child;
6. training in the use of tracheal ventilation, noninvasive ventilation and mechanical cough assist (MAC);
7. managing acute respiratory tract infection: parents are trained to modify the setup of the mechanical ventilator and MAC during episodes of respiratory deterioration. They are allowed to increase ventilation pressures to a maximum of 25 cm water (H_2O) and to increase the respiratory rate. Parents can modify the setting of the cough-assist machine, also. Then they are taught that the inspiratory pressure can be increased to obtain good chest rise and that, however, pressure must be maintained <40 cm H_2O. Expiratory pressures can be raised to 45–50 cm/H_2O.

8.6 Follow-up and Emergency Admissions

A programme of home mechanical ventilation in children must include a scheduled follow-up. This is necessary to verify the patient's health conditions, both respiratory and general. During the follow-up visit, which commonly takes 2–3 days, the main aspects are to: (1) consider the condition of the family, e.g. whether they have trouble carrying the child; (2) evaluate the months spent at home to identify symptoms of poor sleep ventilation (recurrent respiratory infections, morning headache, etc); (3) evaluate the baby's nutritional state and development (with the Bailey rating scale or other scales). Respiratory parameters of carbon dioxide (CO_2) and pulse oximeter oxygen saturation (SpO_2) are evaluated during both sleep and wakefulness with and without the mechanical ventilator. It is important to verify the presence of both hyper- and hypocapnia and the possible negative consequence of the latter [46]. Moreover, it is important to remember that low SpO_2 can indicate the presence of hypercapnia, but hypocapnia can easily go unrecognised without good monitoring. End-tidal CO_2 monitors can give inaccurate values in the presence of leaks, both during NIV and during tracheal ventilation with uncuffed cannula. For these reasons, transcutaneous CO_2 monitoring may be the best choice, considering doing at least one check of the transcutaneous CO_2 and blood.

8.7 Ethics

Respiratory support for children with severe systemic diseases (such as SMA1 or severe cerebral palsy) is not widely accepted. Several important paediatric and paediatric neurology text books, for example, recommend against any mode of artificial ventilation for SMA1 patients [47, 48]. The decision to start support to maintain life in such a severe disease is very difficult. Concern exists about the opportunity to prolong life with artificial means and the risks of prolonging also the patient's suffering without option of care. A survey demonstrated that differences exist among clinicians about attitudes towards offering different options of care for SMA1 patients [49]. In fact although ventilatory support can keep SMA1 patients alive for decades, they continue to suffer severe neurological disability and usually become completely paralysed and unable to speak. The decision as to whether to offer long-term ventilation to parents of such patients is difficult and complex. Although the level of disability is very severe, it is difficult to accurately "estimate" the patient's quality of life. In one study [50], a group of 104 carers (parents, grandparents and nurses) rated the perceived quality of life of 46 children and adolescents with SMA 1 as 7.8 out of 10. This was in stark contrast to 67 physicians who estimated these patients' quality of life at 2.9 out of 10 ($p < 0.0001$). Notably, almost 80% of physicians felt that the decision to initiate long-term ventilation should rest solely with them rather than with the patient's family. The critical question physicians must continually ask themselves is whether our patient's quality of life and, in particular, the benefits that he/she gains from being kept alive, is outweighed by the suffering experienced as a result of the underlying disease and its treatment. This is also the question we must ask the parents, attempting as

we do so to help them understand all the aspects of the disease in relation to their child and to help them make the wisest decision for the future.

It is often very difficult to make parents fully aware of their child's condition, both at the time of diagnosis and upon first clinical symptoms. It is different after several years, as the child will change as the condition and its associated problems change, which are mainly related to joint deformities. We give parents the opportunity to see movies of children affected by the same disease and putting them in contact with families in similar situations through direct contact and contact with family associations and social networks.

8.8 Conclusions

Home mechanical ventilation is a complex issue, as children who require it suffer severe diseases and their lives will be very different with respect to the lives of all healthy children in the world. Those children will suffer pain and have to deal with tubes, machines, alarms and panic situations. Frequently, they will not be able to walk, run, swim or jump; and some will not be able to speak or move at all. The child's condition will change the parents' and siblings' lives as well, often leaving little free time – perhaps even no time to read a book or attend a medical visit. Singles with a child with such a severe condition and who must work for living will be obliged to leave the child in the hospital. The majority of these children will suffer the disease with little treatment available, and some will probably die as a consequence. Nevertheless, such situations are part of life and our world; happiness and sadness do not depend exclusively on illness or wellness but lie in our hearts and in how we feel about each other, particularly about our needful neighbour. Affected children and their families are often happier and emotionally stronger than many other families and children we would consider "normal", and this is independent of any physical problem. As the number of home-ventilated children is increasing in Italy and around the world, it is important that a new culture towards these diseases occurs, allowing all physicians, nurses, health workers and healthy people to interact with them with hope and compassion, hopefully in a less ostentatious society.

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Part V
Cardiovascular Monitoring

The Nexfin Monitor – A Totally Non-Invasive Cardiac Output Monitor

9

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9.1 Introduction

The Nexfin HD monitor (BMEYE, Amsterdam, The Netherlands; http://www.bmeye.com), is a device that measures cardiac output (CO) continuously by an inflatable finger cuff, which is the only interface with the patient. The Nexfin HD measures continuous CO by combining continuous blood pressure (BP) monitoring and a novel pulse contour method (Nexfin CO-Trek) based on the systolic pressure area and a physiological three-element Windkessel model individualised for each patient. The parameters that are measured by the Nexfin HD include continuous BP (systolic, diastolic, mean), heart rate, continuous cardiac output (CCO), stroke volume (SV), systemic vascular resistance (SVR) and an index of left ventricular contractility (dp/dt).

CO is one of the most important physiological parameters, as it is the major determinant of oxygen delivery. Its measurement is of special importance, as so many of our efforts in the care of critically ill and high-risk surgical patients are aimed at increasing its value by various therapeutic means. Many studies have repeatedly shown that clinical evaluation and conventional monitoring alone are inaccurate and unreliable for assessing CO and that adequate resuscitation cannot be based on normalisation of vital signs alone [1–3]. Although there is little evidence that the measurement of CO per se improves outcome, this is also true for all other haemodynamic parameters that are in common daily use. The main technology for measuring CO has been the thermodilution technique (TD) used by the pulmonary artery catheter (PAC). However, many newer technologies offer a less invasive approach than the PAC while measuring CO with similar accuracy. The most recent significant development in this field is the introduction of uncalibrated CCO technologies. The uncalibrated CCO is usually based on pulse contour technology, by which various formulas are used to compute CCO values from the BP waveform without using an intermittent thermodilution for calibration. The absolute accuracy of some of these technologies has not been shown to equal that of intermittent TD [4]. However, their good tracking accuracy provides a useful tool for assessing events with short time constants, e.g. fluid

[1] Disclosure: AP is a consultant and WW and JS are employees of BMEYE.

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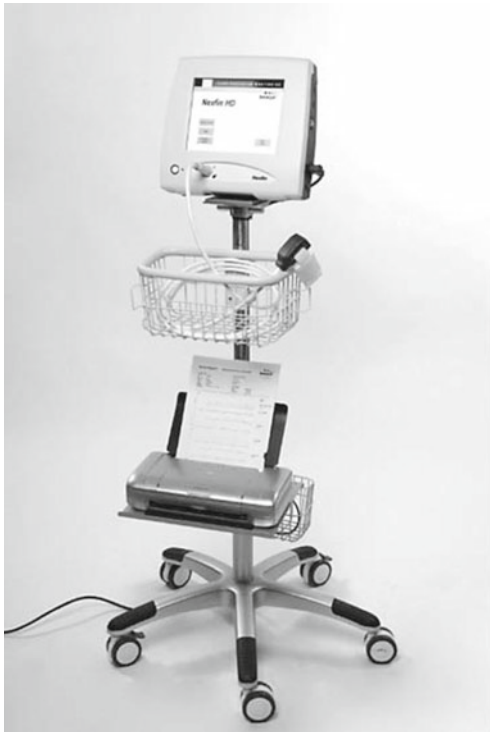

Fig. 9.1 The Nexfin HD device

loading, passive leg raising, start of inotropes etc. The Nexfin HD, which belongs to this category of continuous CCO monitors, offers a unique feature: total non-invasiveness.

9.2 Principles of CCO Measurement by the Nexfin HD

The Nexfin HD (Fig. 9.1) applies three major stages in CCO measurement.

9.2.1 Continuous Measurement of Finger BP

For continuous BP measurement, a cuff (Fig. 9.2) is wrapped around the middle phalanx of the second, third or fourth finger. The finger cuff includes a light-emitting diode (LED) that measures the diameter of the finger arteries running on both sides of the finger's palmar aspect. The cuff inflates and deflates so that the diameter of these arteries is kept constant throughout the cardiac cycle (volume clamp method). The diameter to which the arteries are clamped is determined using the Physiocal method. The pressure needed to keep this diameter constant is directly measured as the real-time pressure waveform.

Fig. 9.2 The finger cuff, the only interface with the patient

9.2.2
Transformation of the Finger BP Curve into a Brachial Artery Waveform

The CCO that is measured by pulse contour algorithms may be significantly influenced by the site of the blood pressure measurement [4]. The Nexfin HD transforms finger BP to a brachial BP waveform and uses this waveform as a robust substitute for aortic pressure as input for CCO measurement.

9.2.3
Calculating CCO from Brachial Arterial Pressure Waveform

Pulse contour algorithms for CCO measurement were initially developed by Wesseling and coworkers. These are the corrected characteristic impedance, or cZ, method [5], and the Modelflow method [6]. The limitations of these methods include the need to determine a calibration factor (K) at least once for each patient (cZ method), being more affected by strong vasoconstriction or vasodilatation, and lesser accuracy in estimating the initial absolute level of CO from finger BP (Modelflow). The Nexfin HD employs a new pulse contour method called CO-Trek, which was introduced in 2007. The CO-Trek method integrates the area under the systolic portion of the measured arterial pressure pulse (PSA), and uses the three-element Windkessel model in a nonlinear, pressure-dependent, time-variant, age-dependent fashion. The three-element Windkessel model of the cardiac afterload (Z_{in}) employed by the Nexfin includes characteristic impedance (Z_c), total arterial compliance (C_w) and total peripheral resistance (R_p). The Nexfin HD derives the aortic characteristic impedance and the Windkessel compliance from the aortic pressure–diameter relationship, whereas the peripheral resistance is provided by the model computations. With input of patient age, gender, height and weight, the components of the three-element Windkessel afterload are individualised for each patient and can be computed for any arterial pressure level and further used for stroke volume computation: $SV = PSA/Z_{in}$.

9.3 Validation of the Nexfin HD

As the Nexfin HD is a new device, there are only a few published validation studies of its new CO-Trek algorithm. However, many clinical studies have validated the previous pulse contour methods, namely the cZ and the Modelflow methods. These studies, done in high-risk surgery (e.g. cardiac, liver transplantation) and intensive care patients, showed excellent correlation with thermodilution CO, which was measured by an automated series of four TD injections equally spread over the ventilatory cycle for better accuracy [7].

In a study from 2007 performed in 24 patients undergoing uncomplicated coronary artery bypass graft (CABG) surgery, excellent results in absolute values as well as in tracking changes in CO were obtained using the Modelflow method. The results were found to be better than those of Wesseling's cZ method and of the LiDCO and PiCCO algorithms [8]. In a more recent study from 2009, the same group of de Wilde et al. studied another small group of patients (13) within 2 h of arrival in the intensive care unit following CABG or mitral valve reconstruction [9]. CO measured by the FloTrac device, the Modelflow method and the transoesophageal ultrasonic HemoSonic system (Arrow) were compared with TD as the reference. CO values were measured during and after four interventions: (1) an increase of tidal volume by 50%; (2) a 10-cm H_2O increase in PEEP; (3) passive leg raising; (4) head-up position. The main finding was that only Modelflow yielded limits of agreement (26%) <30% criteria for a theoretically acceptable alternative to TD CO. The authors concluded that Modelflow had the best performance, whereas the FloTrac overestimated changes in CO, although directional changes in thermodilution CO were detected with a high score by all three methods [9].

In another recent study [10], the authors observed a correlation between TD CO measured by a pulmonary artery catheter and the Nexfin HD CO of $r^2 = 0.83$, with a bias of 0.23 l/min and two standard deviations (SD) of ± 2.1 l/min; the percentage error was 29%. These findings are even more impressive if one takes into account that the study was done in severely ill patients [four post lung transplant, four post liver transplant and two severe acute respiratory distress syndrome (ARDS)], all of whom were receiving norepinephrine at the time of the study. Moreover, data were analysed retrospectively using hourly Nexfin HD CO measurements rather than simultaneously measured CO values. The authors noted that there were no clinical signs of disturbed microcirculation of the fingers in these patients during application of the finger cuff, indicating the safety of the Nexfin HD system. In addition, the Nexfin HD was found to be very easy to use and could be installed within minutes and hence could offer a quick initial haemodynamic overview and allow bridging the time until a longer-lasting invasive monitor could be installed in the case of a deteriorating patient [10].

9.4 Clinical Applications

The totally non-invasive nature of the Nexfin HD allows the measurement of CCO in a much wider variety of patients than was hitherto possible. Originally, the Nexfin HD

was introduced in cardiology clinics for the performance of the tilt-test to detect orthostatic hypotension. A recent study using finger-pressure-derived CCO has shown that the early postoperative postural cardiovascular response is impaired after radical prostatectomy, with a risk of orthostatic intolerance, limiting early postoperative mobilisation. Both the tilt test and the sit–stand test take advantage of the fact that the Nexfin HD provides real-time CCO, allowing immediate detection of the instantaneous response to diagnostic and therapeutic challenges. These include passive leg raising, fluid challenge, start of inotropes, exercise, etc. The continuous real-time CO measurement may be more useful and provide more accurate information about changes in CO than intermittent CO measurements by TD with their inherent variance.

One of the most interesting areas where the potential of the Nexfin HD can be fully expressed is perioperative care. It is well recognised that a small group of patients account for the majority of perioperative morbidity and mortality. By targeting specific haemodynamic and oxygen transport goals at any point during the perioperative period, the outcome of these patients can be improved. Most studies on perioperative optimisation have used repetitive fluid challenges to maximise the CO, which was measured in most of those studies by oesophageal Doppler or FloTrac. However, the oesophageal Doppler can be used only after induction of anaesthesia and for a limited period only, whereas other devices necessitate the presence of an arterial line. Indeed, finger-pressure-derived CCO has already been used for this purpose [11]. The noninvasive nature of the Nexfin HD and its semidisposable finger sensor make using this monitor an ideal fit in this important setting.

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Doppler Echocardiography in ICU Patients: Does it Improve Outcome?

10

J. Poelaert

10.1 Introduction

Modern haemodynamic management at the bedside obliges the use of a highly effective tool with instantaneous availability, flexibility and access to extensive information when needed. Echocardiography provides immediate bedside information about the haemodynamics of the ICU patient, in particular when haemodynamic deterioration occurs. Both morphological and haemodynamic features can be diagnosed instantly and related to clinical practice. In the ICU, this tool is used as a functional haemodynamic monitoring device offering on-line information on systolic function and pre- and afterload of both left and right ventricles.

10.2 Doppler Echocardiography

Doppler echocardiography (echo-Doppler) is now generally accepted as an invaluable tool to assess haemodynamically compromised patients. All morphological and functional aspects of the cardiac chambers, including valves and the respective connective tissue, and major vessels can be evaluated in a physiological approach. Furthermore, haemodynamic monitoring, revealing ventricular function and insufficient preload or excessive afterloading conditions [1] can often be fine-tuned using echo-Doppler [2]. In mechanically ventilated as well as in nonventilated ICU patients, the noninvasive transthoracic mode is often the preferred technique of choice.

Nevertheless, the transoesophageal approach remains a perfect aid, with much better visualisation possibilities. Although the transoesophageal approach is somewhat more invasive, it remains a safe technique [3, 4]. Less than 0.1% of transoesophageal echo (TOE) interventions lead to problems induced by the TOE probe, such as bleeding, hoarseness or throat ache. Recent, still unpublished, guidelines from the European Society of Intensive Care Medicine strongly suggest only operators with an advanced level of training in transoesophageal echocardiography use this technique.

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Contemporary medicine is driven by endpoints and goals, such as outcome, morbidity and length of stay in the ICU and in the hospital. In this chapter, a summary of the potential of echo-Doppler to improve outcome of the critically ill patient is provided.

From a morphological point of view, echo-Doppler in the ICU is particularly useful in patients with haemodynamic instability, high positive end-expiratory pressure (PEEP) ventilation, when high doses of inotropic or vasopressor drugs are necessary or any situation in which inadequate perfusion is present, even with normal cardiac output. One glance at the level of the short axis permits evaluation of both left- and right-ventricle function. In addition, other views should be added to extend the global assessment of ventricular function, regional-wall-segment motion and valve morphology and function. Furthermore, tissue-Doppler imaging (TDI) allows closer assessment of either regional or global evaluation of the function of these chambers [5, 6]. Echo-Doppler's different tools allow insight into functional haemodynamics in conjunction with other, rather invasively obtained, data on the condition that these data are to be integrated and interpreted in a physiological approach. It is therefore perfectly possible to obtain information on ventricular systolic and diastolic function, actual preloading conditions and even afterload.

10.3 Echo-Doppler Diagnostic Tools

The unique combination of several echo-Doppler tools facilitates accurate interpretation of blood flows and motion of both global-ventricle and regional-wall segments within a selected zone. These tools comprise:

- two-dimensional imaging, offering insight into morphology and function;
- colour Doppler, exemplifying scattering and flow direction, within the selected area;
- Doppler, providing information on flow direction, intensity and duration, and the morphology of the Doppler pattern itself can provide indications of the pathology present;
- myocardial Doppler imaging demonstrates relative motion, direction and intensity of the investigated myocardial wall segment and is particularly useful to analyse systolic and diastolic function of the left ventricle (LV), as long as both systolic and diastolic characteristic Doppler waves are preload dependent.

The difficulty with echo-Doppler involves both correct capturing of the different images in conjunction with accurate interpretation: both practical issues and knowledge must be combined to achieve accurate evaluation [7]. Hence, correct interpretation can only be achieved when the physiological meaning is fully understood, applied and integrated within the knowledge of other data. This necessitates a prolonged learning curve, although acquaintance of all facets is not necessary to permit a practical approach [8, 9].

10.4 Immediate Bedside Haemodynamic Information

Performing a complete echocardiogram offers a full picture of the heart as the muscle and

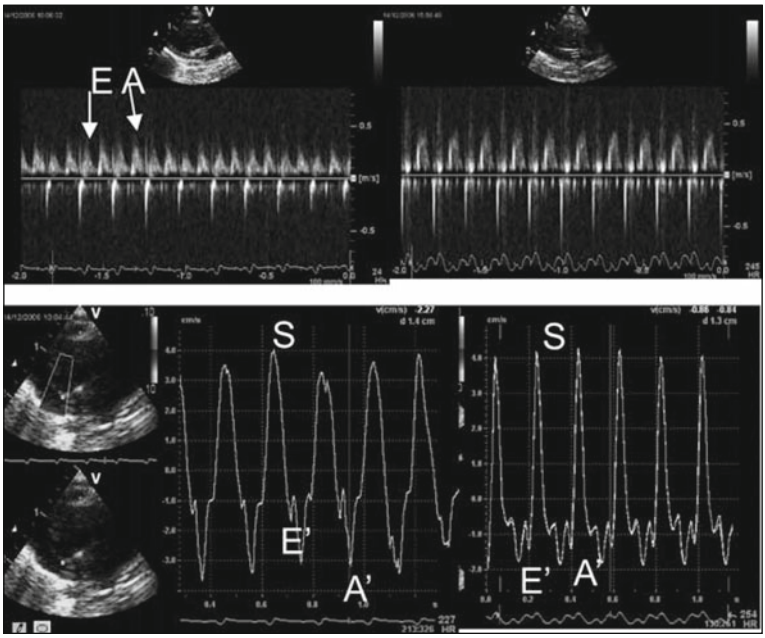

Fig. 10.1 Influence of optimised filling after colloids in a rat model of septic shock (endotoxin injection). The *upper panels* show transmitral Doppler pattern before (*left*) and after (*right*) filling. The *lower panels* depict tissue-Doppler images with a clear shift from E'/A' <1 towards E'/A' >1. *E',* movement of the mitral annulus in early diastole; *A',* myocardial movement at the level of the mitral annulus during atrial contraction

pump of the circulatory system. As with every other (invasive) haemodynamic monitoring tool, all tricks and flaws must be recognised to permit a comprehensive haemodynamic evaluation of a haemodynamically unstable patient. In a hypotensive patient, a quick investigation of cardiac function at the level of the short-axis view permits differentiation between a cardiac and a noncardiac causes of hypotension [1]. A small LV suggests hypovolaemia [10] or a ventricle loaded with a high sympathomimetic intrinsic or extrinsic load [11, 12]. In contrast, a dilated, barely contracting, LV needs inotropic support when the patient is hypotensive or in shock. Therefore, this initial short-axis view and correct interpretation has direct impact on bedside management and hence outcome.

A useful load-dependent variable in daily clinical practice is the systolic velocity of the mitral annulus, assessed with tissue Doppler imaging. Velocities <8 cm/s suggest decreased systolic function, whereas velocities >12 cm/s imply normal left ventricular systolic function. Both preload [6] and afterload [13] appear to have an impact on the amplitude of this Doppler wave.

Rapid diagnosis of LV failure permits immediate intervention, which is indirectly related to improved outcome [14, 15]. As myocardial Doppler imaging provides insight into both systolic and diastolic issues [16, 17], the variables obtained from this technique at the mitral and tricuspid annular levels offer, indeed, an enormously important source of information. Again, the physiologic background should not be ignored, and only if it is

obtained will correct interpretation be attained. The relationship between the early filling velocity (E) and myocardial Doppler early velocity of the mitral annulus (E') provides insight into the left-sided filling pressures [18, 19]. An example is depicted in Figure 10.1, demonstrating a shift of both transmitral early filling wave velocity as well as the early annular velocity after administration of colloids.

10.5 Right Ventricle

A similar differentiation can be made with respect to the right ventricle (RV). A normal RV is depicted as a crescent-shaped structure. A dilated RV (i.e. >0.6 diameter of the LV) most often suggests pressure overload, albeit RV myocardial ischaemia or volume overload [1], with typical approaches of management, belong to the possibilities.

Assessment of regurgitant flows across cardiac valves reveals transvalvular pressure gradients. Typically, from a tricuspid regurgitant flow, a pressure gradient can be assessed to estimate RV systolic pressure (RVSP) (Fig. 10. 2) if right atrial pressure can be assessed [20, 21]. Besides the E/E', RVSP estimation is one of the most important direct measure-

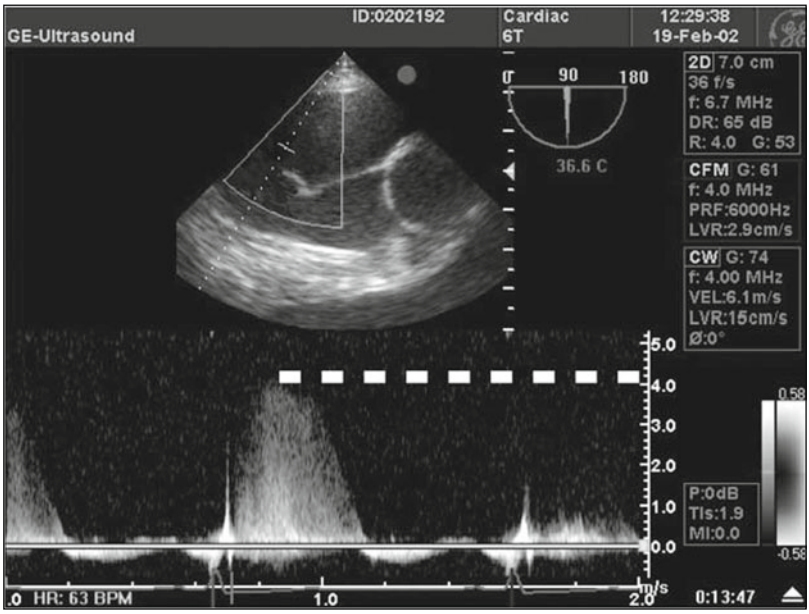

Fig. 10.2 Right-ventricular (RV) end-systolic pressure is estimated from the transtricuspid regurgitant flow velocity. In this particular example, estimated RV systolic pressure is 4^2 + central venous pressure

ments. Knowledge of the presence of a dilated RV in conjunction with increased RVSP, again may be important in direct management of ventilator settings [22], optimisation of preload [23] or reduction of RV afterloading conditions [24-–27], with indirect impact on outcome.

10.6 Preload and Fluid Responsiveness

Preload is the first issue to be assessed whenever hypotension must be managed, and it has been related to improved outcome [28, 29]. Clinically, the leg-raising test is most preferable for evaluating optimal preloading conditions: it does no harm, and provides immediate information about the filling status. The only condition sine qua non is knowledge of ventricular dimensions and function. In this respect, transthoracic echocardiography helps considerably. From a short-axis parasternal view, assessment of LV diastolic area (LVEDA) provides direct indication of filling state, in particular when combined with a dynamic test such as the leg-raising test. LVEDA <5.5 cm^2/m^2 is a sign of low preloading conditions. Although a pure static variable of load, the leg-raising test makes this LVEDA a true dynamic descriptor of fluid responsiveness, when combined with arterial blood pressure assessment.

Other variables are used in mechanically ventilated patients in the ICU and rely on ventilation-induced variation of intrathoracic pressure. In analogy with stroke volume variation, flow variation can be nicely assessed: variation of stroke volume is exemplified by variations of the time–velocity integral (TVI) [30]. In the RV, both inferior [31] and superior [32] caval-vein variations with ventilation can be used. Care should be taken that these variables only provide insight into RV preload. Acute RV failure in conjunction with a hyperdynamic LV will be associated with an absence of ventilation-induced variation of the caval-vein diameter. Again, starting the echo investigation with the short-axis view will eliminate RV dilatation. If the latter is present, a hyperdynamic LV with small LVEDA will suggest a left-sided low-filling status and an increased right ventricular afterload. Assessment of flow variation at the level of the aortic valve will support the hypothesis.

10.7 Conclusions

Echo-Doppler provides immediate insight into the morphological and haemodynamic functional aspects of cardiac and circulatory-related issues. The most important advantage is that proper use will lead to direct action depending on the findings, even with a limited number of views [33], in a quite non-invasive manner, in particular when using the transthoracic approach ICU clinicians faced daily with management of haemodynamically unstable patients should be aware of and knowledgeable about the value of this powerful tool.

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Part VI
Management of Cardiac Arrest

Mild Therapeutic Hypothermia after Cardiac Arrest

11

T. Pellis, V. Mione and W.P. Mercante

11. 1
Introduction

Cardiovascular disease is the world's leading cause of death. Such deaths are often caused by sudden cardiac arrest, and the estimated number of out-of-hospital cardiac arrest cases is 300,000 per year in the United States, where median rate of survival to hospital discharge is 7.9% [1]. Favourable outcome of patients admitted to the hospital ranges between 11% and 48% [2, 3], indicating a large number of patients die after successful resuscitation during hospital stay or develop permanent severe brain damage. The only therapy that has been shown to improve survival and neurological outcome after sudden cardiac arrest is induction of mild therapeutic hypothermia for 12-24 h [4, 5].

Mild hypothermia is an exciting and powerful therapy but is still confronted with underuse in clinical practice [6, 7]. Fortunately, a growing amount of evidence documents its mechanisms of action, safety and effectiveness. However, the full potential of mild hypothermia after cardiac arrest has yet to be explored.

11.2
Mechanisms of Neuroprotection

Hypothermia leads to a progressive reduction in metabolism, reflected by depression of electrical activity in the brain and therefore of oxygen demand and carbon dioxide production. Metabolism is reduced by 5–8% [8, 9] per degree Celsius reduction of core temperature. Metabolism reduction at mild hypothermia alone, however, would not account for its marked protective effect [9]. When hypoxia occurs, depletion of energy-rich compounds such as adenosine triphosphate (ATP) leads to intra- and extracellular acidosis, failure of ATP-dependent sodium- and potassium-dependent adenosine triphosphatase (Na-K-ATPase), a breakdown of cellular Na+ gradient, and calcium (Ca++) influx into neurons. Cellular depolarisation releases excitatory amino acids such as glutamate, which in turn further promotes Ca++ influx. Because Ca++ sequestration is ATP and/or oxygen depen-

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dent, the calcium-buffering capacity of cells fails. These mechanisms ultimately cause cell death. Several steps of this cascade have been shown to be attenuated by hypothermia [10–12]. Glutamate and dopamine release after global ischaemia is inhibited [13], and mild hypothermia induces brain-derived neurotrophic factor, which in turn further reduces glutamate release [14, 15].

Reperfusion after cardiac arrest with normothermic oxygenated blood leads to the formation of reactive oxygen species, which cause cellular damage by lipid peroxidation, DNA toxicity and induction of apoptosis. Several studies have shown that hypothermia attenuates oxidative stress [16–18] and lipid peroxidation [19].

The inflammatory response to an ischaemic insult contributes to delayed tissue injury. Hypothermia functions as an immunomodulator by inhibiting neutrophil infiltration [20] and function [21], reducing lipid peroxidation and leukotriene production [10, 22]. Induction of programmed cell death after ischaemia is influenced by pro- and antiapoptotic factors. Hypothermia affects this process in several ways. Inhibition of apoptosis can be explained partly by mechanisms described above because calcium overload and glutamate release contribute to induction of apoptosis. Translocation of cytochrome C from the mitochondrium into the cytosol – an early step in the initiation of apoptosis [23] – and subsequent caspase activation are attenuated [24, 25]. The antiapoptotic protein Bcl-2, a potent cell-death suppressor, is enhanced, whereas the proapoptotic factor BAX is suppressed by hypothermia [26]. Another beneficial mechanism of hypothermia is the reduction of brain oedema after ischaemia [22].

11.3 Clinical Relevance

11.3.1 Randomised Clinical Trials

Several pilot trials of mild therapeutic hypothermia after cardiac arrest showed improved neurological function when compared with historic controls [27–30]. This led to several randomised trials of therapeutic hypothermia after cardiac arrest. Bernard et al. [5] included 77 comatose survivors after cardiac arrest of cardiac origin with a primary rhythm of ventricular fibrillation (VF) or pulseless ventricular tachycardia. Hypothermia was induced with ice packs and maintained for 12 h. In the hypothermia group (n = 43), 21 (49%) survived to favourable neurological recovery compared with nine (26%) of 34 in the normothermia group ($p = 0.046$).

The European Hypothermia After Cardiac Arrest (HACA) Study Group studied 275 comatose survivors after cardiac arrest of cardiac cause (VF or pulseless ventricular tachycardia) [4]. Hypothermia was induced with cold air and maintained for 24 h. In the hypothermia group (n = 136), 75 (55%) survived to favourable neurological recovery compared with 54 (39%) of 137 in the normothermia group [risk ratio (RR) 1.40; 95% confidence interval (CI) 1.08–1.81]. In addition, a significant reduction of mortality at 6 months (RR 0.74; 95% CI 0.58–0.95) was reported.

Hachimi-Idrissi et al. [13] studied 30 comatose survivors after cardiac arrest who had

asystole and pulseless electrical activity (PEA) as primary rhythms. Hypothermia was induced with local surface cooling and maintained for 4 h. In the hypothermia group (n = 16), two (13%) survived to favourable neurological recovery compared with 0 (0%) of 14 in the normothermia group. This difference was not statistically significant.
A meta-analysis performed on these three trials included individual data of 384 patients and showed a number needed to treat of six for favourable neurological outcome at hospital discharge and neurologically intact survival at 6 months. Based on these trials, the 2005 guidelines by the American Heart Association and the European Resuscitation Council recommend implementing mild hypothermia in the post-cardiac-arrest treatment algorithm when the first documented rhythm is VF or pulseless ventricular tachycardia. It also states that hypothermia should also be considered for treating non-VF rhythms [31, 32].

11.3.2 Nonrandomised Clinical Trials

A growing amount of data from nonrandomised studies demonstrates the benefits of hypothermia after cardiac arrest, not only for VF and pulseless ventricular tachycardia, but also for asystole or PEA. Arrich [33] published the largest and most compelling observational study from the European Resuscitation Council Hypothermia After Cardiac Arrest Registry that followed 587 patients, of whom 462 were treated with therapeutic hypothermia irrespective of the presenting rhythm. This study demonstrates a benefit in terms of neurological outcome (unfavourable outcome 55% in the hypothermia group and 68% in the normothermia group; $p = 0.02$). An analysis of patients presenting with PEA or asystole showed a nonsignificant reduction of unfavourable outcome in hypothermic patients: 89 (72%) of 124 patients in the hypothermic group, and 59 (81%) of 73 patients in the normothermic group; RR 1.5; 95% CI 0.85–2.55 ($p = 0.18$).

In patients after cardiac arrest who show myocardial infarction on ST-elevation (STEMI), it is a logistic challenge to perform early percutaneous coronary intervention (PCI) and rapid cooling at the same time. Knafelj et al. [34] compared 40 consecutive patients with STEMI undergoing PCI who were cooled after cardiac arrest to 32 patients treated with PCI but without cooling. Cooling was started before, during or after PCI. Neurological outcome was significantly improved in the cooling group (55% favourable outcome vs 16%; $p = 0.001$), and the combination of therapeutic hypothermia and PCI proved to be safe and feasible [34]. Whereas most patients in that study were cooled after PCI, Wolfrum et al. induced hypothermia before PCI in 16 consecutive patients with STEMI after successful resuscitation and compared them with 17 historic consecutive patients without cooling. This proved to be safe and feasible and was achieved without delaying door-to-balloon time [35].

11.4 Complications of Mild Therapeutic Hypothermia

Because hypothermia interferes with numerous physiologic and pathologic processes, a wide range of side effects might be expected. Serious complications have not been ob-

served to a significant extent in the major randomised trials. Possible side effects must be kept in mind to prevent or counteract them in a timely manner but should not prevent the use of hypothermia when indicated.

11.4.1 Changes in the Immune System

In addition to immunomodulation, hypothermia might delay infection detection because fever as an indicator of infection is suppressed by active temperature management. Clinical data regarding infection are controversial. The European multicentre trial did not report a significant difference in complication rate, but there was a trend towards more infections and sepsis in the hypothermia group [4]. In an observational study by Wolfrum et al. [35] of 33 patients after cardiac arrest, infections (defined as a rise in inflammatory parameters indicating infection) were detected in 62% of cooled patients vs 24% of the historical control group ($p = 0.04$). Other studies did not report a higher rate of infections after treatment with hypothermia [36, 37]. A meta-analysis of three randomised trials showed a trend towards a higher incidence of sepsis, whereas the incidence of pneumonia did not differ between hypothermia and normothermia groups [38]. A high level of vigilance towards infection seems advisable in cooled patients after cardiac arrest.

11.4.2 Effects on Coagulation

Hypothermia has an anticoagulatory effect proportional to its cooling depth [39, 40]. Pre-existing coagulopathy was therefore an exclusion criterion in the HACA study [4]. However, in none of the clinical trials have major bleeding complications attributable to hypothermia been observed. A trend towards a higher incidence of bleeding episodes is reported in an observational study by Wolfrum et al. in patients cooled after cardiac arrest undergoing immediate percutaneous intervention [35].

Traditionally, hypothermia has been considered as a platelet inhibitor [41]. This has been questioned recently. Hogberg et al. [42] assessed platelet reactivity at 37°C and 33°C in the blood of healthy volunteers before and 24 h after loading with clopidogrel 600 mg. They found platelet function unaltered by mild hypothermia, and platelet inhibition by clopidogrel was even attenuated. Further studies seem necessary to determine the optimal antiplatelet therapy in hypothermic patients undergoing coronary intervention, more so because patients after cardiac arrest due to myocardial infarction show pronounced platelet hyperfunction [43].

11.4.3 Cardiovascular and Haemodynamic Effects

Induced mild hypothermia leads to bradycardia and a rise in systemic vascular resistance [5]. The risk of arrhythmias (bradycardia necessitating pacemaker support, atrial fibrilla-

tion, or VF) rises with temperatures <30°C but is very low at 33°C. Tiainen et al. [44] assessed the incidence of arrhythmias in a subset of 70 patients with 24-h Holter recordings included in the European multicenter trial. Patients randomised to hypothermia had more premature ventricular beats but showed no increased incidence of clinically relevant arrhythmias compared with the normothermia group [44].

Patients who were in cardiogenic shock after cardiac arrest also seem to substantially profit from therapeutic hypothermia. Skulec et al. [45] reported 56 consecutive patients treated with mild hypothermia after cardiac arrest, of whom 28 were in cardiogenic shock. They observed a rise in mean arterial pressure after cooling, and despite the expected higher mortality rate, a neurologic recovery comparable with patients without shock [44]. Oddo et al. [37] analysed the outcome of patients after cardiac arrest who were in shock before the initiation of hypothermia. Of 17, five in the hypothermia group survived vs none of 14 in the control group ($p = 0.027$) [37]. Hovdenes et al. [46] also documented the safety of mild hypothermia in patients in shock after successful resuscitation from VF. Of 50 patients, 23 were treated with an intra-aortic balloon pump, and 14 of those (61%) survived to favourable neurological recovery.

11.4.4 Drug Metabolism

Hypothermia reduces the systemic clearance of cytochrome P450-metabolised drugs by 7–22% per degree Celsius [47]. Although drug levels might rise because of reduced metabolism, the potency and efficacy of certain drugs are diminished by hypothermia. During rewarming, these processes might be reversed, further enhancing the risk of over- or underdosing of drugs. Fukuoka et al. [48] measured drug concentrations in 15 consecutive patients with head injury receiving midazolam 5 mg kg-1 min-1, of whom eight were treated with hypothermia (32–34°C). In the normothermic patients, a steady state of 1,500 ng/ml was achieved, whereas in hypothermic patients, a fivefold increase in concentration was observed. Systemic clearance was 100-fold decreased if the temperature was <35°C [48]. Fentanyl concentration has been found to rise at body temperatures below mild hypothermia. At 29°C, plasma concentrations were increased twofold compared with normothermia in piglets [49]. Propofol concentration has been shown to rise by 28% at 34°C compared with 37°C in healthy volunteers [50]. Duration of action of the neuromuscular blocking agents vecuronium, rocuronium and atracurium is prolonged, so monitoring of the neuromuscular function seems advisable [47]. During hypothermia, the clearance of many more drugs is altered, as a recent comprehensive review demonstrates [47].

11.5 Conclusions

Mild therapeutic hypothermia is a safe and effective therapy after cardiac arrest and is recommended by the International Liaison Committee on Resuscitation for unconscious adult patients with spontaneous circulation after out-of-hospital VF cardiac arrest. It should also be considered for out-of-hospital cardiac arrest from a nonshockable rhythm or cardiac ar-

rest in hospital [31, 32]. It is thus far the only therapy that improved neurological outcome after cardiac arrest in a randomised controlled trial. Hypothermia can be induced safely in haemodynamically compromised patients as well as in patients undergoing PCI.

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Nasopharyngeal Cooling During Cardiopulmonary Resuscitation

12

F. Fumagalli, G. Ristagno

12.1 Introduction

Cardiovascular disease remains the leading cause of death in the Western world, with as many as 400,000 Americans and 700,000 Europeans sustaining cardiac arrest each year [1]. Though the initial success of cardiopulmonary resuscitation (CPR) is approximately 39%, the majority of victims die within 72 h of hospital admission [2–4]. Patients successfully resuscitated following cardiac arrest in fact often present with what is now termed "postresuscitation disease" [5]. Most prominent among these diseases are postresuscitation myocardial failure and ischaemic brain damage. Severe postresuscitation heart contractile failure has been implicated as one of the most important mechanism causing these fatal outcomes [6–9]. However, morbidity and mortality after successful CPR also largely depends on recovery of neurologic function. Up to 30% of survivors of cardiac arrest manifest permanent brain damage [10–12], and in some instances, only 2–12% of resuscitated patients are discharged from hospital without neurological dysfunction [13].

The greatest postresuscitation emphasis has therefore been on minimising postresuscitation myocardial dysfunction and achieving long-term neurologically intact survival [14]. Among all postresuscitation-care interventions suggested and/or recommended as the most persuasive benefits both for the brain and the heart is the use of hypothermia [15–18]. Therefore, hypothermic treatment has become well recognised for providing protection following resuscitation from cardiac arrest [14, 19–22]. The International Liaison Committee and the American Heart Association recommends postresuscitation hypothermia in the range of 32–34 ºC for between 12 and 24 h in adult patients who are comatose following return of spontaneous circulation (ROSC) [14].

12.2 Therapeutic Hypothermia Following Resuscitation from Cardiac Arrest

Therapeutic hypothermia had been advocated for decades prior to its clinical acceptance

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[23, 24]. The concept of hypothermia was, in fact, introduced in the clinical settings in the late 1950s, when moderate hypothermia during open-heart surgery and neurosurgery revealed its preservative role by reducing cerebral oxygen demand by <50% [25]. In the settings of cardiac arrest, however, the concept of hypothermia for protecting against either or both ischaemic and reperfusion injury to the brain represents a pioneering contribution of the late Professor Peter Safar [23, 26, 27]. In 1996, Safar induced hypothermia by instilling Ringer's solution maintained at a temperature of 4°C into the abdominal cavity of dogs after resuscitation from cardiac arrest. Cooling was maintained for 12 h. Functional recovery was associated with minimal histological brain damage [23]. More recently, two of the largest randomised clinical trials on systemic hypothermia [26, 28] objectively demonstrated improvements in neurological outcomes. Since then, and within a short 5-year time frame, this therapeutic intervention has finally proven to be protective and is now a recommended treatment to be initiated following resuscitation from cardiac arrest [24, 26–29].

Hypothermia is a valid intervention for preserving brain and heart function from ischaemic insult following cardiac arrest [30], contributing to improvements in neurological recovery as well as myocardial contractility following ROSC [31]. During reperfusion following ischaemia, hypothermia improved haemodynamic recovery, decreased arrhythmias and reduced myocardial necrotic damage. It also helped preserve myocardial function, coronary flow and oxygen consumption compared with control patients [32]. Interesting data highlighting improved myocardial contractility in animals that received hypothermic treatment following cardiac arrest were reported by Zhao et al. [31]. Hypothermic cardiovascular reperfusion resulted in considerably greater cardiac output, with concomitantly reduced systolic and diastolic myocardial dysfunction during the postarrest period.

Initially, it was presumed that the sole mechanism of action of hypothermia was related to its effect of temperature-dependent reductions in metabolism, leading to decreased demand for oxygen and glucose in the brain and consequent reductions in adenosine triphosphatase (ATP) depletion during ischaemia. The protective effects of mild hypothermia are now known to include suppression of many chemical reactions associated with reperfusion injury. These additional effects are demonstrated on reduced cerebral and myocardial inflammatory responses during reperfusion [33, 34]. Hypothermia also decreases damaging free-radical production [34] and excitatory amino-acid release [35] and promotes neuronal recovery after both focal and global brain ischaemia. In models of ischaemia–reperfusion in cardiomyocytes, cooling prior to reperfusion conferred improved cell viability and attenuated a number of intracellular injury pathway mechanisms, including apoptotic enzymes, in comparison with reperfusion without cooling [30, 36]. More recently, we reported that hypothermia improved myocardial cell contractility, and this effect was associated with improved control of intracellular calcium (Ca_2+) and a greater cell sensitivity to Ca_2+ [37]. These findings further demonstrated that different organ preservation mechanisms are induced by hypothermia.

Optimal timing and techniques for inducing hypothermia after cardiac arrest have not yet been defined and is a major topic of ongoing research [38]. Nevertheless, several experimental investigations raised the importance of beginning hypothermia as soon as possible and also suggested that intra-arrest hypothermia might provide additional survival benefits [31, 39–42]. The theoretical advantages of earlier cooling might include decreasing reperfusion-related injury mechanisms, attenuation of the oxidant burst and inhibition

of reperfusion-related apoptosis. When mild cerebral hypothermia was induced in pigs immediately after ROSC, improved cerebral functional and morphologic outcome in contrast to animals not subjected to cooling were observed, whereas a delay of as little as 15 min in initiating cooling after reperfusion slightly decreased tissue damage but did not improve functional outcome [43]. Subsequently, when hypothermia was initiated during cardiac arrest, early cooling improved neurological outcome and yielded better 72-h survival rates in contrast to delayed hypothermia and normothermia resuscitation [31, 40]. In addition, hypothermia has been reported to reduce defibrillation threshold and thus terminate ventricular fibrillation (VF) and improve ROSC in a porcine model of prolonged cardiac arrest.

By initiating a different method of cooling during CPR that produces rapid selective head cooling, we confirmed improvement on postresuscitation neurological outcome and an increase in coronary perfusion pressure (CPP) during chest compressions, with consequent greater resuscitation success and higher postresuscitation myocardial function and survival rates [41, 44, 45].

12.3 Nasopharyngeal Cooling During CPR

External methods for inducing hypothermia first cool the skin and peripheral compartments. These methods, however, are slow to achieve significant brain cooling because they are targeted at cooling the entire body [29, 46]. The major challenge facing clinicians is the need to maximise the protective effects of brain hypothermia and thus the time to delivery of this type of treatment. Cooling the entire body or total arterial blood to reduce brain temperature may not be necessary, as the brain receives only 20% of resting cardiac output. The long cooling time required with external methods may be reduced if the head only is cooled [47–50]. Selective brain hypothermia using different devices has therefore been proposed [49–52].

Nasopharyngeal cooling is an attractive procedure and represents a novel approach to therapeutic hypothermia. It is achieved by actively spraying a mixture of perfluorocarbon liquid with high-flow oxygen into the nasal passages via a nasal cannula. This natural cavity into the head overcomes the obstacle of cooling the brain through the skull. Rapid evaporation of the liquid produces significant cooling of the nasal passages just under the base of the brain. Due to proximity to the cerebral circulation, this approach likely allows rapid brain cooling via both direct conductive mechanisms and indirect hematogenous mechanisms.

In an initial investigation, we studied the effects of selective head cooling initiated during CPR on resuscitation and postresuscitation neurological and myocardial function and survival in the large animal. When pigs were cooled coincident with CPR onset, the jugular venous temperature was reduced from 38°C to 34°C within 5 min. The likelihood of successful defibrillation after 10 min of untreated cardiac arrest and 5 min of CPR was significantly increased with head cooling. Eight animals cooled in this way survived for 96 h, with full neurological recovery. Only two of eight normothermic controls survived, and both had persistent neurological deficits. Quite unexpectedly and in the absence of an increase of 1.3°C decrease in body temperature over the ensuing hour, left ventricular (LV) systolic function resulted in ejection fraction and fractional area change together with

LV diastolic function [41, 42, 44]. Several mechanisms might have contributed to the observed improvement in myocardial performance. The cooled animals also showed higher defibrillation success rate ($p = 0.034$) and required shorter CPR duration ($p = 0.01$) and less total dose of epinephrine ($p = 0.009$) in comparison with the control group. Greater postresuscitation haemodynamic stability was also observed in cooled animals. Immediately post-ROSC, arterial pressures and coronary perfusion pressures in fact increased in cooled animals and were significantly greater compared with control animals, in which pressures decreased. Brain cooling during CPR therefore improved myocardium perfusion and was reflected in less recurrent VF and ultimately improvements in myocardial performance. These beneficial effects on easing defibrillation and a more benign postresuscitation course were subsequently confirmed in animals in which the duration of untreated cardiac arrest was extended to 15 min [53]. Also unexpectedly, there was remarkably higher coronary perfusion pressure in head-cooled animals, which was consistent with greater defibrillation success ($p < 0.01$).

The mechanism by which selective brain cooling improved the likelihood of ROSC is not fully understood. It is conceivable that targeted cooling of the underside of the brain using nasopharyngeal cooling alters the firing rates of efferent autonomic nerves in the cervical chain. Inhibition of sympathetic firing during systemic hypothermia has been previously reported, as temperature was reduced from 38ºC to 31ºC [54]. Experimental studies in healthy volunteers demonstrated that plasma noradrenaline and total peripheral resistances were reduced during moderately cold head immersion for 20 min [55]. Moreover, hypothermia has been reported to attenuate ischaemia-induced norepinephrine and acetylcholine release in ischaemic regions [56]. Paraventricular nucleus of the hypothalamus is a focal point in the complex of interacting systems regulating stress response [57]. In our model, those brain regions were close to the cooling source. Also, plasma norepinephrine concentration during CPR prior ROSC was lower in cooled animals (Fig. 12.1).

CPR interventions and especially chest compression focused on increasing and maintaining optimal pressures, especially large vessels supplying the brain and heart. It has now become apparent that large-vessel pressure and flow alone may not be predictive of the extent to which microvessels and therefore tissues are perfused [58–61]. Yet it is the microvessels and specifically the capillaries that serve as the ultimate exchange sites for

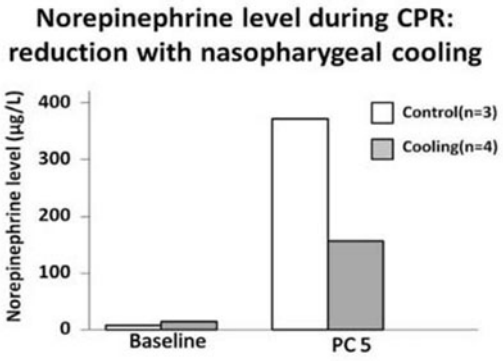

Fig. 12.1 Arterial norepinephrine levels during head cooling vs controls. CPR cardiopulmonary resuscitation, PC5 5 min of precordial compression

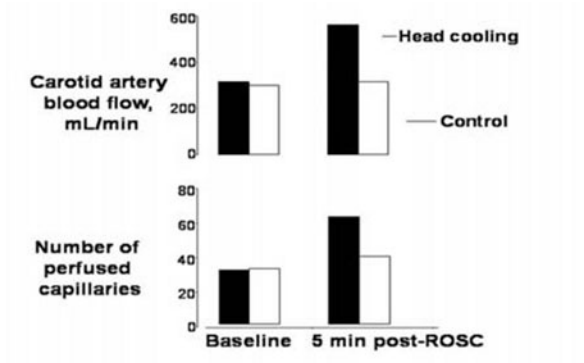

Fig. 12.2 Carotid artery blood flow and cerebral cortex microcirculation in head-cooled and control animals. *ROSC,* return of spontaneous circulation

vital metabolites. Specifically, capillary microvessels provide transport of oxygen, nutrients and fluids to tissues, and therefore the brain and myocardium, and remove carbon dioxide (CO_2) and other waste products.

Based on the improved haemodynamics observed during nasopharyngeal cooling, we were prompted to investigate whether such increases were reflected in improvements in microcirculation and tissue perfusion of the brain and heart. In a very preliminary study on pigs, we addressed cerebral microcirculatory flows in relation to carotid blood flows. After 4 min of untreated VF and 4 min of CPR, carotid artery diameters and flows increased during selective head cooling, even though cardiac output was not changed in comparison with controls at that time point. Increases in carotid blood flows were associated with concurrent increases in the numbers of perfused capillaries visualised in the cerebral cortex (Fig. 12.2) [62].

We then focused on myocardial and cerebral perfusions during nasopharyngeal cooling initiated during CPR and continued following resuscitation results (unpublished data). Ten pigs were subjected to 10 min of untreated VF. CPR, including mechanical chest compression and ventilation with oxygen, was then performed for 5 min prior to attempted defibrillation. Coincident with CPR initiation, animals were randomly assigned to selective head cooling or control. Cerebral and myocardial perfusion was assessed using coloured microspheres (mean diameter 10 ± 0.2 μm). All animals with the exception of one control were successfully resuscitated. Selective head cooling rapidly decreased the brain temperature. At 6 min post-ROSC, brain temperature was already significantly lower in the head-cooled animals (36.5 ± 0.5 vs 37.4 ± 0.4, $p < 0.05$). At 10 and 60 min post-ROSC, brain temperature was further decreased ($p < 0.01$), whereas rectal temperature was only slightly decreased (Table 12.1). At 10 min post-ROSC, cerebral cortex perfusion was greater, although statistical significance was not reached, in animals subjected to head cooling compared with controls (Fig. 12.3). More interestingly, during the post-ROSC period, animals subjected to selective head cooling showed significantly higher CPP ($p < 0.05$) (Table 12.1) accompanied by significant improvements in myocardial perfusion ($p < 0.01$) (Fig. 12.4). In this model, selective head cooling achieved by the nasopharyngeal approach initiated during CPR and continued following resuscitation improved CPP and myocardial and cerebral perfusion after cardiac arrest.

The effects of nasopharyngeal cooling were tested in the clinical scenario in the Pre-ROSC IntraNasal Cooling Effectiveness (PRINCE) study of 200 patients enrolled by 15

Table 12.1 Rectal and brain temperatures in study and control animals (mean ± standard deviation)

	Control	Head cooling
ROSC	4/5	5/5
Rectal temp °C		
BL	37.7 ± 0.5	37.8 ± 0.3
PR 10 min	38.3 ± 0.2	38 ± 0.2
PR 60 min	38.1 ± 0.5	37.7 ± 0.6
PR 240 min	38.3 ± 0.1	33.8 ± 0.6**
Brain temp °C		
BL	37.8 ± 0.3	37.4 ± 0.6
PR 10 min	37.4 ± 0.7	35.9 ± 0.5**
PR 60 min	38.3 ± 0.5	35.2 ± 1.5**
PR 240 min	38.1 ± 0.7	34.1 ± 0.8**
CPP, mmHg		
BL	101 ± 19	102 ± 14
PR 10 min	69 ± 11	88 ± 12*
PR 60 min	67 ± 22	91 ± 6*

ROSC, return of spontaneous circulation; *temp,* temperature; *BL,* baseline; *PR,* postresuscitation; *CCP,* coronary perfusion pressure. *p < 0.05, **p < 0.01 vs control

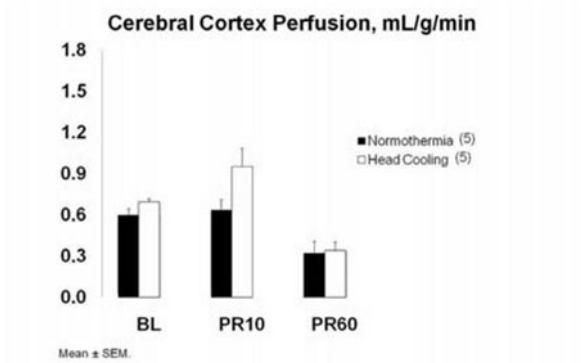

Fig. 12.3 Cerebral cortex perfusion assessed with microsphere technique in animals subjected to head cooling or normothermia. *BL*, baseline; *PR10,* 10 min postresuscitation; *PR60,* 60 min postresuscitation; *SEM,* standard error of mean

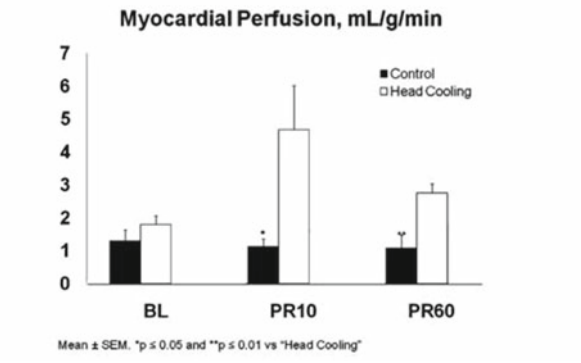

Fig. 12.4 Myocardial perfusion assessed with microsphere technique in animals subjected to head cooling or normothermia. *BL,* baseline; *PR10,* 10 min postresuscitation; *PR60,* 60 min postresuscitation; *SEM,* standard error of mean

emergency medical systems. This study confirmed that intranasal cooling is feasible and safe to use during cardiac arrest. In addition, the target tympanic temperature of 34°C was achieved 3 h faster and time to target core temperature was 2 h faster in patients cooled intranasally in the field compared with those receiving in-hospital cooling alone [63].

12.4 Conclusions

Early instauration of therapeutic hypothermia is emerging as a viable method of preserving cerebral and myocardial function after resuscitation from cardiac arrest. The advantage of cooling via the nasopharyngeal method is that when the cooling power is focused on the brain – the organ most vulnerable to ischaemia–reperfusion injury – much time is saved in reaching target temperature. Selective head cooling with subsequent delayed systemic hypothermia maximises neuroprotection while minimising systemic complications. Moreover, evidence suggests several new implications regarding the beneficial effects on cerebral and myocardial perfusion during selective head cooling.

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Amplitude Spectrum Area as a Predictor of Successful Defibrillation

13

G. Ristagno, Y. Li, A. Gullo and J. Bisera

13.1 Introduction

Cardiac arrest represents a dramatic event that can occur suddenly and often without warning signs. Cardiopulmonary resuscitation (CPR), including chest compression often in conjunction with electrical defibrillation, has the potential to restore spontaneous circulation (ROSC). However, CPR is likely to be successful only if it is instituted within 5 min after the heart stops beating [1–3]. Ventricular fibrillation (VF) is the primary rhythm in many cases of human cardiac arrest, and defibrillation by electric countershock represents the treatment of choice for this otherwise lethal arrhythmia. VF duration remains a main determinant of countershock success. When the interval between estimated VF onset and delivery of the first shock is <5 min, the likelihood is that an immediate defibrillation attempt will be successful [4–6]. When the duration of untreated VF is >5 min, both human and animal studies demonstrate that initial CPR with chest compression prior to delivery of an electrical shock improves the likelihood of ROSC [7–10]. During cardiac arrest, coronary blood flow ceases, accounting for progressive and severe energy imbalance. Intramyocardial hypercarbic acidosis is associated with depletion of high-energy phosphates and correspondingly severe global myocardial ischaemia [11, 12]. The ischaemic left ventricle (LV) becomes contracted [13], ushering in the stone heart [14, 15]. After onset of contracture, the probability of successful defibrillation is remote. Early CPR that restores coronary perfusion pressure (CPP) and myocardial blood flow delays onset of ischaemic myocardial injury and facilitates defibrillation [16].

VF is characterised by three time-sensitive electrophysiological phases: (1) the electrical phase, of 0–4 min; (2) the circulatory phase, of 4–10 min; (3) the metabolic phase, of >10 min. During the electrical phase, immediate defibrillation is likely to be successful. As ischaemia progresses, the success of attempted defibrillation diminishes without CPR. This phase is characterised by transition to slow VF wavelets during accumulation of ischaemic metabolites in the myocardium. Type II VF often fails defibrillation attempts because of its re-entry and recurrence. In the metabolic phase, there is no likelihood of successfully restoring a perfusing rhythm [17].

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More than 50% of all patients initially resuscitated from cardiac arrest subsequently die before leaving the hospital [18–20], and the majority of these deaths are due to impaired myocardial function [21].

The severity of postresuscitation myocardial dysfunction is in part related to the magnitude of the electrical energy delivered during defibrillation [22, 23]. Increases in defibrillation energy are associated with decreased postresuscitation myocardial function [22, 24]. It is therefore important to have noninvasive and real-time monitoring that predicts whether or not shock will yield bring about ROSC.

Current resuscitation methods are constrained in part by the lack of practical and reliable real-time monitoring of the efficacy of CPR interventions and timing for the defibrillation attempt. Electrocardiographic (ECG) analyses of VF waveforms represent the best noninvasive approach to guide intervention priority, namely, chest compression or defibrillation.

13.2 Monitoring Effectiveness of Chest Compression and Predicting Return of Circulation

The quality of chest compression is a major determinant of successful resuscitation [25–27]. Existing and established predictors of good-quality CPR, and thereby successful resuscitation, include CPP [16, 28–30] and end-tidal carbon dioxide ($etCO_2$) [31, 32].

Blood flow generated by chest compression is dependent on the pressure gradient between aortic and venous pressures [33]. CPP, defined as the difference between simultaneously measured minimal aortic pressure and right atrial pressure during compression diastole [34–37] is highly correlated with coronary blood flow during cardiac resuscitation and is recognised as the best single indicator for the likelihood of successful defibrillation [30, 38, 39]. Based on both experimental and clinical observations, ROSC can be predicted when CPP is maintained >15 mmHg during chest compression [30, 39, 40]. Resuscitative strategies that increase CPPs, including high-quality chest compression [41, 42] and the use of vasopressors [43], are supported and considered more effective in restoring circulation.

Expired CO_2 is determined by the body's production of CO_2 and the relationship between minute ventilation and pulmonary perfusion. When the circulatory status is normal, pulmonary perfusion is within the physiologic ranges and $etCO_2$ is determined by minute ventilation. During cardiac arrest and CPR, cardiac output is usually less than one third of normal, and pulmonary flow and $etCO_2$ are dramatically reduced. $etCO_2$ is therefore an indirect measurement of pulmonary blood flow and cardiac output produced by chest compression [31, 32]. As $etCO_2$ is highly correlated with CPP during CPR, it may thereby serve as a noninvasive surrogate for CPP [44, 45] and has emerged has another valuable tool for noninvasively monitoring the effectiveness and quality of chest compression during CPR [31, 32, 41, 46]. When $etCO_2$ exceeds the threshold of approximately 10–15 mmHg during CPR, there is a greater likelihood of successful ROSC [47, 48]. However, this has not been specifically evaluated in the setting of predicting shock success in humans. $etCO_2$ may also provide the earliest clinical evidence of ROSC [32].

Although the importance of blood pressure during CPR is clear and inserting an arterial line provides real-time monitoring of arterial pressure, invasive measurements – including monitoring aortic and right-atrial pressures – are only available or feasible at the time of

resuscitation in a very small minority of patients in critical-care settings. Although $etCO_2$ serves as a predictive measurement of the effectiveness of chest compression and therefore the likelihood of ROSC [31, 44, 49–51], yet this measurement technique is not widely available. Portable infrared capnometers can be successfully employed in prehospital settings during CPR. However, monitoring $etCO_2$ requires endotracheal intubation. Out-of-hospital endotracheal intubation carries both a high failure rate and up to a 30% incidence of traumatic injury to the airway [52, 53]. Moreover, epinephrine administration during CPR causes a significant decrease in $etCO_2$ by increasing pulmonary shunting [54], which may cause an important misinterpretation when monitoring the effectiveness of resuscitative manoeuvres. This is in contrasts with the routine availability of ECG in conjunction with external defibrillators.

Attempts to find a better predictor of ROSC have therefore focused on analysing ECG features of VF.

13.3 Analyses of ECG Features During Ventricular Fibrillation and CPR

The search for a reliable indicator of successful defibrillation obtained from analysing ECG features began more than 20 years ago.

Initial approaches included measuring VF amplitude [54] first and frequency later [55]. Subsequently, to increase ECG sensitivity and specificity predictors for ROSC, more sophisticated methods of VF waveform analyses were introduced and investigated, including wavelet decomposition [56], nonlinear dynamics methods [57] and a combination of different ECG parameter analyses [58].

Earlier investigations using ECGs focused on VF wavelet amplitude or voltage as a predictor of the likelihood of successful defibrillation. VF voltage, or signal amplitude, is defined as the maximum peak-to-trough VF amplitude in a given time window of the ECG signal [59]. Mean VF voltage is calculated as the average over the chosen time interval. It has been established that VF amplitude declines over time and greater amplitudes are associated with correspondingly greater defibrillation success [54, 60–64]. Several studies have shown that this ECG feature reflects vital-organ blood flow and in particular myocardial blood flow and energy metabolism [54, 59, 65–67]. Weaver et al. observed that patients in whom VF amplitude was >0.2 mV have a significantly greater likelihood of resuscitation [54]. VF voltage appeared not only as an ROSC predictor but showed utility as an indicator for timing VF duration since collapse. Amplitude measurement, however, has the disadvantage of depending on the direction of the main fibrillation vector and therefore is subject to a great interindividual variance. VF amplitude might also be modified by electrode size, location, thoracic impedance, skin condition and chest morphology.

Subsequently, it was realised that other parameters could be computed using Fourier transformation analyses in a selected ECG interval, including VF median frequency, peak-power frequency, edge frequency and spectral flatness measure. The starting point for all these calculations was the power spectrum, defined as the square of Fourier amplitudes. Brown et al. [55, 65] specifically developed this technique to analyse VF voltage and frequency to obtain the so-called VF median frequency. VF median frequency served as a predictor of electrical defibrillation success [55, 68].

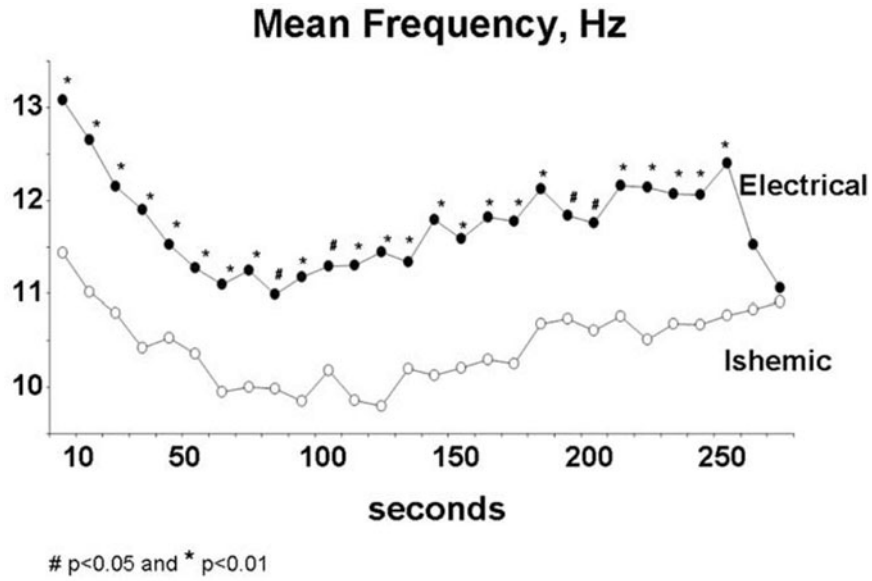

Fig. 13.1 Ventricular fibrillation (*VF*): mean frequency during 5 min of untreated VF. *Closed circle,* VF electrically induced; *open circle,* VF ischaemically induced

In a porcine model of VF and CPR, a median frequency of >9.14 Hz had 100% sensitivity and 92% specificity in predicting successful defibrillation. Frequency analysis of VF wavelets and, specifically, median frequency was also correlated with CPPs in animal models and humans and therefore became the preferred ECG feature for use as predictor of CPR outcome [55, 63, 65, 66, 69–73]. In addition, this parameter appeared as a more accurate indicator for estimating the duration of untreated VF compared with the earlier VF amplitude [65, 71, 74, 75]. To determine the best ECG feature prognosticator, several studies focused on the changes and differences of VF waveform features in relationship to cardiac arrest pathophysiology.

Specifically, investigators focused on the differences between VF as a result of ischaemic heart disease, which represents the main cause of sudden death, and electrically induced VF, which represents the main experimental model employed in laboratories [76, 77]. Indik et al. [78] induced VF in swine in which acute myocardial infarction followed left anterior descending coronary artery (LAD) ligation. The study revealed that VF spectral features, such as median, mean or dominant frequency and bandwidth, were significantly reduced compared with those derived from electrically induced VF [79]. In a different porcine model of ischaemically induced cardiac arrest through acute LAD occlusion, we [80] confirmed lower mean VF frequency in comparison with electrically induced VF (Fig. 13.1). Although VF features might be different in relationship to the cause of cardiac arrest, we observed that those features continuously changed during resuscitative manoeuvres in the ischaemic VF model, as well. In particular, VF amplitude and mean frequency increased during chest compression, and such increases were representative of successful defibrillation [81, 82]. These observations provided evidence that ECG predictors of outcome are at least in part

related to the mechanism by which VF evolves. Of more importance, relationships between VF amplitudes, frequencies and successful defibrillation are maintained in ischaemically induced VF, confirming the utility of ECG predictors of outcome.

Chest compression performed during CPR, however, interferes with ECG signal recording, affecting the extracted parameters and therefore leading to incorrect prediction of defibrillation outcomes.

On the other hand, although CPR might be interrupted for an interval to allow acquisition of reliable parameters, this interruption shortens the period of vital myocardial perfusion and yields worse outcome and greater postresuscitation myocardial dysfunction [83, 84]. Several filters and algorithms to reduce and eliminate ECG artefacts and noise due to chest compression or ambient interferences have been developed and successfully used [59, 63, 66, 85–87]. Among them, the wavelet-transform technique constitutes one of the most promising methods [38, 86].

13.4 Amplitude Spectrum Area (AMSA) as Predictor of Successful Defibrillation

The need for ECG analyses and for predicting successful defibrillation escalated after the introduction of automated external defibrillators (AEDs). In late 1994, Dr. Noc and Prof. Bisera [64] began investigating ECG VF waveforms as predictors of successful cardiac resuscitation. Initially, they focused on the ECG indicator widely investigated at that time and specifically evaluated the possibility of using VF amplitude to predict resuscitability in a well-established rodent model of cardiac arrest and CPR. Increases in CPP during precordial compression were associated with concomitant increases in VF voltage, and greater VF voltages were observed in resuscitated animals. Moreover, greater VF voltages after initiation of cardiac resuscitation were associated with increases in myocardial creatine phosphate and significant decreases in lactate content. Accordingly, increases in VF voltage during cardiac resuscitation reflected increases in myocardial perfusion and favourable changes in myocardial energy metabolism, with consequent greater success of cardiopulmonary resuscitation.

In 1999, the continuous efforts of the same authors [59] led to a new method of analysing VF waveform, the real predecessor of AMSA, in which mean amplitude and dominant frequency were combined. The so-called defibrillation predictor (DP) was calculated by ECG signals obtained with lead-2 monitoring and in which artefacts produced during precordial compression were removed by digital filtering. The DP was tested in a porcine model of cardiac arrest and CPR. Successfully resuscitated animals had significantly greater CPP, dominant VF amplitude, mean VF amplitude and dominant VF frequency. No animals could be resuscitated if the CPP was <8 mmHg, dominant amplitude was <0.48 mV, mean amplitude was <0.25 mV or dominant frequency <9.9 Hz independently of the duration of untreated VF. However, defibrillation attempts uniformly failed when mean amplitude was below the threshold level, even though dominant frequency would have predicted otherwise. When mean amplitude and dominant frequency were combined, predictability was significantly improved. Defibrillations were uniformly unsuccessful if the combination of mean amplitude and dominant frequency did not exceed the threshold values obtained in a derivation study. Mean VF amplitude in combination with dominant VF frequency was

expressed as a numeric score. Using stepwise multiple regression analysis, the investigators identified a single numeric score that was established as a DP and represented by the following equation:

DP = 3.60–4.85 mean VF amplitude – 0.06 VF dominant frequency

This DP served as an objective, noninvasive measurement on a par with that of CPP for predicting successful defibrillation. The ECG predictor nevertheless served as a monitor with which there was essentially total predictability of settings where a defibrillation attempt failed to restore spontaneous circulation. Unfortunately, the positive predictive value (PPV) was still suboptimal, for it accurately predicted only approximately 20% of successful defibrillation attempts. The rudimental defibrillator predictor was later replaced by the amplitude spectrum area.

In early 2000, Pernat et al. [88] and Povoas et al. [38, 89] continued the efforts initiated during the previous decade and ultimately introduced the amplitude spectrum area.

This ECG-derived parameter was obtained starting from conventional ECG scalar limb ECG leads that monitored continuously during uninterrupted chest compression. The frontal-plane lead 2 was used for VF wavelet analyses. ECG signal was continuously sampled and recorded at a frequency of 300 Hz and further digitised.

The signal was selected to be between 4 and 48 Hz to minimise low-frequency artefacts

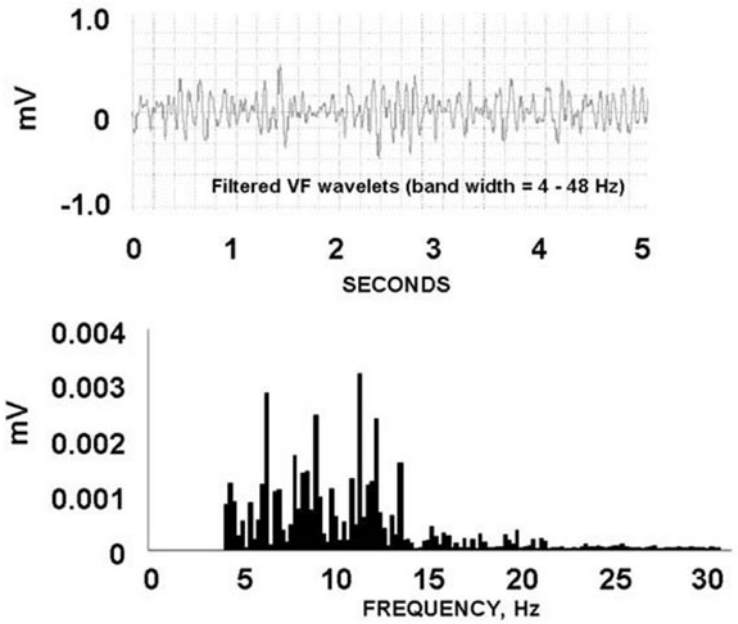

Fig. 13.2 Representative example of amplitude frequency relationship and area under the curve that defines the amplitude spectrum area (*AMSA*)

produced by precordial compression and to exclude electrical interference of ambient noise at frequencies >48 Hz. Peak-to-trough VF amplitudes were obtained, and the average was calculated for a specific ECG interval.

The power spectrum was then obtained by squaring the amplitude of each frequency component obtained from the fast-Fourier transform of the ECG signal (Fig. 13.2). The median frequency represented the frequency at which half of the power of the spectrum was above and half below and is represented by the following equation:

$$MF = \Sigma Fi \times Pi / \Sigma Pi$$

where Fi is the ith frequency component and Pi the relative power at Fi. AMSA was then calculated from the resulting amplitude frequency spectrum according to the following equation:

$$AMSA = \Sigma Ai \times Fi$$

where Ai is the amplitude at the ith frequency Fi.

In an initial investigation, Povoas and Bisera [38] investigated CPP obtained from arterial and right atrial pressures and VF mean amplitude, median frequency and AMSA obtained from ECG recordings from 55 domestic pigs during CPR. From these measurements, threshold values for ROSC were obtained and subsequently validated in another ten animals. CPP and mean amplitude each had a PPV of 100% but negative predictive value (NPV) of only 44% and 22%, respectively. Median frequency predicted successful defibrillation, with a PPV of 75% but an NPV of only 30%. Only AMSA yielded a more optimal combination of PPV and NPV: 86% and 85%, respectively. Among the exciting and impressive results obtained with this new ECG parameter, the high NPV was of special interest because it was recognised that AMSA would minimise repetitive and ineffective electrical shocks during CPR.

In the same period, Pernat confirmed those results, demonstrating the capability of AMSA to optimise ventricular defibrillation timing [88]. In a porcine model of cardiac arrest and resuscitation, AMSA was highly correlated with CPP levels during CPR and AMSA, in a similar manner to CPP, and was significantly greater in resuscitated animals compared with those that were not. In no instance was a perfusing rhythm restored when AMSA was <21 mV-Hz. The AMSA value of 21 mV-Hz predicted perfusing rhythm restoration with sensitivity and specificity >90%. AMSA NPV was 95% and statistically equivalent to that of CPP, mean amplitude and median frequency. However, the PPV that would have prompted continuation of cardiopulmonary resuscitation without interruption for an unsuccessful defibrillation attempt was greatly improved with AMSA: 78% in contrast to the lower predictive values yielded by CPP, mean amplitude and median frequency, which were <40%.

One year later, the same authors [89] further investigated the AMSA ECG signal analysis technique to establish a threshold level that would have predicted whether an electrical shock would reverse VF in a porcine model. The mean AMSA value was 25 mV-Hz for animals in which spontaneous circulation was restored and 14 mV-Hz when the defibrillation attempt was unsuccessful. The investigators confirmed that an AMSA value of 21 mV-Hz had an NPV of 96% and a PPV of 78%. An AMSA value of ≥21 mV-Hz predicted

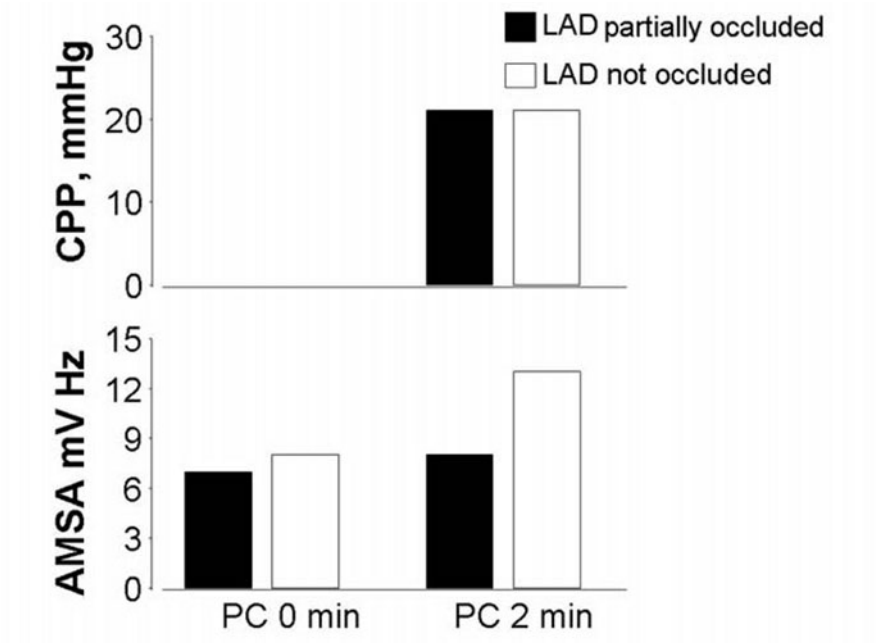

Fig. 13.3 Coronary perfusion pressure (*CPP*) and amplitude spectrum area (*AMSA*) at onset of precordial compressions (*PC*) at 0 min and 2-min later (*PC 2 min*). $p < 0.01$ for AMSA at PC 0 min vs AMSA at PC 2 min in the group with left anterior descending (LAD) artery partially occluded

perfusing rhythm restoration in seven of eight instances, and AMSA of ≤20 mV-Hz correctly predicted electrical resuscitation failure in 24 of 26 instances. It therefore became apparent that AMSA represented a method that potentially fulfilled the need for minimising ineffective and detrimental defibrillation attempts during resuscitative manoeuvres.
In that investigation, AMSA values were displayed in real time for the first time and were continuously updated every 5-s interval during CPR. AMSA was not invalidated by artefacts resulting from precordial compression. The progressive increases in AMSA observed before successful resuscitation further demonstrated that AMSA had the potential to provide an objective guide, offering better CPR quality control. Failure to increase AMSA values to near threshold levels prognosticated defibrillation failure.

The initial empirical trials identified AMSA as representing the area under the curve based on amplitude and spectral frequency as a more optimal predictor for guiding the defibrillation attempt. The subsequent validation studies confirmed that AMSA has impressively higher specificity and PPV compared with the other predictors, maintaining sensitivity, NPV, mean amplitude, and median frequency comparable with CPP. Because AMSA was obtained during precordial compression, it fulfilled the other goal of allowing for uninterrupted precordial compression during ECG analyses. AMSA was well correlated with CPP, which is widely recognised as the gold standard for predicting successful defibrillation. Yet CPP was robust only for negative prediction. It is specificity and PPV, which are assured by AMSA, which are more likely to minimise adverse effects of re-

petitive high-energy shocks during CPR and the resulting postresuscitation myocardial dysfunction.

In more than 65% of the cardiac arrest events, the usual cause is an underlying acute or chronic ischaemic heart disease [90–92]. Accordingly, myocardial ischaemia and reperfusion have been involved in the triggering of malignant ventricular dysrhythmias [93, 94] and both duration and severity of myocardial ischaemia play important roles in causing myocardial cell damage [95]. Thus, VF amplitude and especially VF frequencies are different in instances of ischaemic heart disease.

More recently, Indik et al. [78] confirmed these results and, more interestingly, demonstrated that AMSA values did not change importantly when VF was induced in hearts with underlying ischaemic diseases. During CPR, however, we proved that reduced coronary blood flow significantly affects AMSA values. AMSA was superior to CPP as an indicator of return to a perfusing rhythm after defibrillation under condition of partial occlusion of the LAD coronary artery [96]. In a porcine model of cardiac arrest and resuscitation, partial LAD occlusion of approximately 75% of the internal lumen was maintained during CPR. During chest compression, CPP increased and exceeded threshold value for successful resuscitation. AMSA however, was significantly lower in animals in which partial occlusion of the LAD was maintained during CPR (Fig. 13.3). This was reflected in the greater number of electrical shocks required prior to terminating VF and in the lesser success of resuscitation. CPP is, in fact, an indirect indicator of myocardial flow produced by chest compression and represents a gradient pressure between aorta and right atrium. This gradient might be maintained even in the presence of occlusion of the coronary tree. AMSA, which is instead related to myocardial blood flow and metabolism, has been shown to be capable to substantially decrease when myocardial perfusion is reduced.

Accordingly, the quality of chest compression is a major issue [25–27]. Effectiveness of chest compressions relates to compression depth, rate and chest-wall decompression [97]. Outcomes may have been improved by assuring adequate compression depth in addition to more optimal rates of compression [98, 99]. As chest compression is usually performed without feedback, and because relatively small changes in compression depth profoundly alter haemodynamic effectiveness and outcomes, there is an increasingly recognised need for a monitor of effectiveness of chest compression [100–102]. Li and colleagues [103] therefore investigated the possibility of assessing CPR quality, especially of chest compression depth, using AMSA – which has the important advantage of being noninvasive and calculable from the universally available ECG – as part of the current practices of advanced life support. In a porcine model of VF and CPR, animals were randomised to optimal or suboptimal chest compression after VF onset. Optimal mechanical compression depth was defined as a decrease of 25% in anterior–posterior chest diameter during compression. Suboptimal compression in six animals was defined as a decrease of 17.5% in anterior–posterior chest diameter. All animals had ROSC after optimal compression. This contrasted suboptimal compressions after which no animal had ROSC. As with CPP and end tidal CO_2, AMSA once again has been proved to be predictive of outcomes. Calculated AMSA values during CPR and immediately prior to defibrillation attempts were significantly greater after optimal chest compression, as shown in Figure 13.4. In that experimental setting, the quality of chest compression was closely related to AMSA value and, in turn, to the likelihood of ROSC. As with the CPP threshold value, AMSA threshold value was achieved contingent upon compression depth such that AMSA increased progressively during chest compression and, as with CPP, predicted the likelihood

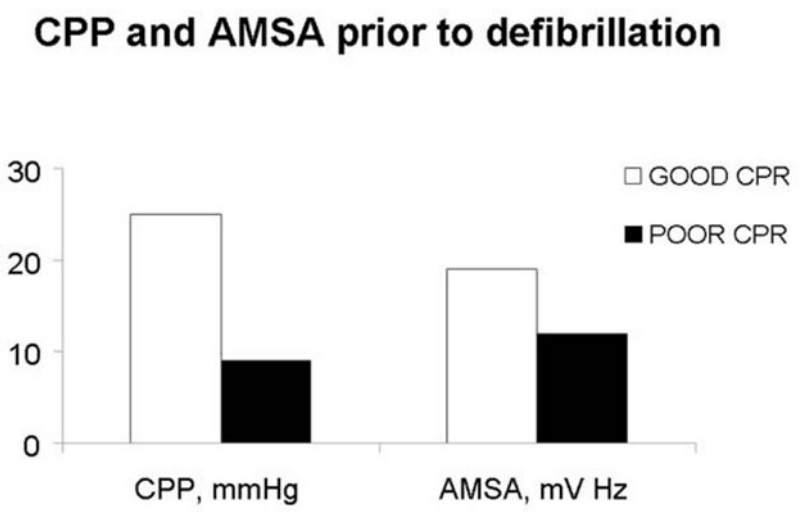

Fig. 13.4 Coronary perfusion pressure (*CPP*) and amplitude spectrum area (*AMSA*) during chest compression prior to defibrillation. *White bar,* good CPR; *black bar,* poor CPR. p <0.01 good CPR vs poor CPR

of successful defibrillation. AMSA therefore was confirmed to serve as a guide to the effectiveness of chest compression and optimal timing of an electrical shock. AMSA measurement to guide chest compression quality is its capability to aid in restoring the electrical robustness of the myocardium through restoring threshold levels of coronary blood flow, as reflected by CPP. When the area under the VF amplitude spectrum curve is of insufficient magnitude, the rescuer is prompted to push harder and perhaps faster.

Current American Heart Association (AHA) guidelines suggest an interval of chest compression prior to defibrillation if the duration of untreated cardiac arrest is >4 min. However in case of unwitnessed cardiac arrest, downtime is not predictable. We therefore hypothesised and subsequently confirmed AMSA efficacy in identifying the duration of untreated cardiac arrest [104]. In nine domestic male pigs, VF was induced and untreated for 15 min. AMSA, more so than VF amplitude and mean frequency, was highly correlated with VF downtime and decreased over the time, as shown in Figure 13.5. Significantly lower AMSA was observed after 3 min of untreated VF. Following the 4th min, AMSA values decreased more rapidly. AMSA therefore emerged as tool able to predict the downtime of untreated cardiac arrest and thereby a guide to better initial intervention.

13.5 Applicability of AMSA to the Clinical Scenario

The subsequent step in the evolution of AMSA as a better indicator of intervention effectiveness and defibrillation guide was confirmation of its efficacy in clinical settings.

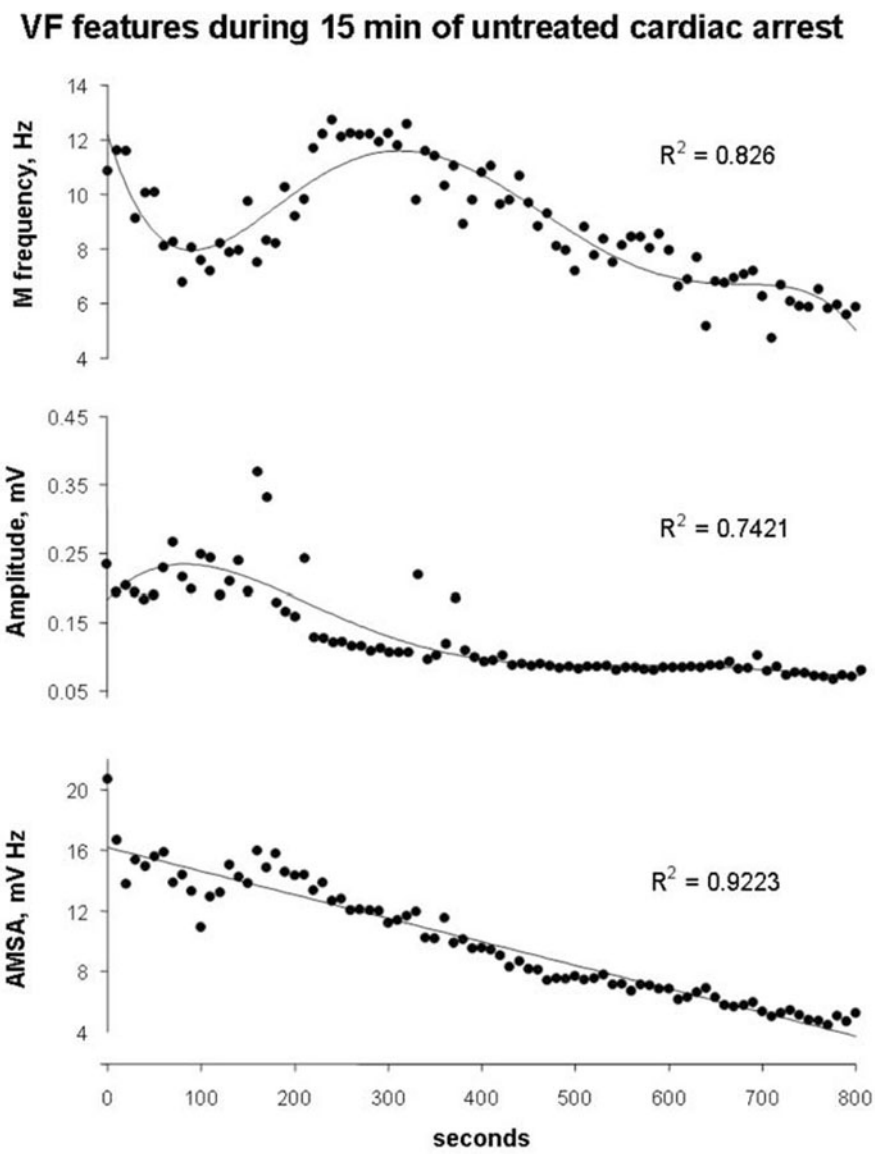

Fig. 13.5 Mean (*M*) frequency, amplitude and amplitude spectrum area (*AMSA*) during 15 min untreated ventricular fibrillation

At present, in fact, chest compression creates artefacts on the ECG signal to the degree that pauses in CPR are mandatory for rhythm analysis prior to attempted defibrillation [105, 106]. Substantial interruptions of chest compression have detrimental effects on the success of cardiopulmonary resuscitation [28, 84, 106], reducing the likelihood of successful defibrillation due to immediate declines in coronary perfusion [13, 84, 107]. Bisera

and co-workers retrospectively applied the AMSA algorithm to human ECG recordings obtained from AEDs employed in out-of-hospital cardiac arrests. The first confirmation of the capability of AMSA to predict successful defibrillation and ROSC in the clinical scenario was reported in late 2004 by Young et al. [108], and those results were recently confirmed by the authors of this chapter [109].

The first study was a retrospective analysis by Young et al. [108] of ECG records of lead-2-equivalent recordings on 108 defibrillation attempts with an automated external defibrillator on 46 patients with out-of-hospital VF-related cardiac arrest. There was an impressive separation between AMSA values and successful VF conversion with ROSC. An AMSA value of 13 mV-Hz predicted successful defibrillation with a sensitivity of 91% and a specificity of 94%. This was the first evidence that the predictive value of AMSA developed in experimental models of cardiac arrest and resuscitation in pigs could be extended to humans.

In 2008, we [109] analysed a new database that included episodes of VF or ventricular tachycardia with defibrillation attempts on humans who experienced out-of-hospital cardiac arrest. ECGs were recorded from AEDs that provided escalating biphasic shock in the sequence 120, 150, 200 j. AMSA was confirmed as a valid tool for predicting the likelihood that any one electrical shock would restore a perfusing rhythm during cardiopulmonary resuscitation in 90 men with out-of-hospital cardiac arrest. Our analysis was performed on a 4.1-s interval of ECG recordings immediately preceding the delivery of defibrillatory shock. For that study, the outcome was defined as being successful if defibrillation restored

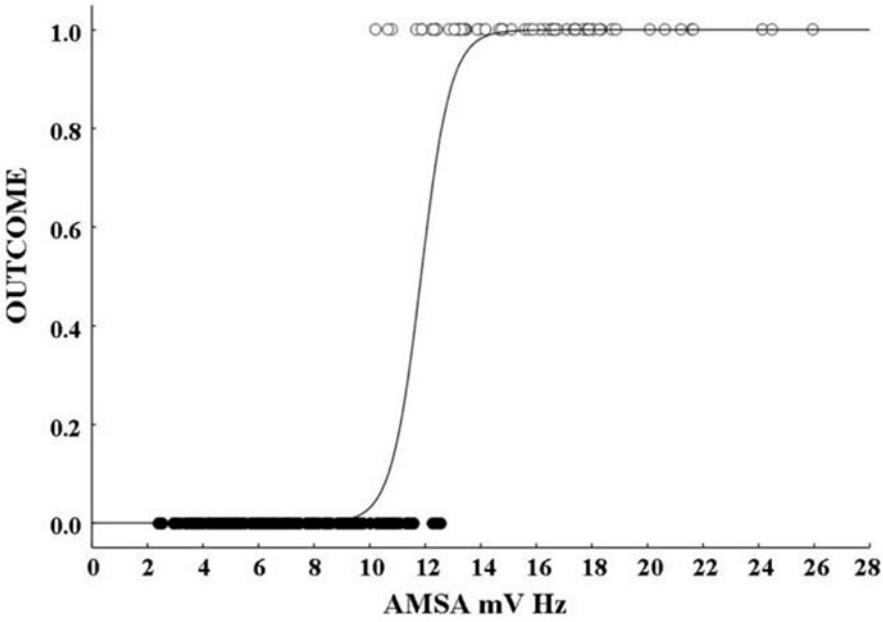

Fig. 13.6 Logistic regression representing amplitude spectrum area (*AMSA*) in relationship to defibrillation outcome

an organised rhythm with heart rate ≥40 bpm commencing within the 1-min postshock period and persisted for a minimum of 30 s. The outcome was considered unsuccessful if VF, ventricular tachycardia (heart rate >150 bpm), asystole or pulseless electrical activity with pauses >5 s occurred. AMSA values were significantly greater in successful vs unsuccessful defibrillation (16 mV-Hz and 7 mV-Hz, respectively; $p < 0.0001$). A threshold value of 12 mV-Hz AMSA was predictive of the success of each defibrillation attempt with a sensitivity of 91% and a specificity of 0.97 (Fig. 13.6). PPV, which refers to the proportion of shocks that correctly predicted perfusing rhythm restoration, was 95%. NPV, which refers to the proportion of shocks that predicted failure and actually failed to restore a perfusing rhythm, was 97%.

The results of that study were consistent with the previous retrospective analysis [107, 108] of human cardiac arrest patients. A very close AMSA threshold value was calculated, and a high sensitivity and specificity of this approach was confirmed. Of particular interest was that although defibrillators by different manufactures were employed in the two studies, results were consistent. This is therefore further confirmation that AMSA represents an excellent predictor of success of an electrical shock attempt, and this capability is independent of the defibrillatory energies and waveforms used.

Although several limitations were clarified by the authors of those studies, such as the potential confounding variables of "hands-off time before defibrillation" that was not controlled for, and the old "three-shocks" protocol employed during that period, clinical efficacy of AMSA was confirmed.

Finally, in a recent study of 267 CPR sequences from 77 patients with out-of-hospital cardiac arrest, Eftestøl and colleagues [110] confirmed AMSA as one of the most powerful predictors of defibrillation success.

13.6 Conclusions

CPP and $etCO_2$ represent useful tools for monitoring the effectiveness of chest compression and predicting CPR success. These measurements, however, are not feasible in out-of-hospital cardiac arrest situations. Investigators therefore focused their attention on VF waveform morphology as a success predictor of resuscitation. Greater VF amplitude with dominant and median frequency was associated with improved outcomes. However, the challenge is to ensure high sensitivity and specificity, especially during precordial compression, to identify the ideal moment to deliver the defibrillatory shock. AMSA analysis represents an accurate predictor for successful defibrillation and is a simple parameter that can be easily obtained by a conventional surface ECG, which is part of routine practice of advanced cardiac life support. Moreover, this method has the potential advantage in that it is not invalidated by artefacts produced by chest compression and thereby can be used during CPR without detrimental interruptions of chest compression and ventilation. Experimentally, consistent evidence of AMSA validity has been proved in data from both animals and humans. Accordingly, AMSA has now emerged as a clinically applicable method derived from ECG tracing that may provide a real-time indicator for chest compression efficacy and predict defibrillation success. We therefore anticipate that the AMSA algorithm incorporated into conventional AEDs will minimise interruption in chest compression and

thus decrease the delivery of futile and detrimental electrical shocks, leading to more optimal defibrillation timing.

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Part VII
Advances in Experimental and Clinical Research

Physiopathology and Severity of Postresuscitation Myocardial Dysfunction: Effects of Sodium–Hydrogen Exchanger Isoform-1 (NHE-1) Inhibitors and Erythropoietin

14

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14.1 Introduction

The working heart is a highly metabolic organ that under normal resting conditions extracts nearly 70% of the oxygen supplied by the coronary circulation [1, 2], representing close to 10% of the total body oxygen consumption. However, the heart has minimal capability for extracting additional oxygen, and increases in metabolic demands can only be met by autoregulatory increases in coronary blood flow through vasodilation of the coronary circuit [3]. Consequently, a severe energy imbalance develops when cardiac arrest occurs and coronary blood flow ceases. The severe energy imbalance continues during the ensuing resuscitation effort when current closed-chest resuscitation techniques are used because of the very limited capability for generating systemic and coronary blood flow [4]. The magnitude of energy imbalance is contingent upon the metabolic requirements and is particularly severe in the presence of ventricular fibrillation (VF), when oxygen requirements are comparable with or exceed those of the normally beating heart [5, 6]. A lesser energy deficit is expected during cardiac arrest with a quiescent or minimally active heart (i.e. asystole or pulseless electrical activity precipitated by asphyxia or exsanguination). Moreover, with reperfusion during resuscitation, multiple pathogenic mechanisms – collectively known as reperfusion injury – are activated and further contribute to myocardial injury. Primary contributors to reperfusion injury are mitochondrial calcium (Ca^{2+}) overload [7, 8] and generation of reactive oxygen species (ROS) [9]. Limited oxygen supply and concomitant reperfusion injury compromise the mitochondrial capability for regenerating adenosine triphosphatase (ATP) through oxidative phosphorylation. Limited amounts of ATP, however, are generated at the substrate level from anaerobic glycolysis and breakdown of creatine phosphate. Taking these processes together, the myocardium develops a marked lactic acid increase, rapid creatine phosphate depletion and relatively slow ATP depletion during cardiac arrest and resuscitation [10]. Accordingly, the resuscitation effort typically proceeds – and occasionally succeeds – in the presence of ischaemia and in the midst of reperfusion injury.

APICE 23. Antonino Gullo (Ed.)

14.2 Functional Manifestations

Various functional myocardial abnormalities develop consequent to ischaemia and reperfusion during cardiac arrest and resuscitation efforts that exert effects detrimental to cardiac resuscitation. These abnormalities can be grouped into those that manifest during the resuscitation effort and those that manifest after the return of spontaneous circulation. The former include reductions in left ventricular (LV) myocardial distensibility and increased resistance to electrical defibrillation; the latter includes reperfusion arrhythmias and postresuscitation myocardial dysfunction.

14.2.1 Reductions in Left Ventricular Myocardial Distensibility

Studies in various animal models of VF and resuscitation have shown progressive thickening of the LV wall accompanied by parallel reductions in LV cavity without changes in intracavitary pressures during the resuscitation effort [11, 12]. A functionally similar phenomenon – known as ischaemic contracture – was reported in the early 1970s during open heart surgery when operations were conducted under normothermic conditions and in fibrillating hearts [13, 14] and more recently after prolonged intervals of untreated VF [15]. However, ischaemic contracture is associated with profound reductions in myocardial ATP and often leads to a "stony heart", heralding irreversible ischaemic injury [16].

Reductions in LV myocardial distensibility observed during cardiac resuscitation is a different phenomenon:

1. it occurs much earlier than the stony heart;
2. onset and subsequent progression coincide with the interval of reperfusion during resuscitation [11, 17];
3. it is associated with less ATP depletion [10];
4. it has been attributed to myocardial energy deficit compounded by cytosolic and mitochondrial Ca^{2+} overload, precluding complete relaxation of individual cardiomyocytes;
5. it evolves into diastolic dysfunction upon return of spontaneous circulation [18];
6. it is largely reversible [19].

14.2.1.1 Haemodynamic Consequences of Reductions in Left Ventricular Myocardial Distensibility

As blood returns to the heart during the relaxation phase of chest compression, distensible ventricles are important to properly accommodate the returning blood and establish an adequate preload for the subsequent compression. The larger the distensibility, the larger the preload, and the larger the amount of blood that can be ejected by chest compression. This mechanism is akin to the Frank–Starling law [20] of the beating heart and presumes

that blood is ejected from the LV into the aorta during chest compression. Progressive decreases in LV myocardial distensibility during chest compression contribute to progressive decline in haemodynamic efficacy of closed-chest resuscitation. Studies in a VF porcine model have shown that the severity of this phenomenon is proportional to the duration of untreated VF [11].

Work in our laboratory demonstrated that reductions in LV myocardial distensibility can be prevented by pharmacologic interventions targeting reperfusion injury, resulting in more haemodynamically stable closed-chest resuscitation [17, 21]. In one study, progressive LV wall thickening with reductions in cavity size were mitigated by administration of the sodium/hydrogen exchanger 1 (NHE-1) inhibitor cariporide [17]. This effect prevented haemodynamic deterioration that characteristically occurs during chest compression, maintaining a stable coronary perfusion pressure above the resuscitability threshold of 10 mmHg in pigs and yielding higher resuscitation rates [17].

14.2.1.2
Clinical Evidence of Reductions in Left Ventricular Myocardial Distensibility

Takino and Okada [22] reported in 1996 on 59 adult patients who suffered nontraumatic out-of-hospital cardiac arrest and underwent open-chest direct manual cardiac compression in the emergency department after failure of closed-chest resuscitation. A "firm" myocardium was noticed during manual cardiac compression in 36 cases that predominantly affected the LV. In the remaining 23 cases, the hearts were "soft". The authors also noted that some hearts became "firm" during compression. The presence of a firm myocardium was associated with reduced haemodynamic efficacy of cardiac compression, as evidenced by a lower end-tidal carbon dioxide (CO_2) tension ($P_{ET}CO_2$) – which is a well-documented surrogate measurement of systemic and regional blood flow during cardiac resuscitation [4, 23–25]. Hearts with very firm myocardium never regained spontaneous contractions. Hearts with less firm myocardium showed some, albeit insufficient, spontaneous contractions. Hearts with soft myocardium regained contractions and were able to generate a peripheral pulse in most instances.

14.2.2
Resistance to Defibrillation

Electrical shocks delivered immediately after VF onset are consistently effective in re-establishing cardiac activity. Even short delays (i.e. up to 3 min) may not be substantially detrimental, resulting in >50% likelihood of successful resuscitation [26]. However, longer intervals of untreated VF – as usually occurs after out-of-hospital cardiac arrest – predictably decreases the effectiveness of defibrillation attempts in which electrical shocks – even of higher energy levels – may fail to reverse VF or may precipitate asystole or pulseless electrical activity. Under these conditions, haemodynamic efficacy of the resuscitation technique becomes of paramount importance for successful defibrillation.

14.2.3
Reperfusion Arrhythmias

Premature ventricular complexes and episodes of ventricular tachycardia and VF commonly occur during the early minutes after return of cardiac activity. Postresuscitation episodes of VF – which require additional electrical shocks – have been reported in up to 79% of patients, with some studies showing and inverse relationship between the number of episodes and survival [27]. The underlying cell mechanisms are complex but prominently involve cytosolic Ca^{2+} overload and after-depolarisations. There are repolarisation abnormalities that include shortening of the action potential duration, decreased action potential amplitude and development of action potential alternans, creating conditions for re-entry. Experimentally, these repolarisation abnormalities are short-lived (5–10 min) and coincide with the interval of increased propensity for ventricular arrhythmias and recurrent VF [17]. These repolarisation abnormalities and reperfusion arrhythmias can be markedly attenuated by NHE-1 inhibition [17].

14.2.4
Postresuscitation Myocardial Dysfunction

Variable degrees of systolic [28–31] and diastolic [17, 32] dysfunction develop after resuscitation from cardiac arrest. Dysfunction occurs despite full restoration of coronary blood flow and is largely reversible, conforming to the definition of myocardial stunning. Systolic dysfunction is characterised by decreases in contractility – documented by load-independent indices derived from varying end-systolic pressure-volume relationship – leading to reductions in LV ejection fraction, cardiac index, LV stroke work [29, 30] and poor tolerance to afterload increases [33]. Diastolic dysfunction is characterised by LV wall thickening with reductions in end-diastolic volume and impaired relaxation [17]. Diastolic dysfunction appears to be maximal immediately after spontaneous circulation restoration, with the magnitude of wall thickness closely correlated with wall thickness during VF [18], suggesting a common pathogenic thread. From a functional perspective, diastolic dysfunction may limit the compensatory ventricular dilatation required to overcome decreases in contractility according to the Frank–Starling mechanism [20].

14.3
Novel Intervention Targeting the Pathophysiology of Myocardial Injury

Two lines of research developed at the Resuscitation Institute at Rosalind Frank University show promising new interventions that can ameliorate myocardial injury and have beneficial effects for initial resuscitation and postresuscitation myocardial dysfunction. One line of research involves using NHE-1 inhibitors in various animal models of cardiac arrest [10, 12, 17, 21, 34–38]. The other relates to more recent work using erythropoietin in a rat model of cardiac arrest [39] and in a small clinical study in patients suffering out-of-hospital cardiac arrest [40]. Both lines of research support the rationale and feasibility of using

either an NHE-1 inhibitor or erythropoietin for preserving LV myocardial distensibility during cardiac resuscitation and function after return of spontaneous circulation.

14.3.1 NHE-1 Inhibitors

14.3.1.1 Cell Mechanism

Cessation of coronary blood flow during cardiac arrest causes a metabolic shift to anaerobic metabolism, prompting rapid development of intense and sustained intracellular acidosis [41–43]. Intracellular acidosis activates the sarcolemmal NHE-1, initiating an electroneutral sodium/hydrogen (Na^+–H^+) exchange that brings Na^+ into the cell [44]. During the ensuing resuscitation effort, the myocardium is reperfused with blood that typically has a normal pH, resulting in the washout of protons that accumulated in the extracellular space during the preceding interval of no-flow cardiac arrest. This intensifies sarcolemmal Na^+–H^+ exchange and the resulting Na^+ entry [34, 44, 45]. Na^+ accumulates in the cytosol because the Na^+–K^+ ATPase activity is concomitantly reduced [46], such that progressive and prominent increases in cytosolic Na^+ occurs. Na^+ may also enter the cell through Na^+ channels and the Na^+–bicarbonate (HCO_3^-) cotransporter. The cytosolic Na^+ excess, in turn, drives sarcolemmal Ca^{2+} influx through reverse-mode operation of the sarcolemmal Na^+–Ca^{2+} exchanger, leading to cytosolic and mitochondrial Ca^{2+} overload [47], causing a myriad of detrimental effects.

Cytosolic Ca^{2+} overload during ischaemia and reperfusion has been identified as a primary effector of mitochondrial injury. Mitochondria can sequester large amounts of cytosolic Ca^{2+}, a process regulated by the Ca^{2+} uniporter for influx and by the Na^+–Ca^{2+} exchanger for efflux [48]. However, as matrix Ca^{2+} levels progressively rise, the mitochondrial Na^+–Ca^{2+} exchanger becomes saturated and mitochondrial Ca^{2+} overload ensues [48]. Mitochondrial Ca^{2+} overload can worsen cell injury in part by compromising its capability to sustain oxidative phosphorylation [49] and by promoting the release of proapoptotic factors [50].

The relevance of this mechanism of injury is highlighted by a large preclinical database demonstrating consistent attenuation of myocardial injury caused by ischaemia and reperfusion when Na^+ entry to the cell is limited, as when NHE-1 activity is inhibited [44] or when Na^+ channels are blocked [51, 52].

14.3.1.2 Effects of NHE-1 Inhibition on Resuscitation

Research over the last decade in our laboratory using various translational rat and pig models of cardiac arrest has shown consistent myocardial benefit associated with inhibition of NHE-1 activity during resuscitation from VF [10, 12, 17, 21, 34–38, 53–57]. Mechanistically, these benefits are associated with less cytosolic Na^+ overload, less mitochondrial

Ca^{2+} overload and preservation of oxidative phosphorylation. Some of these studies, highlighting key aspects of NHE-1 inhibition during resuscitation pertinent to this application, are succinctly discussed below.

Effects on Left Ventricular Myocardial Distensibility

The initial findings suggesting that NHE-1 inhibition could attenuate reductions in LV myocardial distensibility during resuscitation and also prevent postresuscitation diastolic dysfunction were made in an isolated (Langendorff) rat model of VF and simulated resuscitation [34, 35], establishing the rational for subsequent studies in intact rat and intact pig models of VF and resuscitation. Findings in one of our pig studies paralleled the aforementioned findings in the isolated rat heart, corroborating in a clinically relevant model preservation of LV myocardial distensibility during closed-chest resuscitation evidenced by preservation of wall thickness and cavity size. Preservation of LV myocardial distensibility enabled the generation of higher coronary perfusion pressures, leading to higher resuscitability rates (2/8 vs 8/8; $p < 0.05$) [18].

Subsequent studies were conducted in our intact rat model of VF and closed-chest resuscitation designed to measure – using fluorescent microspheres – the effects of NHE-1 inhibition (using cariporide) on systemic and organ blood flow as a function of compression depth [21]. We reasoned that if LV myocardial distensibility – and therefore preload – could be preserved by NHE-1 inhibition, then higher forward blood flows could be generated for a given compression depth, thus shifting the relationship between flow and compression depth to the left. Two series of 14 experiments each were conducted in which rats were subjected to 10 min of untreated VF followed by 8 min of chest compression before attempting defibrillation. Compression depth was adjusted to maintain an aortic diastolic pressure between 26 and 28 mmHg in the first series and between 36 and 38 mmHg in the second series. Within each series, rats were randomised to receive cariporide (3 mg/kg) or NaCl 0.9% (control) before starting chest compression. In rats that received cariporide, the compression depth required to generate a given level of systemic and organ blood flow was markedly reduced compared with in rats that received the vehicle control.

These studies also suggested that higher coronary perfusion pressures could be generated when administering a vasopressor agent, given the larger blood flow generated in the presence of an NHE-1 inhibitor for a given compression depth. This was the case when cariporide was combined with epinephrine in our pig model [12] and when combined with epinephrine and with vasopressin in our rat model [37].

Effects on Cytosolic Na^+ and Mitochondrial Ca^{2+}

A rat model of VF and closed-chest resuscitation was used to examine the effects of NHE-1 inhibition and of Na^+ channel blockade (interventions collectively referred to as Na^+-limiting interventions) on intracellular Na^+ levels, mitochondrial Ca^{2+} levels, cardiac function and plasma levels of cardiospecific troponin I (cTnI) after resuscitation [38]. For these studies, hearts were removed at specific time events; namely: (1) at baseline; (2) at 15min of untreated VF; (3) at 15min of VF with chest compression provided during the last

5min of VF; and (4) at 60min postresuscitation. Rats from the last two time events were randomised to receive Na^+-limiting intervention immediately before starting chest compression or vehicle control. Na^+-limiting interventions included a newly developed NHE-1 inhibitor, AVE4454 (1 mg/kg), lidocaine (5 mg/kg), and the combination of AVE4454 and lidocaine. Limiting sarcolemmal Na^+ entry attenuated increases in cytosolic Na^+ and mitochondrial Ca^{2+} overload during chest compression and the postresuscitation phase. Attenuation of cytosolic Na^+ and mitochondrial Ca^{2+} increases was accompanied by preservation of LV myocardial distensibility during chest compression, less postresuscitation myocardial dysfunction and lower levels of cTnI.

Effects on Energy Metabolism

An open-chest pig model of electrically induced VF and extracorporeal circulation was developed to study the myocardial energy effects of inhibiting NHE-1 under conditions of controlled coronary perfusion pressure [10]. For this study, VF was induced by epicardial delivery of an alternating current and left untreated for 8min. After this interval, extracorporeal circulation was started and systemic (extracorporeal) blood flow adjusted to maintain a coronary perfusion pressure at 10 mmHg for 10min before attempting defibrillation and restoration of spontaneous circulation. The target coronary perfusion pressure was chosen to mimic the low coronary perfusion pressure generated by closed-chest resuscitation. Two groups of eight pigs each were randomised to receive the NHE-1 inhibitor zoniporide (3 mg/kg) or vehicle control as a right atrial bolus immediately before starting extracorporeal circulation. As in a previous study using the NHE-1 inhibitor cariporide [17], zoniporide also prevented reductions in LV myocardial distensibility during the VF interval and extracorporeal circulation, which in control pigs was characterised by progressive reductions in cavity size and progressive thickening of the LV wall.

Importantly, these effects occurred without changes in coronary blood flow or coronary vascular resistance, indicating that the favourable myocardial effects of NHE-1 inhibition during resuscitation are not likely the result of increased blood flow and oxygen availability (e.g. by less extrinsic compression of the coronary circuit). Instead, myocardial tissue measurements indicated that zoniporide administration prevented progressive loss of oxidative phosphorylation during the interval of simulated resuscitation. Animals that received zoniporide: (1) maintained a higher creatine phosphate to creatine (pCr/Cr) ratio; (2) maintained a higher ATP/adenosine diphosphate (ADP) ratio; and (3) had lesser increases in adenosine. These measurements are consistent with regeneration of ADP into ATP by mitochondria instead of downstream degradation into adenosine, with the newly formed ATP being used to regenerate creatine phosphate. All these findings are indicative of preserved mitochondrial bioenergetic function. These changes were accompanied by prominent amelioration of myocardial lactate increases, attaining levels inversely proportional to the pCr/Cr ratio at 8min of VF and extracorporeal circulation, suggesting a shift away from anaerobic metabolism consequent to preservation of mitochondrial bioenergetic function in pigs treated with zoniporide. After return of spontaneous circulation, pigs treated with zoniporide had higher LV ejection fraction (0.57 ± 0.07 vs 0.29 ± 0.05; $p < 0.05$) and higher cardiac index (4.8 ± 0.4 vs 3.4 ± 0.2 l/min/m^2; $p < 0.05$) [10], replicating previously reported favourable effects of NHE-1 inhibition on postresuscitation

myocardial function [12, 17, 34, 35].
These energy effects are consistent with NHE-1 inhibition protecting mitochondrial bioenergetic function – probably as a result of limiting mitochondrial Ca^{2+} overload – and supportive of the concept that LV myocardial distensibility during resuscitation is likely to be preserved by activating mitochondrial mechanisms capable.

14.3.2 Erythropoietin

14.3.2.1 Cell Mechanism

Erythropoietin is a 30.4-kDa glycoprotein best known for its action on erythroid progenitor cells and regulation of circulating red cell mass. However, several studies have recently shown that erythropoietin also activates potent cell survival mechanisms during ischaemia and reperfusion through genomic and nongenomic signalling pathways in a broad array of organs and tissues, including the heart [58–63], brain [64, 65], spinal cord [66], retina [67], kidney [68], liver [69] and skin [70].

Activation of these protective mechanisms involves binding of erythropoietin to a specific cell membrane receptor (epoR) member of the type 1 superfamily of single-transmembrane cytokine receptors, prompting cross-phosphorylation and activation of Janus tyrosine kinases (JAK) 1 and 2. JAK activation causes phosphorylation of tyrosine residues, creating docking sites for recruitment and activation of multiple signalling proteins that have Src-homology-2 (SH2) domains resulting in well-established antiapoptotic [59], anti-inflammatory [71, 72] and proliferative effects (i.e. neovascularisation) [73, 74], with time courses that vary contingent upon the specific signalling mechanism and duration of erythropoietin binding to the EpoR. Although important in other settings, these effects are not likely to play a role for initial cardiac resuscitation. We hypothesise that erythropoietin signalling is important for resuscitation through pathways that result in preservation of mitochondrial bioenergetic function, leading to functional effects similar to those elicited by NHE-1 inhibition (albeit through quite distinct cell mechanisms).

14.3.2.2 Effects of Erythropoietin on Resuscitation

Studies in Rats

The effects of erythropoietin were studied in our rat model of VF and closed-chest resuscitation using human recombinant erythropoietin (epoetin alpha, Amgen, Thousand Oaks, CA, USA) [39]. Rats were subjected to 10 min of untreated VF followed by 8 min of closed-chest resuscitation before attempting defibrillation. The depth of compression was adjusted to maintain an aortic diastolic pressure between 26 and 28 mmHg. This level of

diastolic aortic pressure secured a coronary perfusion pressure above the resuscitability threshold of 20 mmHg in rats. The relationship between the coronary perfusion pressure and compression depth (CPP/depth) was used to assess changes in LV myocardial distensibility. Successfully resuscitated rats were observed for 120min before euthanasia.

Three groups of ten rats each were randomised to receive a right atrial bolus of epoetin alpha (5,000 IU/kg) at baseline 15min before induction of VF (EPO_{BL} -15-min), at 10min of VF before starting chest compression (EPO_{VF} 10-min) or to receive 0.9% NaCl solution (control), with the investigators blinded to the treatment assignment. Erythropoietin given coincident with the beginning of chest compression after 10min of untreated VF – but not before inducing VF – promoted haemodynamically more effective chest compression such that the coronary perfusion pressure to compression depth (CPP/depth) ratio averaged during the interval of chest compression was 2.0 ± 0.3 mmHg/mm in EPO_{VF} 10-min, 1.6 ± 0.2 mmHg/mm in EPO_{BL} -15-min and 1.6 ± 0.3 mmHg/mm in the control group ($p < 0.05$ EPO_{VF} 10-min vs EPO_{BL} -15-min and vs control). This difference represented a 25% improvement in the haemodynamic efficacy of chest compression with erythropoietin given at the beginning of chest compression. Postresuscitation, EPO_{VF} 10-min rats had significantly higher mean aortic pressure associated with numerically higher cardiac index and higher peripheral vascular resistance. The diminished effectiveness of erythropoietin when given before VF is intriguing and worth of additional investigation.

Similar observations were made in a recent series of experiments in the same rat model of VF and closed-chest resuscitation described above. However, the protocol was modified such that the chest was compressed to the maximum depth of 17 mm in rats. Under this clinically more relevant protocol, 5,000 IU/kg of erythropoietin given at the beginning of chest compression prompted haemodynamically more effective chest compression, yielding a coronary perfusion pressure approximately 5 mmHg higher than in control rats and substantial improvement in postresuscitation myocardial dysfunction.

Studies in Humans

A clinical study was performed in collaboration with Dr. Štefek Grmec and the Maribor Emergency Medical Services system in the city of Maribor, Slovenia and adjacent rural areas, encompassing a population of approximately 200,000 inhabitants [40]. Resuscitation was attempted using regionally developed protocols that incorporate International Liaison Committee on Resuscitation (ILCOR) 2005 [75] recommendations by a two-tier system composed of basic life support and advanced life support teams, with the latter led by a physician. Patients assigned to erythropoietin received 90,000 IU of beta-epoetin (NeoRecormon, Hoffman La Roche) as a bolus within 1 or 2min after starting chest compression, followed by a 10-ml bolus of 0.9% NaCl. Beta-epoetin was kept refrigerated (2–8°C) in the ambulance until immediately before use. In every instance, erythropoietin was given before any other drug. The primary end-point was intensive care unit (ICU) admission. The secondary end-points were return of spontaneous circulation (ROSC) in the field, survival at 24 h and survival at hospital discharge.

The study was originally designed to be prospective and randomised. However, disruption in the supply of erythropoietin prompted investigators to administer erythropoietin or 0.9% NaCl control based on availability, allocating 24 patients to erythropoietin and 30 to 0.9% NaCl between April 2007 and May 2008. The control group for the analysis was des-

ignated as concurrent controls. Post hoc, a second control group was included in which 48 of 126 patients were selected who had out-of-hospital cardiac arrest treated with the same resuscitation protocol the year before. These 48 patients were selected using propensity scores assigning two controls for each erythropoietin-treated patient. Propensity scores were calculated using multiple logistic regression: entering age, male sex, witnessed arrest, time from call to start of cardiopulmonary resuscitation (CPR), pulseless electrical activity, asystole and bystander CPR as pretreatment predictors of outcome. The control group was designated as matched controls. The same variables used to calculate propensity scores were used to adjust odds ratios (OR) for comparison between erythropoietin and the concurrent controls and between erythropoietin and the matched controls.

By univariate analysis, administration of erythropoietin – when compared with concurrent controls – was associated with higher rates of ICU admission, ROSC, 24-h survival and survival to hospital discharge and – when compared with matched controls – was associated with higher rates of ICU admission, ROSC, and 24-h survival. After adjustment by pretreatment covariates (listed above), comparison with concurrent controls reduced the OR but retained statistical significance for ICU admission and ROSC, whereas comparison with matched controls increased the OR, demonstrating statistical significance for all four outcomes.

To assess whether the beneficial effects on resuscitation outcomes could have been linked to beneficial effects on LV myocardial distensibility – as suggested by our preceding study in rats [39] – we examined the effects on $P_{ET}CO_2$. As discussed earlier, $P_{ET}CO_2$ is a good surrogate measurement of forward blood flow during chest compression [4, 23–25]. In the study, rescuers were trained and retrained to provide consistent compression depth and rate, and the $P_{ET}CO_2$ values in both control groups were already indicative of high-quality chest compression. If, as hypothesised, erythropoietin preserved myocardial distensibility, for a given compression depth, one would expect higher forward blood flow in the presence of erythropoietin and therefore higher $P_{ET}CO_2$. This was indeed the case. Patients who received erythropoietin had significantly higher $P_{ET}CO_2$ during chest compression.

14.4 Conclusions

These preclinical and clinical observations suggest that myocardial injury can be attenuated during resuscitation from cardiac arrest leading to functional benefits that enable haemodynamically more effective chest compression and improved postresuscitation myocardial function. Future effort should focus on the translation of these concepts through additional clinical trials that could not only support these findings but also quantitate their treatment effects paving the way for ultimately clinical implementation.

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Experimental Treatment for Preservation of Mechanically Competent Cardiac Activity Following Cardiac Arrest

15

I.M. Ayoub, J. Radhakrishnan and R.J. Gazmuri

15.1 Introduction

It has been suggested that sudden cardiac arrest may affect as many as 6.8 million individuals annually (~1:1,000 people) [1, 2]. In the United States, every year approximately 300,000 individuals suffer an episode of out-of-hospital sudden cardiac arrest [3]. Efforts to reestablish life are formidably challenging, requiring not only that cardiac activity be reestablished but that injury to vital organs be prevented, minimised, or reversed. Resuscitation methods yield an average survival and hospital discharge rate with intact neurological function that approaches 7.9% in the United States [4], 10.7% in Europe [5], and only 1.0% in the rest of the world [6]. In the United States, efficient emergency medical service systems can initially reestablish cardiac activity in approximately 30% of individuals [7–9] with >40% dying before hospital admission [10]. Of those admitted to hospital, nearly 75% die before hospital discharge due to variable degrees of myocardial or neurological dysfunction, systemic inflammation, intercurrent illnesses, or a combination thereof [10–12]. Thus, initial reestablishment of cardiac activity using available resuscitation treatments does not ensure ultimate survival.

During cardiac arrest and resuscitation, the myocardium constitutes a prime target of injury, leading to distinct functional abnormalities that can adversely affect resuscitability and survival. To restore cardiac activity, blood flow must be first generated by artificial means (e.g. chest compression) to reperfuse the heart and other organs that have been ischaemic for variable periods. Reperfusion eventually restores aerobic metabolism, enabling resumption of organ function. However, reperfusion also activates multiple pathogenic mechanisms, known as reperfusion injury, which have been credited with postischaemic cell dysfunction and cell death. At the organ level, reperfusion injury has been linked to the myocardial dysfunction observed after resuscitation from cardiac arrest that leads to dismal survival outcomes.

Effectual myocardial reperfusion is frequently necessary to reverse the continuum of lethal electromechanical myocardial states associated with sudden cardiac arrest and include ventricular tachycardia (VT), ventricular fibrillation (VF), pulseless electrical activ-

APICE 23. Antonino Gullo (Ed.)

ity (PEA), and asystole. VF has been described as the most common initial state in cardiac arrest victims [13] and if left untreated degenerates into asystole. VF in adults is often triggered by a local ischaemic event that disrupts the coordinated propagation of the electrical impulse through the ventricles, leading to multiple reentrant wave fronts of electrical excitation circulating throughout the myocardium [14, 15]. Even though the fibrillating heart performs no external work, its energy utilisation is comparable with or higher than that of the normally beating heart [16–18]. As a result, cessation of myocardial blood flow when the heart is fibrillating leads to severe energy imbalance accompanied – among other effects [19, 20] – by intracellular sodium (Na^+) and calcium (Ca^{2+}) overload, which further exacerbate cell injury.

15.1.1 Na^+-induced Cytosolic Ca^{2+} Overload

During cardiac arrest and resuscitation, an important mechanism that precipitates postresuscitation myocardial injury is Na^+-induced intracellular Ca^{2+} overload. The cessation of coronary blood flow during cardiac arrest prompts a shift to anaerobic metabolism in the myocardium, leading to rapid development of intense and sustained intracellular acidosis. Intracellular acidosis activates the sarcolemmal sodium–hydrogen exchanger isoform-1 (NHE-1), initiating an electroneutral Na^+–hydrogen (H^+) exchange that brings Na^+ into the cell [21].

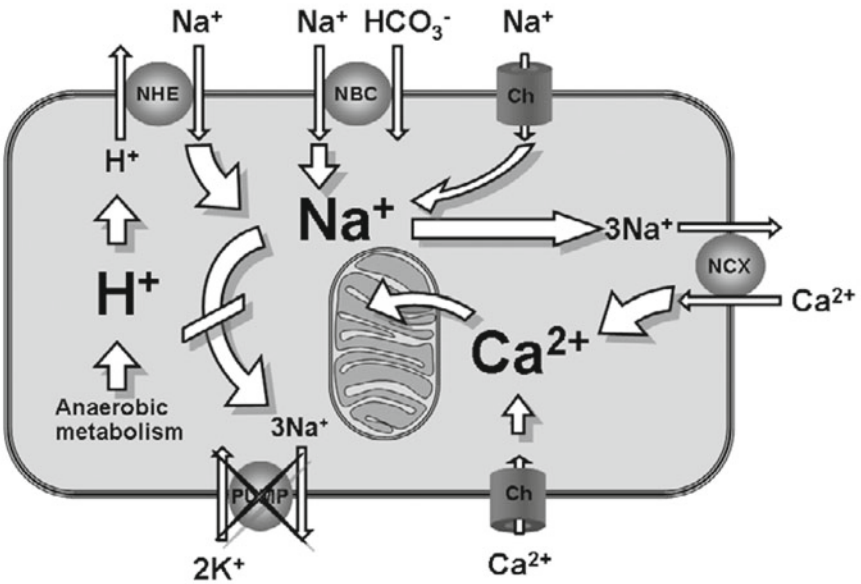

Fig. 15.1 Cardiomyocyte during ischaemia and reperfusion depicting sodium (Na^+)-induced cytosolic and mitochondrial calcium (Ca^{2+}) overload. *NHE,* sodium–hydrogen exchanger isoform-1; *NBC,* Na^+-bicarbonate (HCO_3^-) cotransporter; *NCX,* Na^+–Ca^{2+} exchanger; *Ch,* channel

Reperfusion with normal blood pH during cardiac resuscitation washes out H^+ accumulated extracellularly during the preceding interval of no-flow. This improves the gradient for Na^+–H^+ exchange, leading to further Na^+ entry [21–23]. This process is compounded by decreases in Na^+–K^+ adenosine triphosphatase (ATPase) activity [24], such that progressive and prominent cytosolic Na^+ overload occurs. Cytosolic Na^+ overload drives sarcolemmal Ca^{2+} influx through reverse-mode operation of the sarcolemmal Na^+–Ca^{2+} exchanger (NCX), with consequent cytosolic Ca^{2+} overload [18, 22, 25] (Fig. 15.1). Such Ca^{2+} accumulation is a central manifestation of ischaemia and reperfusion injury.

Cytosolic Ca^{2+} overload has been identified as a primary effector of mitochondrial injury. Mitochondria can sequester large amounts of cytosolic Ca^{2+}, which is regulated by the Ca^{2+} uniporter for influx and by the Na^+–Ca^{2+} exchanger for efflux [26]. However, as matrix Ca^{2+} levels continue to increase, the mitochondrial Na^+–Ca^{2+} exchanger becomes saturated, and mitochondrial Ca^{2+} overload ensues [26]. Mitochondrial Ca^{2+} overload can worsen cell injury in part by compromising its capability to sustain oxidative phosphorylation [27] and by promoting the release of proapoptotic factors [28].

15.1.2 NHE-1 Inhibition during Ischaemia and Reperfusion

Numerous studies have demonstrated that limiting cytosolic Ca^{2+} overload via NHE-1 inhibition during ischaemia and reperfusion protects the myocardium [29, 30]. In neonatal rat cardiomyocytes subjected to oxidative injury [i.e. hydrogen peroxide (H_2O_2)], the NHE-1 inhibitor cariporide lessened mitochondrial injury, as evidenced by preventing externalisation of phosphatidylserine, caspase-3 cleavage and propidium iodide uptake. Additionally, mitochondrial membrane potential was better preserved [31].

In a rat model of VF and closed-chest resuscitation, administration of Na+-limiting interventions (NHE-1 inhibitor AVE4454B and the Na^+ channel blocker lidocaine) attenuated increases in cytosolic Na^+ (Fig. 15.2) and prevented increased mitochondrial Ca^{2+} (Fig. 15.3) during closed-chest resuscitation and the postresuscitation interval. Limiting sarcolemmal Na^+ entry was also associated with beneficial myocardial functional effects and ameliorated postresuscitation cardiospecific troponin I levels (cTnI) [32]. In another rat study, cariporide enhanced the haemodynamic efficiency of closed-chest resuscitation demonstrated by limiting progressive increases in depth of compression required to maintain a target aortic diastolic pressure between 36 and 38 mmHg (Fig. 15.4) and enabling improved forward blood flows to be generated at a given depth of compression. Systemic and regional blood flows were measured using fluorescence microspheres at different time intervals [33].

In an open-chest pig model of VF and controlled coronary perfusion by extracorporeal circulation (ECC), NHE-1 inhibitor zoniporide attenuated myocardial injury during resuscitation from VF through beneficial effects on energy metabolism independent of effects on coronary blood flow or vascular resistance. During the resuscitation period, NHE-1 inhibition prevented reductions in left ventricular (LV) volume and wall thickening (Fig. 15.5) while favouring higher myocardial creatine phosphate to creatine ratios, lower myocardial adenosine and lower myocardial lactate (Fig. 15.6). NHE-1 inhibition was also

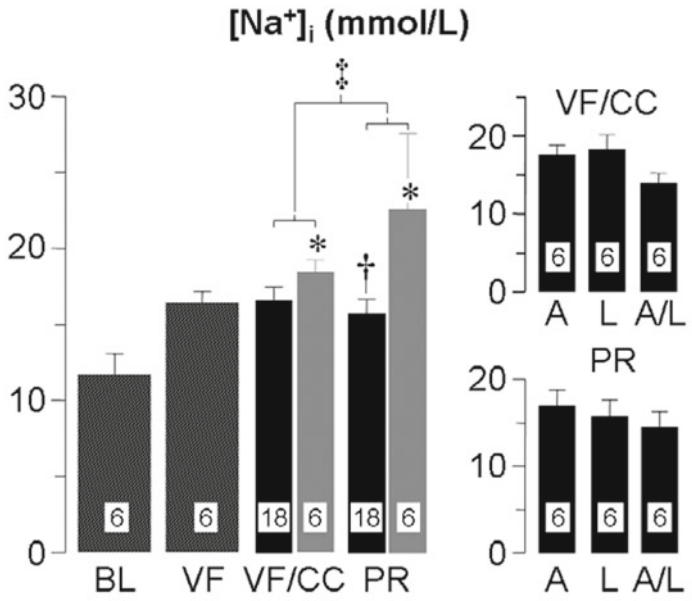

Fig. 15.2 Intracellular sodium (*[Na⁺]i*) in left ventricular (*LV*) tissue of rats at baseline (*BL*), at 15 min of untreated ventricular fibrillation (*VF*), at 15 min of VF accompany by 5 min of chest compression (*CC*) and at 60 min postresuscitation (*PR*). *Hatched bars* represent measurements without pharmacological treatment. *Black bars* represent rats treated with Na^+-limiting interventions. *Gray bars* represent rats treated with vehicle control. The individual Na^+-limiting interventions are shown on the *right panels*: *A*, selective sodium–hydrogen exchanger isoform-1 inhibitor AVE4454; *L,* lidocaine; *A/L* combination of AVE4454 and L. Numbers within bars denote number of hearts processed for the measurement. Values are mean ± standard error of mean (SEM). ∗$p < 0.05$ vs BL by Kruskal–Wallis one-way analysis of variance (ANOVA) on ranks using Dunn's method for multiple comparisons; †$p < 0.05$ vs control by Student's t test in PR groups; ‡two-way ANOVA using time factor (VF/CC vs PR) and treatment factor (control vs Na^+-limiting interventions) was significant for treatment factor ($p = 0.013$). (Adapted from [32])

associated with improved postresuscitation LV ejection fraction and cardiac index. The study suggested mitochondria are important targets of myocardial injury during cardiac arrest and linked the favourable functional effects of NHE-1 inhibition to preservation of bioenergetic function, most probably as a result of less mitochondrial Ca^{2+} overload [34].

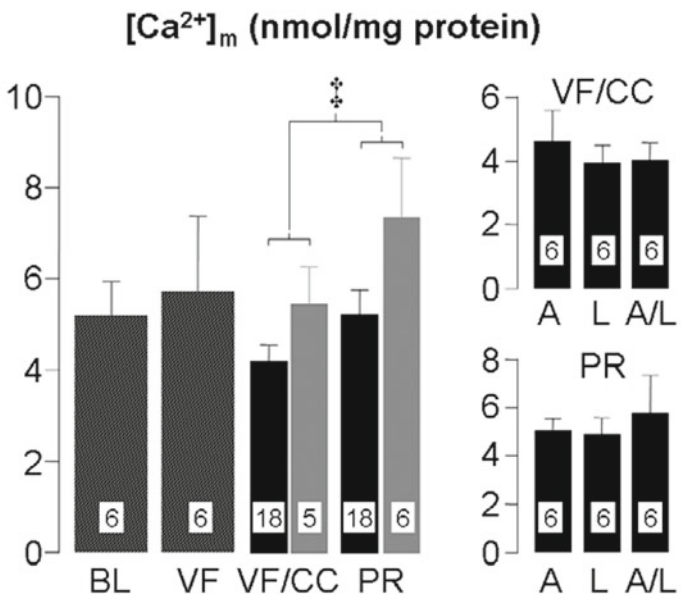

Fig. 15.3 Mitochondrial calcium (Ca^{2+}) ($[Ca^{2+}]m$) in left ventricular (LV) tissue of rats. For interpretation of bars and abbreviations, refer to legend for Fig. 15.2. ‡Two-way analysis of variance (ANOVA) using time factor [ventricular fibrillation/chest compression (*VF/CC*) vs postresuscitation (*PR*)] and treatment factor [control vs sodium (Na^+)-limiting interventions] was significant for both time factor ($p = 0.045$) and treatment factor ($p = 0.021$). (Adapted from [32])

15.2 NHE-1 Inhibition Promotes Return of Electrically Stable and Mechanically Competent Cardiac Activity

In a recently published study [35], we examined the effect NHE-1 inhibition on the cardiac electrical and mechanical activity during VF and resuscitation. The electrical and mechanical abnormalities associated with VF during cardiac resuscitation have been well characterised by our group and others and include: (1) decreases in myocardial compliance, partly explaining reductions in the haemodynamic efficacy of closed-chest resuscitation [33, 36, 37]; (2) ventricular arrhythmias upon return of spontaneous circulation, accompanied by episodes of VF [13, 37–39]; and (3) postresuscitation systolic and diastolic LV dysfunction of varying severity, which can compromise haemodynamic function and survival [10, 40–44].

Establishing stable electrical activity after successful resuscitation from cardiac arrest is critical, as the occurrence of ventricular arrhythmias is common, with a reported incidence of VF as high as 79% and with an average frequency of two episodes per patient [13]. Some studies have reported an inverse relationship between the number of VF episodes

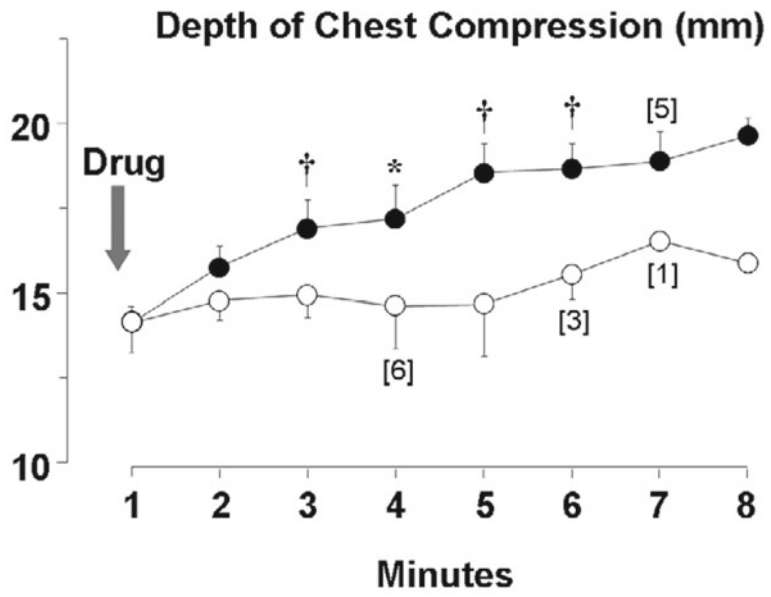

Fig. 15.4 Depth of chest compression (maximum 20 mm) required to maintain aortic diastolic pressure between 36 and 38 mmHg during closed-chest resuscitation. Depth was recorded using a displacement transducer in rats randomised to cariporide (*open symbol*, n = 7) or 0.9% sodium chloride (NaCl) (*closed symbol*, n = 7). *p < 0.05, † p < 0.01 vs. 0.9% NaCl by one-way analysis of variance. Numbers in brackets indicate rats remaining in ventricular fibrillation. (Adapted from [33])

and survival [13]. These episodes were noted to occur within a time window of 23–115 s, with a median of 45 s after the return of spontaneous circulation [13]. These postresuscitation ventricular arrhythmias, including episodes of VF, are to a large extent a manifestation of cytosolic Ca^{2+} accumulation in cardiomyocytes [25, 45, 46].

Along with reperfusion arrhythmias, the myocardium during the postresuscitation period suffers varying degrees of global dysfunction that can compromise haemodynamic function [40, 41]. These electrical and mechanical abnormalities occur early in the postresuscitation phase, coinciding with the prehospital phase, and may account for the nearly 40% of deaths reported before hospital admission in initially resuscitated patients [10]. Thus, treatments that could provide initial electrical and mechanical stability could have potential survival benefits for those who experience out-of-hospital cardiac arrest.

In this study we examined the effects of NHE-1 inhibition using cariporide on postresuscitation ventricular arrhythmias and myocardial dysfunction in a pig model of VF and closed-chest resuscitation. Two groups of ten pigs each were subjected to 6 min of untreated VF and randomised to receive a bolus of either 3 mg/kg cariporide or 0.9% sodium chloride (NaCl) before attempting 8 min of closed-chest resuscitation. No differences in haemodynamic variables were observed between groups at baseline. From the second to the eighth min of closed-chest resuscitation, the averaged coronary perfusion pressure was 16

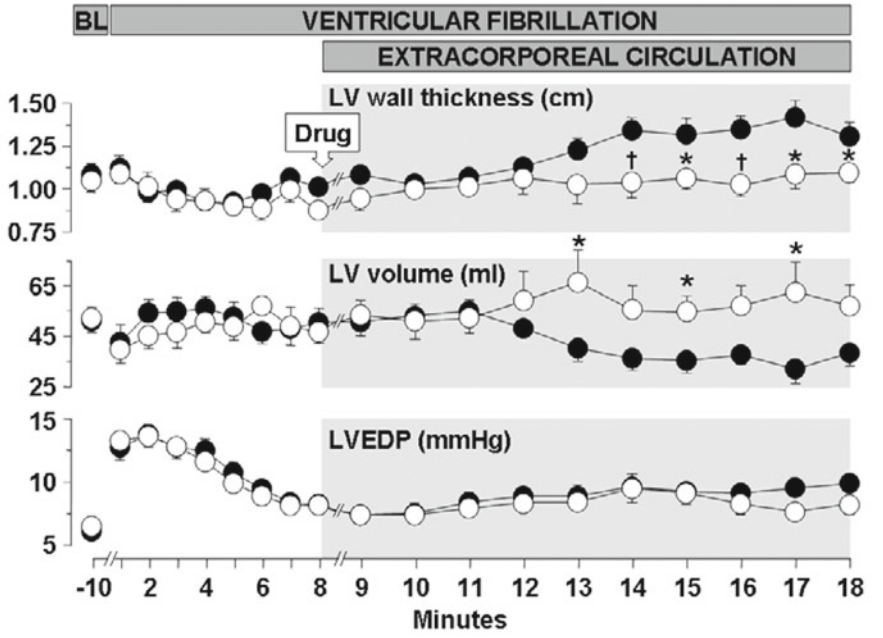

Fig. 15.5 Left ventricular (*LV*) wall thickness, volume, and end-diastolic pressure (*LVEDP*) in pigs randomised to receive either zoniporide (*open symbols*, n = 8) or sodium chloride (NaCl) (*closed symbols*, n = 8) immediately before extracorporeal circulation. Baseline (*BL*) measurements were obtained during diastole. Mean ± standard error of mean (SEM). *p < 0.05, †p < 0.01 vs NaCl. (Adapted from [34])

± 4 mmHg in pigs treated with cariporide and 15 ± 3 mmHg in control pigs. During the same interval, the partial pressure of end-tidal carbon dioxide ($P_{ET}CO_2$) was higher in the cariporide group (30 ± 6 vs 27 ± 6 mmHg), but the difference was not statistically significant.

Seven of ten pigs in each group were successfully resuscitated using biphasic defibrillation (Fig. 15.7). Failure to resuscitate was associated in the cariporide group, with pulseless electrical activity in two pigs and with refractory VF in one pig; and in the control group, with pulseless electrical activity in one pig and with refractory VF in two pigs. More electrical shocks (4.6 ± 1.5 vs 2.9 ± 1.6, p = 0.06) and higher cumulative energy (407 ± 224 vs 207 ± 184 J, p < 0.05) was required to terminate VF in successfully resuscitated pigs treated with cariporide. The energy level of the shock that terminated VF was numerically higher in pigs that received cariporide (129 ± 39 vs 86 ± 38 J, p = 0.06). During the initial 5 min after return of spontaneous circulation, intense ventricular ectopic activity was observed in control pigs, contrasting with electrical stability in cariporide-treated pigs (Table 15.1). Postresuscitation episodes of VF occurred only in control pigs (4/7 vs 0/7, p = 0.07), which required the delivery of additional electrical shocks (5.3 ± 7.8 vs 0.0 ± 0.0, p = 0.073) and therefore additional cumulative energy (529 ± 778 vs 0.0 ± 0.0 J, p = 0.073) to reestablish spontaneous circulation.

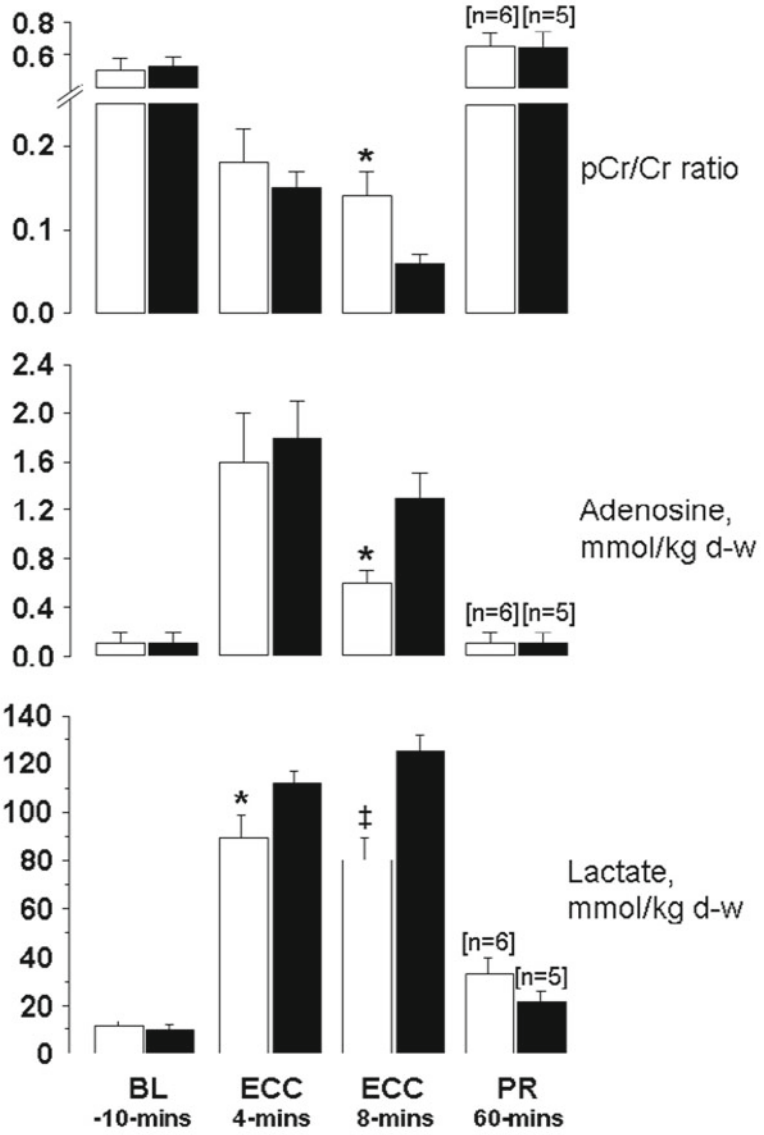

Fig. 15.6 Creatine phosphate/creatine (*pCr/Cr*) ratios, adenosine levels, and lactate levels in left-ventricular tissue measured in pigs randomised to receive either zoniporide (*open bars* n = 8) or sodium chloride (NaCl) (*closed bars* n = 8) immediately before extracorporeal circulation (*ECC*). Numbers in brackets indicate when sample size decreased from the initial 8 or from the preceding sample size. Mean ± standard error of mean (SEM). *d-w*, dry weight; *BL,* baseline; *ECC* extracorporeal circulation; *PR,* postresuscitation. *p < 0.05, ‡p < 0.001 vs NaCl. (Adapted from [34])

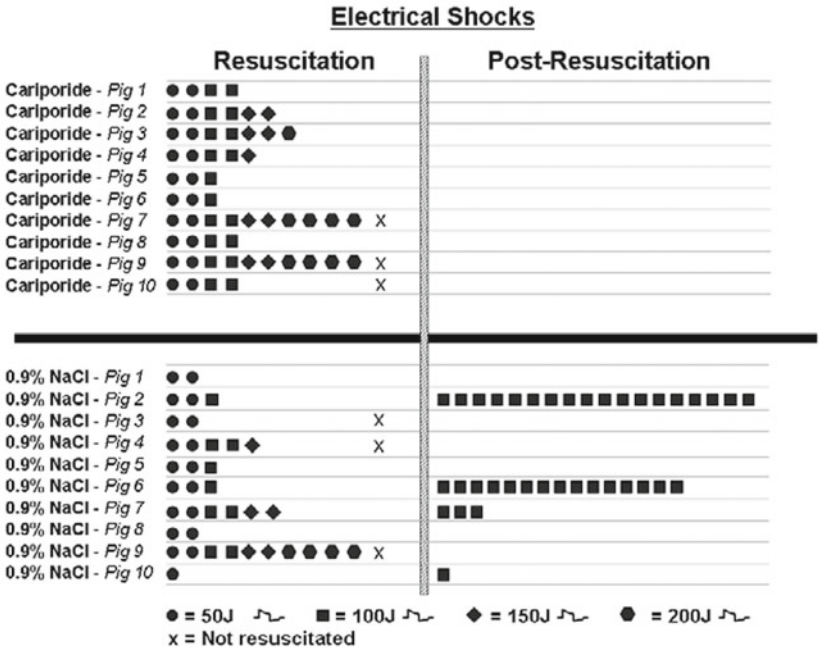

Fig. 15.7 Electrical shocks required to initially terminate ventricular fibrillation (VF) (resuscitation) and subsequently reverse episodes of refibrillation (postresuscitation). Pigs marked by X during resuscitation failed to regain spontaneous circulation. (Adapted from [35])

Table 15.1 Ventricular ectopic activity during the initial 5-min postresuscitation period

	Number of Singlets mean ± SD	Number of Bigemini mean ± SD	Number of Salvos mean ± SD	Episodes of VT mean ± SD	Episodes of VF mean ± SD
Cariporide (n = 7)	5 ± 5†	1 ± 3*	4 ± 8	0 ± 0	0 ± 0
0.9% NaCl (n = 7)	26 ± 21	33 ± 25	17± 24	1 ± 1	4 ± 6

VT, ventricular tachycardia; *VF,* ventricular fibrillation; *SD,* standard deviation; *NaCl,* sodium chloride. *p < 0.05 vs 09% sodium chloride using one-way analysis of variance

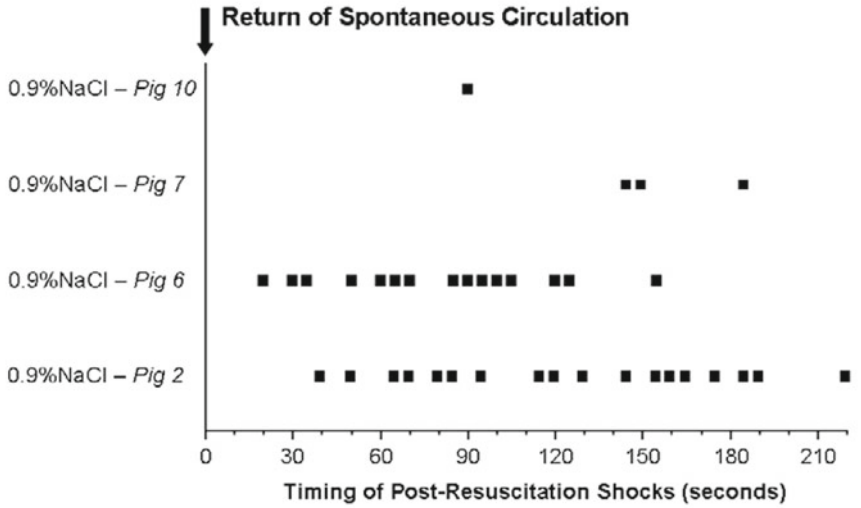

Fig. 15.8 Timing of each electrical shock (s) delivered after return of spontaneous circulation to 0.9% sodium-chloride (NaCl)-treated pigs during refibrillation. (Adapted from [35])

Time course and severity of ventricular arrhythmias in our pig model was remarkably similar to that reported in individuals with out-of-hospital cardiac arrest. VF spontaneously occurred after return of spontaneous circulation in four of seven control pigs (57%) within a time window of 20–220 (median 103) s and with an average of approximately five episodes per pig (Fig. 15.8). Mechanistically, reflected abnormalities were linked to ischaemic myocardium reperfusion, in which Na^+-induced cytosolic Ca^{2+} overload plays a prominent role. Electrophysiologically, repolarisation abnormalities occur, including shortening of the action-potential duration [47]. In a previous study [37], this effect was evident immediately upon return of spontaneous circulation, with gradual resolution within approximately 15 min. This time window coincides with restoration of electrical stability. In this study, cariporide suppressed VF episodes during the postresuscitation interval and attenuated ventricular ectopic activity (Table 15.1). We [48] and others [49] previously reported that cariporide – for reasons not well understood – attenuates shortening of the action potential duration upon reperfusion. Thus, the beneficial effects of cariporide on ventricular ectopic activity coincide in time with its effect on action-potential duration.

Postresuscitation, pigs experienced reversible haemodynamic and myocardial dysfunction that lasted approximately 120 min but was less prominent in cariporide-treated pigs (Fig. 15.9). Averaged over the initial 60-min postresuscitation observation interval, cariporide-treated pigs had higher cardiac index (6.1 ± 0.7 vs 4.4 ± 1.1, L/min/m^2, $p < 0.01$), LV stroke-work index (45 ± 9 vs 36 ± 10 gm-m/beat/m^2, $p < 0.05$) and numerically higher mean aortic pressure (104 ± 11 vs 91 ± 12 mmHg, $p = 0.054$). All resuscitated pigs survived 120 min. Pigs that received cariporide during chest compression had less myocardial dysfunction during the early postresuscitation interval which is consistent with previous reports by our group in a rat model of VF and closed-chest resuscitation [32, 50], in a pig

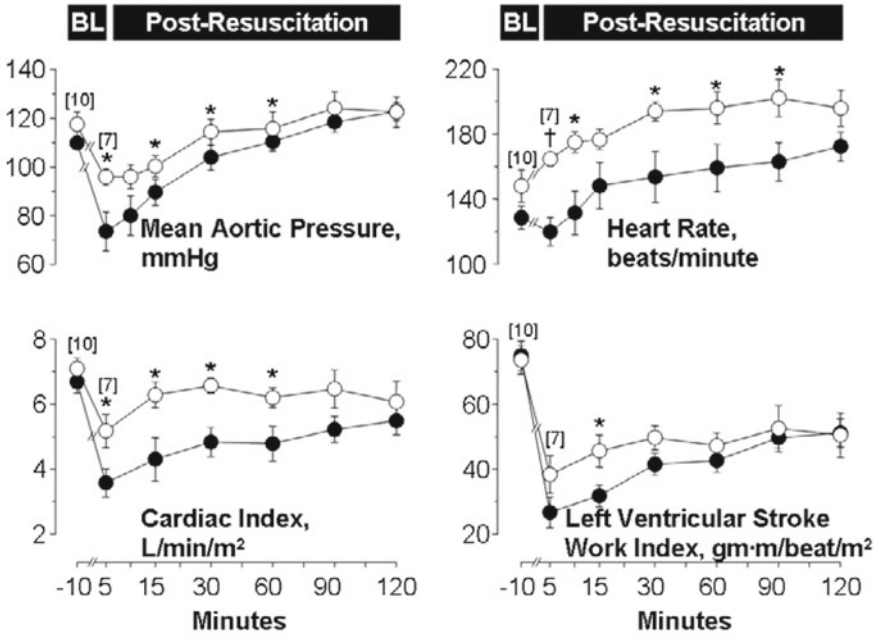

Fig. 15.9 Baseline (*BL*) and postresuscitation left ventricular and haemodynamic function in pigs randomised to receive cariporide (*open symbols*) or 0.9% sodium chloride (NaCl) (*closed symbols*). Numbers in brackets indicate sample size. Values are mean ± standard error of mean (SEM). *p < 0.05, †p < 0.001 vs 0.9% NaCl analysed by one-way analysis of variance. (Adapted from [35])

model of VF in which epinephrine was used during chest compression [51], and in an open-chest pig model of VF and resuscitation using extracorporeal circulation [34]. Resuscitation from cardiac arrest is commonly associated with varying severity of reversible LV systolic and diastolic dysfunction [10, 52]. Preventing or reversing postresuscitation myocardial abnormalities is challenging because the underlying pathogenic mechanisms are poorly understood. As previously described, Na^+-induced Ca^{2+} overload is an important mechanisms of injury that contributes to postresuscitation myocardial dysfunction [37]. Accordingly, limiting Na^+-induced Ca^{2+} overload using cariporide could provide more competent myocardial function during the early postresuscitation interval.

15.2.1 Clinical Implications of NHE-1 Inhibition Treatment during Cardiac Arrest

There is strong experimental evidence supporting the use of NHE-1 inhibitors to limit myocardial injury and improve resuscitability in people who experience sudden cardiac arrest. Promoting return of cardiac activity with electrical and mechanical stability early after resuscitation following out-of hospital cardiac arrest could potentially impact survival

by reducing the nearly 40% early deaths reported to occur between return of spontaneous circulation and hospital admission. Thus, cariporide or equivalent pharmacological interventions could promote haemodynamic stability for safer transport of these cardiac arrest patients to a receiving hospital.

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Erythropoietin Facilitates Return of Spontaneous Circulation and Survival in Victims of Out-of-Hospital Cardiac Arrest

16

Š. Grmec, M. Strnad and R.J. Gazmuri

16.1 Introduction

Erythropoietin (EPO) is a 30.4-kDa glycoprotein best known for its action on erythroid progenitor cells and regulation of circulating red cell mass. However, several studies have shown that EPO also activates potent cell-survival mechanisms during ischaemia and reperfusion through genomic and nongenomic signalling pathways in a broad array of organs and tissues, including the heart [1–6] and brain [7–9].

Activation of these protective mechanisms involves binding of EPO to a specific cell membrane receptor, a member of the type I superfamily of single-transmembrane cytokine receptors, prompting cross-phosphorylation and activation of Janus tyrosine kinases (JAK) 1 and 2 (Fig. 16.1). Activation of JAK causes phosphorylation of tyrosine residues, creating docking sites for recruitment and activation of multiple signalling proteins that have Src-homology-2 (SH2) domains, resulting in well-established antiapoptotic [10], anti-inflammatory [10, 11] and proliferative effects (i.e. neovascularisation) [12, 13], with time courses that vary contingent upon the specific signalling mechanism and the duration of EPO binding to the EPO receptor (EPO-R).

Although important in other settings, these effects are not likely to play a role in initial cardiac resuscitation. Singh et al. [14] hypothesised that important for resuscitation is EPO signalling through pathways that result in mitochondrial bioenergetic function preservation, leading to functional effects similar to those elicited by sodium hydrogen exchanger (NHE)-1 inhibition (albeit through quite distinct cell mechanisms). These mechanisms, the authors hypothesised, involve activation of protein kinase C epsilon (PKCε) and protein kinase B (Akt), as shown in Figure 16.1 and succinctly described below.

PKCε activation is a well-established mechanism of myocardial protection believed to be responsible for preconditioning and acute protection [15, 16]. PKCε is primarily located in the cytosol. Its phosphorylation by EPO prompts translocation to the mitochondria where it could: (1) open putative mitochondrial adenosine triphosphate (ATP)-sensitive potassium (KATP) channels; (2) activate cytochrome c oxidase (complex IV of the respiratory electron transport chain) [17]; (3) activate aldehyde dehydrogenase (ALDH2) [18];

APICE 23. Antonino Gullo (Ed.)

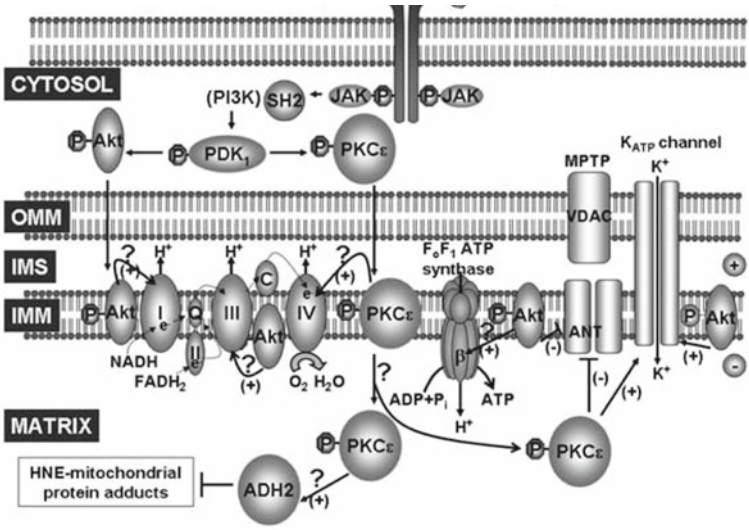

Fig. 16.1 Intracellular signalling pathways modulated by erythropoietin and hypothesised to enable preservation of mitochondrial bioenergetic function during cardiac resuscitation. (+), activation; (–), inhibition; *?,* hypothesised effects; *Akt*, protein kinase B; *ADH2,* aldehyde dehydrogenase 2; *ADP,* adenosine diphosphate; *ATP,* adenosine triphosphate; *C,* cytochrome c; *e-,* electron; *FADH2,* flavin adenine dinucleotide (reduced); H^+, proton; *HNE*, 4-hydroxynonenal; *IMM,* inner mitochondrial membrane; *IMS*, intermembrane space; *JAK,* janus-activated kinase; K^+, potassium; *MPTP,* mitochondrial permeability transition pore; *NADH,* nicotinamide adenine dinucleotide (reduced); *OMM,* outer mitochondrial membrane; *PDK1,* phosphoinositide dependent kinase-1; *Pi*, inorganic phosphate; *PI3K,* phosphatidyl inositide kinase; *PKCε,* protein kinase c epsilon; *Q,* coenzyme Q; *SH-2*, src-homology domain-2; *I, II, III, IV,* respiratory chain complexes

and (4) inhibit the mitochondrial permeability transition pore [19]. Opening of KATP channels increases mitochondrial K+ conductivity. This is an energetically advantageous [20, 21] effect likely to limit mitochondrial calcium (Ca2+) overload [22, 23], exerting effects similar to those of NHE-1 inhibition. Activation of cytochrome c oxidase could improve the efficiency of electron flow from cytochrome c to molecular oxygen, enhancing the capability for ATP synthesis. Activation of ALDH2 could reduce the formation of toxic 4-hydroxynonenal (HNE)-Michael adducts and serve to preserve mitochondrial respiration.

Akt activation is a powerful survival signal that shown to mediate myocardial protection during late preconditioning and after reperfusion [23]. EPO mediates Akt phosphorylation through phosphorylation of phosphoinositide-dependent kinase-1 (PDK1) upon activation of phosphatidylinositide kinase (PI3K). Activated Akt can translocate to mitochondria, where it exerts beneficial effects, including: (1) opening of mitochondrial KATP channels with the anticipated effects described above; (2) activating respiratory-chain complexes and FoF1 ATPase; and (3) inhibiting the mitochondrial permeability transition pore.

16.2 Effects on Resuscitation

16.2.1 Studies in Rats

The effects of EPO were studied in a rat model of ventricular fibrillation (VF) and closed-chest resuscitation using human recombinant EPO (epoetin alpha, Amgen, Thousand Oaks, CA, USA) [14]. Rats were subjected to 10 min of untreated VF followed by 8 min of closed-chest resuscitation before attempting defibrillation. The depth of compression was adjusted to maintain an aortic diastolic pressure between 26 and 28 mmHg. This level secured a coronary perfusion pressure above the resuscitability threshold of 20 mmHg. The relationship between coronary perfusion pressure and compression depth (CPP/Depth) was used to assess changes in left ventricular (LV) myocardial distensibility. Successfully resuscitated rats were observed for 120 min before euthanasia.

Three groups of ten rats each were randomised to receive a right atrial bolus of epoetin alpha (5,000 IU/kg) at baseline 15 min before VF induction (EPOBL -15-min), at 10 min of VF before starting chest compression (EPOVF 10-min) or to receive 0.9% sodium chloride (NaCl) solution (control), with the investigators blinded to treatment assignment. EPO given coincident with the beginning of chest compression after 10 min of untreated VF – but not before inducing VF – promoted haemodynamically more effective chest compression such that the CPP/Depth ratio averaged during the interval of chest compression was 2.0 ± 0.3 mmHg/mm in EPOVF 10-min, 1.6 ± 0.2 mmHg/mm in EPOBL -15-min and 1.6 ± 0.3 mmHg/mm in the control group ($p < 0.05$ EPOVF 10-min vs EPOBL -15-min and vs control). This difference represented a 25% improvement in the haemodynamic efficacy of chest compression with EPO given at the beginning of chest compression.

The possibility that this effect resulted from a vasopressor action of EPO seemed unlikely; baseline haemodynamic measurements in rats that received EPO 15 min before VF induction (EPOBL -15-min) demonstrated a statistically borderline decrease (not increase) in systemic vascular resistance, from 1.092 ± 0.147 to 1.010 ± 0.133 mm Hg/ml/min/kg ($p = 0.077$ by paired t test).

Defibrillation restored spontaneous circulation in eight EPOBL -15-min, eight EPOVF 10-min and nine controls. Postresuscitation, EPOVF 10-min rats had significantly higher mean aortic pressure associated with numerically higher cardiac index and higher peripheral vascular resistance. The diminished effectiveness of EPO when given before VF is intriguing and worth additional investigation.

16.2.2 Clinical Study

16.2.2.1 Patients and Methods

A clinical study was performed in the Maribor Emergency Medical Services (EMS) system in the city of Maribor, Slovenia, and adjacent rural areas, encompassing a population of approximately 200,000 [24].

Resuscitation was attempted using regionally developed protocols that incorporate the International Liaison Committee on Resuscitation (ILCOR) 2005 recommendations by a two-tier system composed of basic (BLS) and advanced (ALS) life-support teams, with the latter led by a physician. Upon arrival of the ALS team, the trachea was intubated – verifying proper placement by capnography – and positive-pressure ventilation started with a tidal volume of approximately 6 ml/kg at ten breaths per minute unsynchronised to compressions. The ALS team also established a peripheral vascular access (within approximately 30 s). Patients assigned to EPO received 90,000 IU of beta-epoetin (NeoRecormon, Hoffman La Roche) as a bolus within 1 or 2 min after chest compression began, followed by a 10-ml bolus of 0.9% NaCl. Beta-epoetin was kept refrigerated (2–8°C) in the ambulance until immediately before use. In every instance, EPO was given before any other drug.

Patients who had return of spontaneous circulation (ROSC) were started on 0.9% NaCl solution cooled at 4°C (30 ml/kg infused at 100 ml/min) and given 0.08–0.10 mg/kg of vecuronium bromide (Norcuron®, Organon) to initiate hypothermia while en route to the hospital. For haemodynamic stability, patients received dopamine (5–10 mcg/kg/min) for systolic blood pressure <90 mmHg, dobutamine (2.5–20.0 mcg/kg/min) for suspected cardiogenic shock or norepinephrine (8–12 mcg/kg/min) if systolic blood pressure remained <70 mmHg despite the preceding measures.

Upon arrival at the hospital, patients were directly admitted to the intensive care unit (ICU) and cooled to a core temperature between 32° and 34°C by external means until they regained consciousness or had completed 24 h. Patients with ST-segment-elevation myocardial infarction had percutaneous coronary interventions. Inotropic and vasopressor agents were infused, guided by haemodynamic monitoring using a pulmonary artery catheter and transthoracic echocardiography.

The study was originally designed as prospective and randomised. However, disruption in the supply of EPO prompted investigators to administer EPO or 0.9% NaCl control based on availability, allocating 24 patients to EPO and 30 to 0.9% NaCl between April 2007 and May 2008. The control group was designated as concurrent controls. Post hoc, a second control group was included consisting of 48 of 126 patients who had out-of-hospital cardiac arrest treated with the same resuscitation protocol the year before. These 48 patients were selected using propensity scores, assigning two controls for each EPO-treated patient. Propensity scores were calculated using multiple logistic regression. Entering age, male sex, witnessed arrest, time from call to start of cardiopulmonary resuscitation (CPR), pulseless electrical activity, asystole, and bystander CPR as pretreatment were predictors of outcome. The control group was designated as matched controls. The same variables

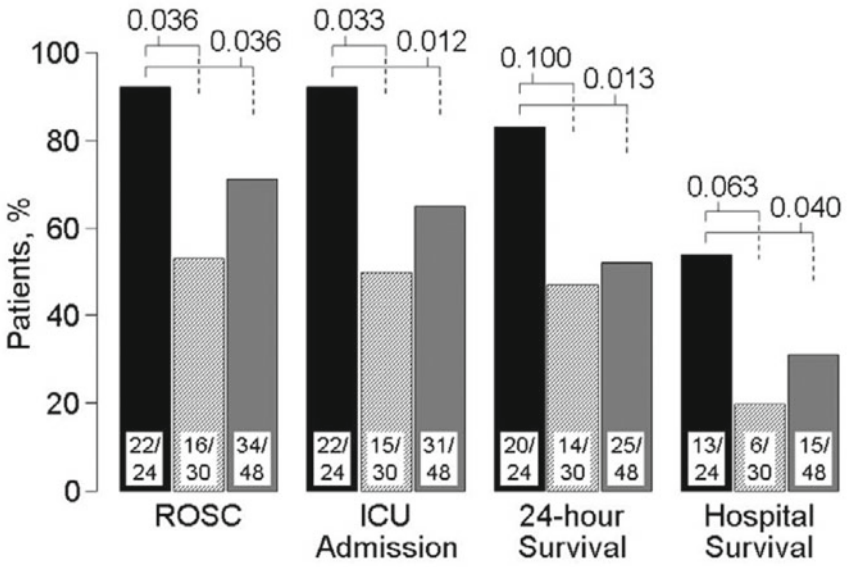

Fig. 16.2 Resuscitation and survival outcomes in patients who received erythropoietin (*black bars*, n = 24) compared with concurrent controls (*hatched bars*, n = 30) and with matched controls (*gray bars*, n = 48). P values were calculated using Wald statistics and adjusted by pretreatment covariates, which could influence outcomes [i.e. age, male sex, witnessed arrest, time from call to start cardiopulmonary resuscitation (CPR), pulseless electrical activity, asystole, and bystander CPR]. *ROSC*, return of spontaneous circulation; *ICU*, intensive care unit. Numbers inside bars denote patients for each outcome, with the bar representing the percentage of the initial cohort (from [24])

used to calculate propensity scores were used to adjust odds ratios (ORs) for comparison between EPO and concurrent controls and between EPO and matched controls.

16.2.3 Results

By univariate analysis, administration of EPO when compared with concurrent controls was associated with higher rates of ICU admission, ROSC, 24-h survival and survival to hospital discharge and when compared with matched controls was associated with higher rates of ICU admission, ROSC, and 24-h survival. After adjustment by pretreatment covariates (listed above), comparison with concurrent controls reduced the OR but retained statistical significance for ICU admission and ROSC, whereas comparison with matched controls increased the OR, demonstrating statistical significance for all four outcomes (Fig. 16.2).

To assess whether the beneficial effects on resuscitation outcomes could have been linked to beneficial effects on LV myocardial distensibility, as suggested by our preceding study in rats [14],we examine the effects on partial pressure of end-tidal carbon dioxide

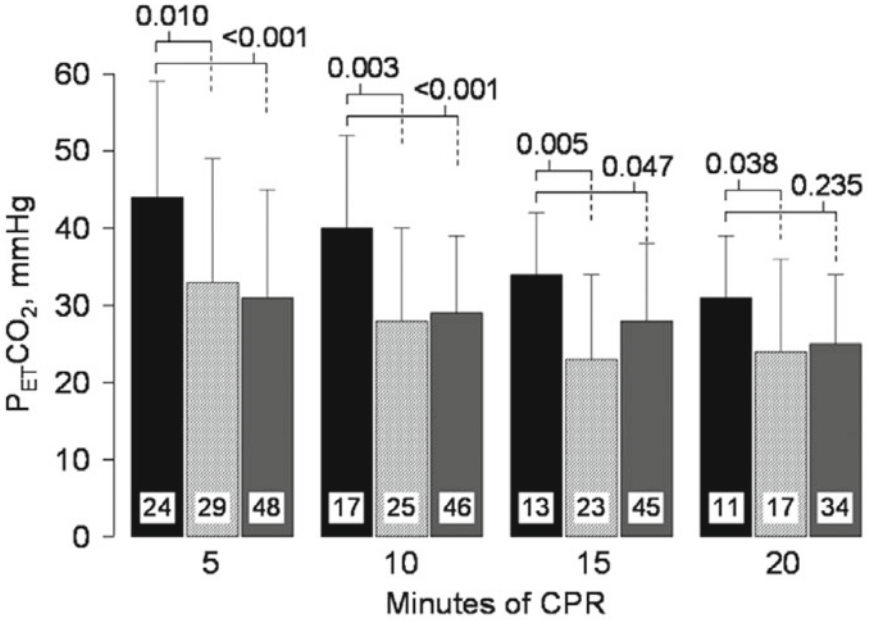

Fig. 16.3 Partial pressure of end-tidal carbon dioxide ($P_{ET}CO_2$) during cardiopulmonary resuscitation in patients who received erythropoietin (*black bars*, n = 24) compared with concurrent controls (*hatched bars*, n = 30) and with matched controls (*gray bars*, n = 48). Numbers inside bars denote patients remaining in cardiac arrest and receiving cardiopulmonary resuscitation. Data are presented as mean values with one standard deviation. P values were calculated by unpaired t test or by Mann–Whitney rank sum test for each time period and shown above bars (from [24])

($P_{ET}CO_2$), which is a good surrogate measurement of forward blood flow during chest compression [25–27]. In the study, rescuers were trained and retrained to provide consistent depth and rate of compression, and $P_{ET}CO_2$ values in both control groups were already indicative of high-quality chest compression (Fig. 16.3). If, as hypothesised, EPO preserved myocardial distensibility, for a given compression depth, one would expect higher forward blood flow in the presence of EPO and therefore higher $P_{ET}CO_2$. This was indeed the case. Patients who received EPO had significantly higher $P_{ET}CO_2$ during chest compression (Fig. 16.3).

Because a single dose was administered, substantial effects on erythropoiesis were not anticipated. In fact, haemoglobin and haematocrit in the present study were not statistically different than controls at 48 h and at 72 h.

Accordingly, these clinical observations, though based on a small sample size, are consistent with the hypothesis that by preserving myocardial distensibility, EPO leads to haemodynamically more effective chest compression, resulting in higher resuscitation and survival rates.

16.3 Erythropoietin in Cardiocerebral Resuscitation: Potentially Neuroprotective Role of Erythropoietin?

Cerebral ischaemia is inevitable during cardiac arrest and to some extent during the postresuscitation period. Hypoxia-inducible-factor (HIF) isoforms from astrocytes stimulates EPO expression in these cells, accumulates early in the phase of recovery from cardiac arrest and persists for several days [28–30]. The majority of brain cells are capable of producing EPO and its receptor, and after hypoxic insult, there is an up-regulation of EPO expression in the brain. EPO in turn protects neuronal tissue from oxygen deprivation and other noxious stimuli, promotes neuroangiogenesis, inhibits hypoxia-induced apoptosis in neurons and thus supports neuron survival in the ischaemic brain [31–35]. Evidence shows that the brain remains hypoxic during the first few hours of recovery from cardiac arrest, but no more than 2 days [33]. The protective role of exogenous EPO was noticed in focal as well as global brain ischaemia [36, 37].

In summary, upregulation of EPO in the hypoxic–ischaemic human brain, the ability of exogenous EPO to cross the blood–brain barrier after peripheral application, its neuroprotective role in animal and human studies, pleiotropism and clinical tolerance give a strong rationale for further research into the impact of EPO on neurological recovery after successful CPR in humans.

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Part VIII
Infections, Sepsis and Organ Dysfunctions

Pathophysiology of Resistance amongst Aerobic Gram-negative Bacilli in Particular Acinetobacter Species

17

N. Taylor, L. Silvestri and H.K.F. van Saene

17.1 Introduction

Selective decontamination of the digestive tract (SDD) is an antimicrobial prophylaxis consisting of parenteral cefotaxime and enteral and topical polymyxin E/tobramycin/amphotericin B (PTA). SDD prevents severe endogenous and exogenous infections of lower airways and blood and reduces mortality in the critically ill requiring treatment in the intensive care unit (ICU) [1].

17.2 Philosophy: Carriage

SDD is based on the observation that critical illness changes body flora by two methods: qualitatively and quantitatively. When a patient is critically ill, carriage of normal flora is eroded and then replaced by abnormal flora, and the density of growth shifts from low to high grade (gut overgrowth). Normal flora consists of six potential pathogens: Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis (found in the oropharynx only); Escherichia coli (found in the gut) and Staphylococcus aureus and Candida albicans (found in both the oropharynx and gut). Abnormal flora consists of nine abnormal potential pathogens, eight aerobic Gram-negative bacilli (AGNB) and methicillin-resistant Staphylococcus aureus (MRSA) (found in both the oropharynx and gut). The eight AGNB are Klebsiella, Enterobacter, Citrobacter, Proteus, Morganella, Serratia, Acinetobacter, and Pseudomonas spp.

17.2.1 Low- and High-grade Carriage

Low-grade to high-grade carriage is the quantitative change brought about by critical illness. Low-grade carriage is defined as <105 potential pathogens/millilitre of saliva or

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Table 17.1 Carriage classification of severe infections of lower airways and blood

Infection	PPM	Timing	Frequency	Manoeuvre
1. Prim endog	6 normal[a], 9 abnormal[b]	<1 week	55%	Parenteral antimicrobials
2. Sec endog	9 abnormal[b]	>1 week	30%	Hygiene and enteral antimicrobials
3. Exogenous	9 abnormal[b]	Anytime during ICU treatment	15%	Hygiene and topical antimicrobials

PPM, potentially pathogenic microorganism; *Prim endog*, primary endogenous; *Sec endog*, secondary endogenous

[a]Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis, Candida albicans, Staphylococcus aureus, Escherichia coli

[b]Klebsiella, Enterobacter, Citrobacter, Proteus, Morganella, Serratia, Acinetobacter, Pseudomonas spp and methicillin-resistant Staphylococcus aureus

grams of faeces, whereas high-grade carriage is defined as ≥105 potential pathogens/millilitre of saliva or grams of faeces. High-grade carriage is synonymous with gut overgrowth and is the crucial event that precedes endogenous infection.

17.2.2 Types of Infections

Infection, when classified according to the carrier state, has three classifications: (1) primary endogenous; (2) secondary endogenous; (3) exogenous. All require a different prophylactic manoeuvre (Table 17.1). Primary endogenous infection occurs when the causative microorganism is present in the admission flora; it generally occurs within 1 week of admission. The frequency is 55% and parenteral antimicrobials are the manoeuvre to treat/prevent this type of infection [2]. Secondary endogenous infection occurs when the causative microorganism is not present in the admission flora but the patient acquires the abnormal flora during treatment in the ICU and subsequently develops the carrier state in overgrowth concentrations preceding the infection. Secondary endogenous infection occurs after a week of ICU treatment; frequency is 30%. The manoeuvre to impact this type of infection is enteral antimicrobials and good hygiene [3]. Exogenous infection may occur at anytime during ICU treatment and develops when the abnormal flora is introduced directly into the patient, bypassing the carrier state. Approximately 15% of all ICU infections are exogenous. The manoeuvre designed to combat this infection is hygiene and topical antimicrobials [4].

Handwashing is widely accepted as the cornerstone of infection control [5]. The main mechanism for transmission of potential pathogens including Acinetobacter baumannii is spread via the hands of healthcare workers. Adequate hand hygiene is therefore thought to

be crucial in preventing transmission of A. baumannii [6]. There is low-level evidence for the efforts to control infection with handwashing [5]. Poor compliance cannot be blamed as the only reason for the failure of handwashing to control infection. Handwashing by healthcare workers on its own does not abolish, but only reduces, transmission, as it is dependent on the bacterial load on the hands. Recent studies using surveillance cultures of throat and rectum have shown that, under ideal circumstances, handwashing can only influence secondary endogenous and exogenous infections (approximately 45% of all infections). In many hospitals, alcohol-based hand rubs, consisting of varying concentrations of ethyl or isopropyl alcohol, often in combination with chlorhexidine and organic emollients, have found wide-spread acceptance as an alternative to handwashing. Recent work has shown that A. baumannii is able to readily metabolise low concentrations of ethyl alcohols and, furthermore, this leads to both enhanced growth and pathogenicity via secretion of a protein identified as outer membrane protein A (OmpA) [7].

17.3 Mechanisms of Action Explaining Efficacy: Control of High-Grade Carriage or Overgrowth

Two points require understanding to appreciate the reason for SDD efficacy:

1. acknowledgement of carriage classification. In order to accept SDD, it must be understood that carriage occurs. Primary carriage occurs when the patient is admitted with flora in the digestive tract and secondary carriage when the patient acquires flora in the digestive tract whilst being treated in the ICU;
2. antimicrobials selected for SDD were chosen for specific reasons and invariably clear high-grade carriage (Table 17.2):
   - parenteral cefotaxime clears carriage of "normal" bacteria;
   - enteral polyenes clear "normal" fungal carriage;
   - enteral polymyxin/tobramycin with or without vancomycin clears carriage of "abnormal" bacteria AGNB and MRSA.

SDD antimicrobials are required in high concentrations against prevailing microorganisms (Table 17.3). These concentrations are deemed more important than sparing colonisation resistance. Colonisation resistance is the mechanism whereby indigenous flora is a barrier against abnormal flora acquired, for example, from food, and then carried in the digestive tract.

Gut overgrowth harms the critically ill in four main ways:

1. infection. There is a quantitative relationship between surveillance and diagnostic samples. As soon as there is overgrowth in surveillance samples, the diagnostic samples become positive, which is the first stage in the development of infection [8];
2. immunosuppression. Overgrowth of abnormal AGNB (and associated endotoxin) has been shown to impair systemic immunity due to generalised inflammation following absorption of AGNB and/or endotoxin [9];
3. inflammation. Overgrowth of abnormal AGNB and/or endotoxin has been shown to lead to cytokinaemia and inflammation of major organ systems [10];
4. resistance. The abnormal carrier state in overgrowth concentrations guarantees increased spontaneous mutation, leading to polyclonality and antibiotic resistance [11].

Table 17.2 The full four components of selective decontamination of the digestive tract

Target PPM and antimicrobials	Total daily dose (4 times daily)		
	< 5years	5–12 years	>12 years
1. Parenteral antimicrobials: normal PPM Cefotaxime (mg)	150/Kg	200/kg	4,000/kg
2. Hygiene with enteral antimicrobials: Abnormal PPM			
A. Oropharynx:			
1. AGNB: polymyxin E with tobramycin	2 g of 2% paste or gel		
2. MRSA: vancomycin	2 g of 4% paste or gel		
Yeasts: amphotericin B or nystatin	2 g of 2% paste or gel		
A. Gut			
1. AGNB: polymyxin E (mg)	100	200	400
with tobramycin (mg)	80	160	320
2. MRSA: vancomycin (mg)	20–40/kg	20–40/kg	500–2,000
Yeasts: amphotericin B (mg)	500	1,000	2,000
or nystatin units	2×10^6	4×10^6	8×10^6
1. Hygiene with topical antimicrobials: abnormal PPM	2% PTA paste/4% vancomycin paste		
2. Surveillance swabs of throat and rectum on admission, Monday, Thursday			

PPM, potentially pathogenic microorganisms; *AGNB*, aerobic Gram-negative bacilli; *MRSA*, methicillin-resistant Staphylococcus aureus

Table 17.3 Effective concentrations against prevailing microorganisms are more important than sparing the colonisation resistance flora

Antimicrobials selected for SDD	Concentrations (mg/L) in		
	Saliva	Bile	Faeces
Cefotaxime	6	20	
Polymyxin E			16–1,000
Tobramycin			100
Amphotericin B			60
or Nystatin			<100
Vancomycin			3,000–24,000

SDD, selective decontamination of the digestive tract

SDD is a prophylactic measure using selected antimicrobials to control gut overgrowth, thereby reducing the four harmful side effects of the latter, i.e., infection, immunosuppression, inflammation and resistance.

17.3.1 Efficacy

SDD has been assessed in 11 meta-analyses [12–22] covering 60 randomised controlled trials (RCTs) (Table 17.4). Of the 11 meta-analyses, lower airway infection was the endpoint in six. All meta-analyses invariably demonstrated a significant reduction in lower airway infections [odds ratio (OR) 0.28, 95% confidence interval (CI) 0.20–0.38]. Bloodstream infection was the endpoint in three meta-analyses and was significantly reduced (OR 0.63, 95% CI 0.46–0.87). When dividing bloodstream infection into categories, AGNB septicaemias were significantly reduced, Gram-positive ones increased but not significantly and fungaemia was reduced but not significantly due to the low incidence in the control group (Table 17.4). Multiple organ dysfunction syndrome was the endpoint in one of the most recent meta-analyses. The relative reduction of 50% was significant. Mortality was the endpoint in eight meta-analyses. SDD consistently reduced mortality as long as the sample size was large enough; the sample size was too small in three meta-analyses.

17.3.2 Safety

SDD safety relies on long-term level of resistance not emerging against the SDD antimicrobials [23]. The concept of exposing vast numbers of critically ill patients to broad-spectrum multiple-drug cocktails runs counter to existing theoretical models (and dogma) related to genesis and promotion of antimicrobial resistance in pathogens acquired in the ICU [24]. The dynamics of resistance are driven by three mechanisms:

1. import. The patient is admitted to the ICU with resistant microorganisms in overgrowth concentrations in the gut [2];
2. acquisition from transmission. Thirty-three percent of patients admitted as normal carriers to a mixed ICU develop abnormal carriage of multi-drug-resistant K. pneumoniae and/or A. baumannii, the two abnormal AGNBs endemic in the ICU at 1-year prospective observational study [3]. A higher "severity of illness" score on admission was a significant risk factor; the simplified acute physiological score (SAPS) was 13 ± 4.6 in carriers versus 11.3 ± 5 in noncarriers ($p = 0.0006$);
3. de novo development. Gut overgrowth defined as ≥ 105 potential pathogens per gram of faeces has been identified as a risk factor for de novo resistance development [11, 25]. The gut of the critically ill patient with microbial overgrowth is the ideal site for de novo development of new clones, following increased spontaneous mutation, termed hypermutation. In hypermutation, microbial populations start mutating vigorously at random, presumably as an adaptive mechanism that may cause a mutant to arise that would enable them to overcome the unfavourable surroundings, resulting in polyclonality. A high proportion of patients who require long-term treatment in the

Table 17.4 Efficacy of selective decontamination of the digestive tract (SDD): 60 random controlled trials (RTCs) and 11 meta-analyses

Author	No. RCTs	Sample Size	Lower airway infection OR (95% CI)	Bloodstream infection OR (95% CI)	Multiple organ dysfunction syndrome OR (95% CI)	Mortality OR (95% CI)
Vandenbroucke-Grauls [12]	6	491	0.12; 0.08–0.19	NR		0.92; 0.45–1.84
D'Amico [13]	33	5,727	0.35; 0.29–0.41	NR		0.80; 0.69–0.93
Safdar [14]	4	259	NR	NR		0.82; 0.22–2.45
Liberati [15]	36	6,922	0.35; 0.29–0.41	NR		0.78. 0.68–0.89
Silvestri [16] yeasts	42	6,075	NR	0.89; 0.16–4.95		NR
Silvestri [17]	51	8,065	NR	0.63; 0.46–0.87		0.74; 0.61–0.91
Silvestri [18] Gram-negative Gram-positive	54	9,473	 0.07; 0.04–0.13 0.52; 0.34–0.78	 0.36; 0.22–0.60 1.03; 0.75–1.41		 NR NR
Silvestri [19]	21	4,902	NR	NR		0.71; 0.61–0.82
Liberati [20]	36	6,914	0.28; 0.20–0.38	NR		0.75; 0.65–0.87
Silvestri [21]	7	1,270	NR	NR	0.50 0.34 to 0.74	0.82 0.51–1.32
Silvestri [22]	12	2,252	0.54; 0.42–0.69	NR		NR

OR, odds ratio; *CI*, confidence interval; *NR*, not reported

ICU receive parenteral antimicrobials, which are invariably excreted via the bile into the gut. Although low and fluctuating, the antibiotic levels will kill sensitive clones but allow mutating ones to become resistant to the antibiotics [26, 27].

Each mechanism is responsible for a third of the antimicrobial resistance in the ICU. The common denominator of all three mechanisms is gut overgrowth.

The main category in which antimicrobial resistance is a problem in the ICU is aerobic Gram-negative bacilli (AGNB):

1. sensitivity to decontaminating agents polymyxin/tobramycin: de Jonge et al. conducted a prospective open-label RCT in which 934 critically ill adult patients were randomly assigned on admission to either a medical/surgical ICU using routine SDD or a similar ICU in the same hospital that did not use SDD [28]. Study participants were patients with expected duration of mechanical ventilation of at least 48 h and/or ICU stay of >3days. Surveillance cultures from the throat and rectum were obtained on ICU admission and at discharge, weekly during treatment in the ICU and for the first week postdischarge. The in-hospital mortality rate was significantly lower for SDD compared with control patients (24% vs 31%; $p = 0.02$). Carriage of AGNB resistant to polymyxin E, tobramycin, ceftazidime, ciprofloxacin and imipenem was significantly reduced in SDD patients compared with controls (16% vs 26%; $p = 0.001$). Similar results were observed by de Smet et al. in their cluster RCT [29]. Monthly point prevalence surveys for carriage of multi-drug-resistant AGNB were obtained. The proportion of rectal swabs with resistant AGNB was lower for SDD compared with standard care;
2. resistant to decontaminating agents polymyxin/tobramycin:
    - there is only one potential pathogen intrinsically resistant to polymyxin/tobramycin, and that is Serratia spp. In case of Serratia endemicity, polymyxin/tobramycin requires replacement by paromomycin [30, 31];
    - extended-spectrum beta-lactamase (ESBL)-producing AGNB are often resistant to tobramycin but always sensitive to polymyxin [30]. In case of ESBL-producing AGNB endemicity, tobramycin needs to be replaced by another aminoglycoside, e.g. neomycin, paromomycin [30–32].

17.3.3 Meta-analysis of Resistance during SDD

Five RCTs of SDD [28, 29, 32–34] evaluating 5,229 patients (2,631 SDD, 2,598 controls) reported data on resistance. There were 74 (2.8%) patients with resistant microorganisms in the SDD group and 124 (4.8%) in controls, indicating a 44% reduction in the odds of resistance by SDD (OR 0.56, 95% CI 0.41–0.76; $p < 0.001$) (Fig. 17.1). Heterogeneity was not shown ($\chi 2 = 2.58888$, $p = 0.63$; $I^2 = 0$).

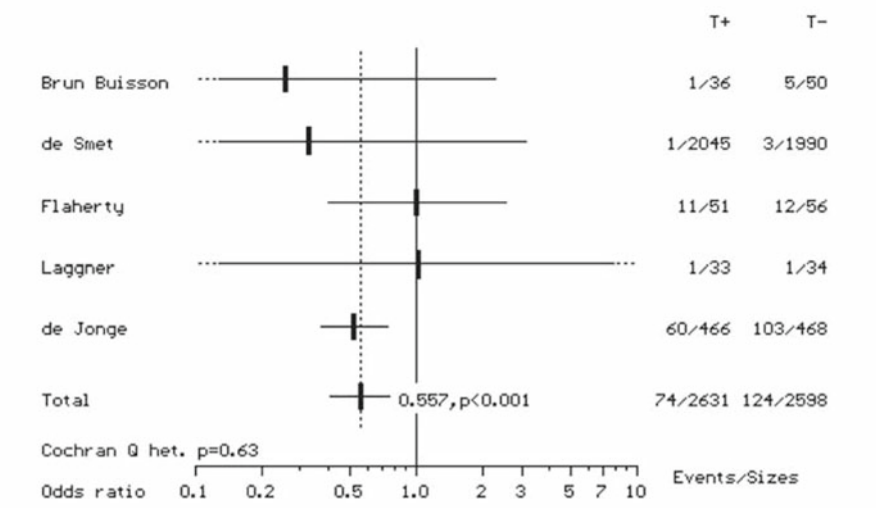

Fig. 17.1 Meta-analysis of five random controlled trials of selective decontamination of the digestive tract (SDD), including resistance data. Odds ratio <1 favours SDD; odds ratio >1 favours controls. Results presented with the fixed-effect model, as heterogeneity was not demonstrated. *T+*, test; *T-*, control

17.3.4 Subgroup Analysis

We explored the impact of SDD on resistance among subgroups with different types of regimens used (Table 17.5). Three studies using the full SDD protocol of parenteral and enteral antimicrobials [28, 29, 33] consisted of 5,076 patients (2,612 SDD, 2,566 controls). Resistance was demonstrated in 76 (2.9%) patients in the SDD group and 118 (4.6%) in the control group, resulting in a significant 44% reduction in the odds of resistance. In contrast, in studies using only enteral antimicrobials [32, 34] comprising 153 patients (69 SDD, 84 controls), the number of patients with resistant microorganisms was two (2.9%) in the SDD group and six (7.14%) in the control group. This reduction was not significant. However, sensitivity analysis showed that after excluding the de Jonge trial [28], the reduction in resistance was not significant (OR 0.75, 95% CI 0.35–1.61; p = 0.46; heterogeneity not significant).

17.4 Conclusions

Gut overgrowth has been recognised as the main risk factor in the pathophysiology of antimicrobial resistance amongst AGNB, including A. baumannii. Handwashing cannot possibly impact gut overgrowth, and this observation may be the fourth reason for the failure of handwashing in controlling infection due to resistant microorganisms [2]. Enteral

Table 17.5 Results of subgroup analysis of the impact of the type of selective decontamination of the digestive tract (SDD) regimen on resistance

Subgroup	No. RCTs	No. patients		No. events		OR (95% CI)	P	P Het	I^2
		SDD	C	SDD	C				
Type of SDD regimen									
Parenteral/enteral	3	2562	2514	72	118	0.56 (0.41-0.78)	<0.001	0.38	0
Enteral only	2	69	84	2	6	0.43 (0.08-2.45)	0.34	0.45	0

ORs were calculated with the fixed effect model as heterogeneity was absent. The use of the random effect model did not change the results

antimicrobials, as an essential part of SDD, prevent and eradicate – if already present – gut overgrowth and contribute to the control of antimicrobial resistance. Additionally, SDD, in eradicating carriage in overgrowth concentrations, reduces the level of hand contamination below which transmission occurs. In this way, handwashing becomes more effective in controlling transmission of potential pathogens such as A. baumannii and subsequent secondary endogenous and exogenous infections.

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What Have We Learned from the Surviving Sepsis Campaign?

18

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18.1 Introduction

The Surviving Sepsis Campaign (SSC) was an initiative of the European Society of Intensive Care Medicine (ESICM), the International Sepsis Forum (ISF) and the Society of Critical Care Medicine (SCCM). It was developed with the aim of improving the diagnosis and treatment of sepsis. Now, 2 years after the three planned phases of the SSC reached a conclusion in December 2008, is a good time to reflect on what the SSC has taught us.

18.2 What was the SSC?

The ultimate aim of the SSC was to decrease global mortality from sepsis by 25% by the year 2009. To achieve this, a three-phase campaign was envisaged sponsored by unrestricted educational grants from three large pharmaceutical companies and supported by several leading international intensive care societies.

The first phase involved a general introduction of the campaign to the wider intensivist community and an attempt to increase awareness of healthcare professionals, governments, funding agencies and the public to the problems associated with sepsis. The second phase was the development of evidence-based guidelines for managing patients with severe sepsis or septic shock. The first guidelines, developed by a group of about 50 international critical-care and infectious-disease experts in the diagnosis and management of infection and sepsis using a modified Delphi methodology, were published in 2004 [1, 2]. The guidelines were revised by 55 experts in intensive care medicine in 2008 [3, 4]. Following criticism of the initial guidelines related to potential influence from the industry, these revised guidelines received no industry support. A new grading system was also implemented:

[1] Disclosure: Dr. Vincent has participated in Eli Lilly and Co. sponsored clinical trials, has served as a paid consultant for Eli Lilly and Co. and has been an invited speaker at conferences supported by Eli Lilly and Co.

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Table 18.1 Sepsis bundles (from http://www.ihi.org/IHI/Topics/CriticalCare/Sepsis). *ED*, emergency department; *ICU*, intensive care unit

Sepsis resuscitation bundle (6-h)
1. Measure serum lactate
2. Obtain blood cultures prior to antibiotic administration
3. Administer broad-spectrum antibiotics within 3 h after presentation for ED admissions and 1 h for non-ED ICU admissions
4. In the event of hypotension and/or lactate > 4 mmol/L (36 mg/dl):
a. Deliver an initial minimum of 20 ml/kg of crystalloid (or colloid equivalent)
b. Apply vasopressors for hypotension not responding to initial fluid resuscitation to maintain mean arterial pressure >65 mmHg
5. In the event of persistent hypotension despite fluid resuscitation (septic shock) and/or lactate > 4 mmol/L (36 mg/dl):
a. Achieve central venous pressure (CVP) of >8 mmHg
b. Achieve central venous oxygen saturation ($ScvO_2$) of >70% (or mixed venous oxygen saturation, SvO_2, >65%)
Sepsis management bundle (24-h)
1. Administer low-dose steroids for septic shock in accordance with a standardised ICU policy
2. Administer drotrecogin alpha (activated) in accordance with a standardised ICU policy
3. Maintain blood glucose control > lower limit of normal, but <150 mg/dl (8.3 mmol/L)
4. Maintain inspiratory plateau pressures <30 cmH_2O for mechanically ventilated patients

Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) [5], in which each recommendation is graded according to the quality of evidence [from high (A) to very low (D)] and the strength of the recommendation (1 strong; 2 weak). The third phase concentrated on encouraging implementation of the guidelines into clinical practice and assessing how effective they were at improving outcomes. For this purpose, the SSC developed a partnership with the Institute for Healthcare Improvement (IHI) to develop sepsis bundles – groups of guideline-based interventions that, when executed together, result in better outcomes than when implemented individually (http://www.ihi.org/IHI/Topics/CriticalCare/Sepsis). Eleven recommendations from the guidelines were brought together to form two key "bundles" (Table 18.1):

1. the Severe Sepsis Resuscitation Bundle, which includes seven tasks that must be accomplished within the first 6 h of patient presentation;
2. the Sepsis Management Bundle, which includes four management goals that must be completed within 24 h of patient presentation.

The bundles were designed to serve as templates from which individual intensive care units (ICUs) could develop protocols customised to their local environment and structure. To determine how effective the introduction of bundles was at improving sepsis outcomes, units using the bundle concept were encouraged to register with the IHI Web site, where tools for bundle application, data gathering, process analysis, successful protocol formation etc. were available.

18.3 Clinical Trials Using the SSC Bundles

Several publications have reported the results of studies in which the sepsis bundles have been used (Table 18.2) [6–18]. In an observational study of 101 patients, Gao et al. [6] showed that compliance with the 6-h sepsis bundle was associated with a more than two-fold decrease in hospital mortality (49% vs 23%), and compliance with the 24-h bundle showed a trend to reduced mortality; however, compliance with both bundles was only 52% for the 6-h bundle and 30% for the 24-h bundle. In a prospective observational study, Nguyen et al. reported that implementation of a severe sepsis bundle in the emergency department setting was associated with decreased in-hospital mortality (20.8% vs. 39.5%, $p < 0.01$) [7]. In a before–after study in 59 Spanish medical–surgical ICUs, Ferrer et al. [8] reported that a national educational effort to promote bundles of care for severe sepsis and septic shock was associated with improved guideline compliance and lower hospital mortality (44.0% vs 39.7%; $p = 0.04$). However, compliance rates were still low, and the improvement in compliance with the resuscitation bundle lapsed by 1 year. In a prospective observational study in our ICU, we noted that compliance with the 6-h bundle was obtained in 72% of patients and with the 24-h bundle in 67% (30/44) of eligible patients [9]. Patients in the 6-h-compliant group had a lower mortality rate (16% vs 41%, $p = 0.04$) and a shorter length of ICU stay than patients in the noncompliant group. The mortality rate and duration of ICU stay were the same in the 24-h compliant and noncompliant groups, but patients who complied with the 24-h sepsis bundle after only 12 h had a lower mortality rate (10% vs 39%, $p = 0.036$) and a shorter length of stay than those in whom compliance was achieved in the 24-h period, suggesting that earlier implementation of the 24-h management bundle (by 12 h instead of 24 h) could result in better outcomes. More recently, the first data from the SSC database, including 15,022 patients from 165 sites entered between January 2005 and March 2008 were published [10]. The results showed that compliance with both bundles increased during the study period (11–31%, $p < 0.0001$, for the resuscitation bundle and 18–36%, $p = 0.008$ for the management bundle). Hospital mortality rates decreased from 37% to 31% ($p = 0.001$) during the same period. In a recent before–after study, Castellanos-Ortega et al. [11] reported that in-hospital mortality was reduced from 57.3% in the historical group of 96 patients to 37.5% in the intervention group of 384 patients ($p = 0.001$). The after group also had shorter hospital and ICU stays. These authors reported that the benefits depended on the number of interventions accomplished within the time limits, with the 6-h resuscitation bundle showing greater compliance and effectiveness than the 24-h-management bundle. Finally, a recent meta-analysis of eight trials of sepsis bundles – one randomised and the others using historical controls as comparators – reported that sepsis bundles were associated with a consistent and significant increase in survival (odds ratio 1.91; 95% confidence interval 1.49–2.45; $p < 0.0001$) [19]. Interestingly, apart from antibiotics, which were more appropriate and given more rapidly in patients treated according to the SSC bundles, use of other bundle components (administration of fluids, vasopressors, inotropes and packed red blood cells titrated to haemodynamic goals, corticosteroids and human recombinant-activated protein C) changed heterogeneously across studies, making it difficult to assess their contributions to the change in survival rates.

Table 18.2 Published studies reporting impact of sepsis bundles on outcomes of patients with severe sepsis or septic shock

Authors [ref], publication date	Study design	Number of patients	Results/comments
Gao et al [6], 2005	Prospective observational	101 from 2 hospitals	Noncompliance with the 6-h sepsis bundle was associated with a more than twofold increase in hospital mortality. Noncompliance with the 24-h sepsis bundle resulted in a non-statistically significant 76% increase in risk for hospital death
Shapiro et al [12], 2006	Before–after	167 (51 before, 116 after)	Sepsis protocol associated with change in clinical practice but no change in mortality
Micek et al [13], 2006	Before–after	120 ED patients	Standardised order set for sepsis associated with reduced 28-day mortality
Nguyen et al [7], 2007	Prospective observational	330 ED patients	Reduced in-hospital mortality
Zambon et al [9], 2008	Prospective observational	69 from medical-surgical ICU	Compliance with 6-h bundle and compliance with the 24-h bundle after just 12 h were associated with reduced mortality
Ferrer et al [8], 2008	Before–after	2,566 from 59 Spanish medical ICUs	Reduced hospital mortality with bundle use. Improvement with resuscitation bundle compliance lapsed by 1 year
El Solh et al [14], 2008	Prospective observational with historical control	87 elderly patients in medical–surgical ICU	Reduced 28-day mortality with bundle use. Bundle use independently associated with reduced mortality in Cox regression analysis
Orford et al [15], 2008	Before–after	110 (44 before, 66 after) in level III ICU	Sepsis protocol based on SSC guidelines not associated with reduced mortality
Girardis et al [16], 2009	Prospective observational	67 from medical-surgical ICU	Reduced in-hospital mortality with both bundles
Levy et al [10], 2010	Database analysis	15,022 from 165 sites worldwide	Unadjusted hospital mortality decreased from 37% to 30.8% over 2 years
Castellanos-Ortega et al [11], 2010	Quasi-experimental with historical control	384 from 3 medical-surgical ICUs	Reduced hospital mortality. The 6-h resuscitation bundle was more effective at reducing mortality than the 24-h management bundle.
Pestana et al [17], 2010	Retrospective	182 surgical ICU patients from 2 hospitals	ICU survival greater in bundle-compliant patients
Cardoso et al [18], 2010	Multicentre prospective cohort	778 with community-acquired sepsis from 17 ICUs in Portugal	Compliance with 6-h bundle associated with reduced 28-day mortality, corresponding to a number needed-to-treat of 6 patients to save one life

18.4 Limitations of the SSC Bundles

Severe sepsis is the leading cause of death in noncoronary ICUs and is associated with mortality rates of 30–50% [20]. Clearly, strategies are urgently needed to improve outcomes, and with no curative drugs in sight, implementing packages of best practice care may be a means of optimising patient outcomes. The SSC has certainly raised awareness of sepsis amongst physicians across the globe. However, has implementation of the bundles themselves led to improved outcomes, or is it just that the quality of care in general has improved because of improved sepsis diagnosis and increased attentiveness to management goals? The bundle approach has some limitations, which should be remembered when interpreting the associated data. First, many bundle components lack strong evidence of efficacy. For example, low-dose steroids, tight glucose control and drotrecogin alpha (activated) are all therapies for which data are conflicting or debated, yet they are included in the management bundle. In the resuscitation bundle, fluids and vasopressors are included, but does it make a difference which fluid or vasopressor is used? High-quality, randomised controlled trial data in support of an intervention are relatively rare in intensive care medicine as a whole and in sepsis in particular [21]. As long as evidence for some bundle components remains disputable, how can the impact of the bundles as a whole be assessed and interpreted? Moreover, institution of sepsis bundles with unproven components may lead physicians to provide inappropriate or even harmful care [19]. Second, as new study results are published, when and how should the bundles be adapted? Third, there is considerable evidence that early diagnosis and initiation of appropriate therapy is crucial in patients with sepsis – e.g. early goal-directed resuscitation [22], early effective antibiotics [23], early initiation of drotrecogin alpha (activated) [24] – have all been associated with improved outcomes. Yet, the SSC bundles have somewhat artificially imposed time limits. Rather than encouraging completion of a bundle within 6 or 24 h, it may be better to encourage completion of each component “as soon as possible” (and, of course, to record it). Our recent study suggested that outcomes could have been improved if the sepsis management bundle had been completed within 12 h rather than the recommended 24-h [9].

18.5 Conclusion: So What Have We Learned?

The SSC has shown that it is possible to raise awareness among physicians and lay persons of an important disease process. It has taught us important lessons about guideline development and highlighted the lack of good-quality evidence in intensive care medicine. The development of sepsis bundles has helped promote discussion of the optimal approach to sepsis management and has introduced some degree of uniformity to the process of treating patients with severe sepsis. It has encouraged a more standardised approach to patient management at a global level. Importantly, the SSC bundles should not be seen as rigid sets of orders but as guides to best practice, and they need to be adapted to local policy and to new evidence as it appears. The advantages of SSC bundle use are perhaps most evident in hospitals in which patient care is substandard – because of lack of trained staff or facili-

ties – and where mortality rates are at the higher end of the range. Where the management of patients with sepsis is already optimal and follows best practice, starting to use bundles of care is unlikely to make any difference to mortality rates and may even represent a step backwards by restricting the freedom of trained intensivists to use their skills and expertise to adapt management to the individual patient.

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Source Control

19

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19.1 Introduction

Source control is defined as all those physical measures necessary to eradicate a focus of infection as well as to control factors that maintain infection, promote microbial growth or impair host antimicrobial defences [1]. Sepsis is defined as infection plus systemic manifestations of infection. Severe sepsis is defined as sepsis plus sepsis-induced organ dysfunction or tissue hypoperfusion [2, 3]. The term source control was first used in the early twentieth century but regained attention over the past 10 years when a panel of experts was asked to provide guidelines for treating severe sepsis and septic shock during the Surviving Sepsis Campaign project. The campaign was promoted by the European Society of Intensive Care Medicine (ESICM), the International Sepsis Forum (ISF) and the Society of Critical Care Medicine (SCCM) to increase awareness of and improve outcomes in severe sepsis [4]. The last updated guidelines were published in 2008 [5]. Recently, the campaign provided "bundles" to help improve guideline outcomes. Bundles help to simplify the complex processes of a septic patient's care. A bundle is a simple principle of care resulting from evidence-based practice guidelines that, when implemented as a group, have a significant effect on outcomes beyond implementing the individual elements alone. Each hospital can elaborate a sepsis protocol, but it must meet the standards created by the bundle [6].

19.2 Concepts

Early sepsis diagnosis is key to successful treatment. However, sepsis often requires time to manifest and may rapidly develop with fatal consequences. Any infection starts with the invasion of host tissues by microorganism, which creates human immune system response, which activates an inflammatory process to challenge the invasion. The consequences of this activation (local vasodilatation, activation of coagulation cascade and

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Table 19.1 Principles of source control

Principles of source control
• Drainage of an abscess or local focus of infection • Debridement of infected necrotic tissue • Removal of potentially infected device • Definitive control of a source of ongoing microbial contamination

endothelial cells, recruitment of defensive cells such as neutrophils and macrophages, tissue injury and necrosis) and the creation of an abscess often prevent microbial dissemination but also protect the milieu from systemic host defence [7, 8]. Understanding this pathophysiological cascade permits clarifying the principles of source-control: drainage, debridement and definitive measures to control the effects of injury and restore the previous correct function [4].

The first step to treat and control an infection is to identify it. To achieve this identification, the clinician should always consider clinical and laboratory signs of sepsis. Furthermore, an early identification (according to the guidelines in the first 6 h) improves outcomes, reducing both mortality rates and costs [4, 5, 9, 10]. Once an infection site has been identified, the clinician should consider which procedure is more effective and safest for the patient: supported source-control measures are draining an abscess or local focus of infection, debriding infected necrotic tissue, removing a potentially infected device or definitively controlling a source of ongoing microbial contamination (Table 19.1) [4, 5, 11, 12]. To avoid more invasive procedures, percutaneous and endoscopic treatment is preferred to surgery when possible [13]. Foci of infection readily amenable to source-control measures mainly include those of intra-abdominal (IA) localisation (abscesses, gastrointestinal perforations, cholangitis or pyelonephritis, intestinal ischaemia), necrotising soft-tissue infection and other deep-space infection. Such infectious foci should be controlled as soon as possible following successful initial resuscitation and antibiotic treatment [12–14]. The only exception to these criteria is peripancreatic necrosis, as a randomised, controlled trial comparing early vs. delayed surgical intervention showed better outcomes with a delayed approach [15]. Antibiotic treatment must be started rapidly, but any kind of microbiological identification must be performed prior to beginning antibiotic treatment [11]. Promptly removing intravascular access devices that are potentially the source of severe sepsis or septic shock, after establishing another vascular access, is an important source-control measure [12].

19.3 Drainage

Draining an abscess permits control of a closed-space infection by creating communication with an epithelium. Drainage may occur spontaneously or can be obtained with surgical intervention or percutaneously. When evaluating the drainage method, the physician should choose the one that permits full drainage of the septic collection with the least

Table 19.2 Indications for the treatment of intra-abdominal sepsis. Percutaneous drainage

Absolute indications	Extended indications
Non loculated fluid collections No communication between abscess and viscus No fungal aetiology	Multi loculated and multiple abscesses Abscesses with fistula Pancreatic fluid collections Abscesses secondary to appendicitis or acute diverticulitis Retroperitoneal abscesses Pelvic abscesses

physical trauma to the patient. There are no randomised trials comparing techniques of abscess drainage. Percutaneous abscess drainage using ultrasound or computed tomography (CT) guidance has gained importance over the past decade, especially when the abscess is single, small, and anatomically accessible (Table 19.2) [13, 16–18]. Laparoscopic drainage of abdominal abscesses showed no significant advantage over open surgery or percutaneous technique [19]. A plastic drain is normally left in to support the communication created by any of these techniques. This technique may be obtained with a laparostomy also. The open-abdomen approach has the potential advantages of reducing IA pressure and permitting easier re-exploration if necessary, but it is also characterised by high fluid loss and wound complications, such as early evisceration and late hernia formation [20, 21]. Failure to drain an IA abscess is most common with small abscesses, pancreatic abscesses and fungal abscesses [22, 23].

19.4 Debridement

Debridement is the process of physically removing devitalised, infected or necrotic tissue from a wound bed. There are four main methods of debridement: autolytic, mechanical, enzymatic and surgical. Surgical debridement remains the standard of care and consists of removal of devitalised tissue by a physician using a scalpel, scissors or other sharp instrument [4, 11]. Autolytic and enzymatic debridements are enzymatic processes that liquefy nonviable tissues [24]. Physicians help autolysis with moist wound dressings (mainly hydrocolloids and hydrogels), whereas a direct enzymatic action is obtained with topical ointments, such as collagenase, promoting debridement. Mechanical debridement generally occurs when patients use dressings that adhere to wounds, which are usually wet-to-dry dressings [25]. With any of these methods, debridement is of paramount importance, as it permits the development of a clear demarcation between necrotic and adjacent vital tissue.

Timing for debridement differs in many conditions characterised by different risks and different evolution. In necrotising fasciitis, the spread of tissue necrosis is quick, so it needs early and aggressive debridement to attain a good outcome [14]. In other types of infections, such as retroperitoneal infections, the high risk of complications suggests delaying the debridement to guarantee a safer procedure [15].

Relatively "old" debridement techniques that are obtaining new importance are biological methods: for example, larval therapy for superficial leg infections [26]. On the other hand, negative-pressure wound therapy and platelet-rich gel have shown significant beneficial effects on the wound-healing process [27–29].

19.5 Definitive Measures

The third milestone in source control is definitive measures that are able to correct the anatomic derangement and restore the previous state. The choice of primary or secondary restoration is based on the pathological condition and the source-control strategy chosen. Regardless, a less invasive but nondefinitive source-control method is preferred; definitive measures should be delayed and performed electively, as the initial source of infection has not yet been removed. Examples are sepsis secondary to gangrenous cholecystitis, with primary percutaneous cholecystostomy and delayed cholecystectomy; or diverticulitis, when the intervention can be performed while the infection is walled off by the host immune system and antibiotic treatment and an abscess has formed. On the other hand, if percutaneous drainage or less invasive treatment are not feasible (for example, perforated diverticulitis with diffuse peritonitis), an open treatment must be undertaken, and definitive measures can be performed directly (for example, restoring the perforated colon and, if possible, immediate anastomosis) [21, 22].

19.6 Timing to Reopen an Abdomen: Examples of Source-control Strategies

The most frequent indication to reopen an abdomen is IA sepsis. Relaparotomy is necessary when the cause of sepsis (abscesses, dehiscence) is documented. On the other hand, when a diagnosis of sepsis is given with a suspected but not documented source of infection, many authors suggest an explorative relaparotomy to detect the source of sepsis. The main debates on abdominal surgery centre around the risks (because of frequent critical conditions) and the real utility of interventions usually taken early in accordance with source-control principles.

Patients with surgical abdominal sepsis need rapid diagnosis and treatment, as untreated foci of sepsis generally evolve in a short time frame in multiple organ failure (MOF). Although percutaneous drainage is often possible and indicated (Table 19.2), many cases cannot be treated without an open procedure [16].

Relaparotomy can be divided into three groups (Table 19.3): (1) directed relaparotomy, including surgical intervention in case of radiologically documented peritonitis or IA abscesses; (2) nondirected (or blind or empiric or a la demand) relaparotomy, when IA origin is only suspected in patients with clinical signs of sepsis [22, 30]; (3) in patients with diffuse abdominal septic localisations, the initial relaparotomy may not be sufficient to clean and drain the foci: in these cases, a scheduled (or programmed or planned) relaparotomy is indicated to attain progressive cleansing and sepsis control. These types of "second look" are usually performed every 24–72 h, irrespective of the patient's clinical condition, to prevent

Table 19.3 Surgical guidelines for the treatment of intra-abdominal sepsis. Surgical procedures

Laparotomy. Historical procedures
• Radical surgical debridement (Hudspeth, 1975) • Continuous postoperative peritoneal lavage (Stephen-Lowenthal, 1979)
Relaparotomy
• Directed relaparotomy • Non-directed (or blind or empiric or à la demande) relaparotomy • Scheduled (or planned or programmed) relaparotomy
Open Abdomen (Laparostomy)
• Open abdomen • Zipper, meshes • Marsupialisation

development of further septic fluid collections, thus precluding their systemic effects. Adverse effects of planned relaparotomies are frequent and include damage to abdominal-wall structures and IA viscera [31].

When a patient needs continuous control of the abdominal status, open-abdomen techniques are indicated. Open management facilitates frequent reexploration and, by treating the entire peritoneal cavity as one large infected collection, continuous exposure for maximal drainage. Furthermore, it serves to reduce the high IA pressure caused by peritoneal oedema associated with fluid resuscitation and inflammation, thus obviating the deleterious systemic consequences of abdominal compartment syndrome. Gastrointestinal fistulas and abdominal-wall defects plague simple open management. These complications should be minimised by introducing temporary abdominal closure devices, such as artificial mesh-zipper techniques [32].

19.7 Conclusions

Source control is defined as any physical measures able to eradicate the focus of infection, to prevent ongoing contamination and ultimately to restore optimal anatomy and function. It is essential for increasing the survival rate, especially in the critically ill patient in the intensive care unit. Drainage, debridement and definitive surgical management are the usual consecutive steps to be carried out, but in many circumstances, the procedure must be tailored to the individual patient. Therefore, once an infection site has been identified, the clinician should always consider which procedure will be most effective, and at the same time safer, for the patient. Successful source control and antibiotic management is associated with resolution of clinical features of systemic inflammation and reversal of organ dysfunction. Progression or failure of organ dysfunction resolution suggests disease persistence and the need for further intervention.

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Immunoglobulins in Sepsis

20

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20.1 Introduction

For decades, intravenously administered immunoglobulin preparations (IvIg) have been extensively used in different categories of critical diseases, including sepsis, polyneuritis of different origins and myasthenia gravis (MG). From this short list, it is evident that IvIg have been administered either to boost or to downregulate patients' immunologic response. These apparently opposing indications are a result of their pleiotropic effects on the immune system, which include: (a) immune response augmentation through an increase in opsonisation and phagocytosis and complement system activation; and (b) reduced inflammatory response via decreased production of tumour necrosis factor-α (TNF-α) and other inflammatory mediators and increased release of soluble receptors for a number of cytokines [1, 2]. This dual effect of IvIg makes them a valuable therapeutic tool either in the phase of full-blown inflammation or in the subsequent compensatory anti-inflammatory response syndrome (CARS) [3], which is associated with an overall reduction of the immunologic response [4].

On the basis of these considerations, it appears that the immunological treatment of septic patients may involve two distinct approaches. The first consists of IvIg administration to impede, or at least blunt, perpetuation of the initial response by attenuating the response to the trigger substance(s). These IvIg are directed primarily either against antigens present on the surface of the infecting microorganisms or towards factors released, including endotoxin, peptidoglycans and lipoteichoic acid, when the organism is killed by antibiotics. The second approach is based on administering antibodies directed against specific sepsis mediators or on neutralising their receptors on the cell surface. Despite sound pathophysiological and experimental bases for IvIg use, results of several randomised controlled trials (RCTs) aimed at investigating the clinical effects of the second approach have been largely below expectations, and only a modest survival benefit, if any, was demonstrated in small groups of patients during post hoc analyses [5].

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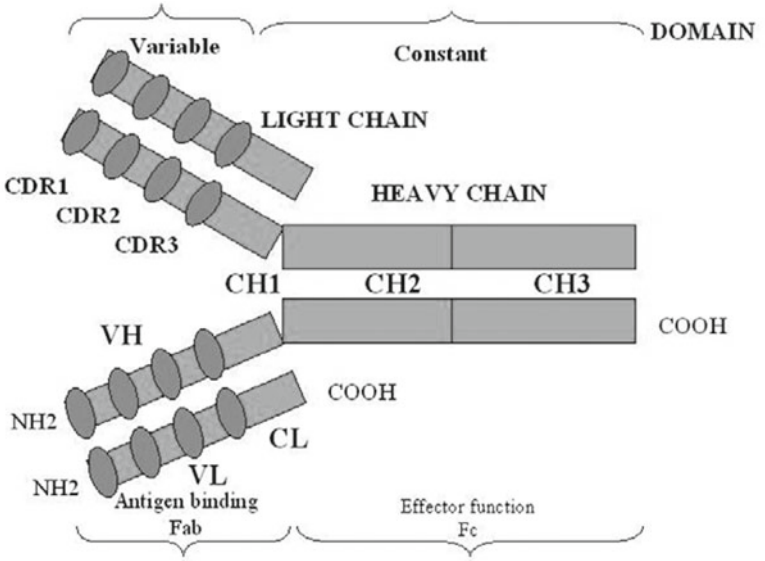

Fig. 20.1 Two-dimensional structure of an IgG molecule. The different epitopes are recognised by the variable regions located on both light (*VL*) and heavy (*VH*) chains (Fab region). The CDR segments are hypervariable domains located in the Fab regions, which are separated from each other by relatively constant polypeptide chains. The Fc region binds to complement and to receptors located on the surface of the RES cells and triggers their activation. *CDR*, complementary determining region; *COOH*, carboxyl; *C*, constant; *Fab*, fragment antigen binding; *Fc*, fragment crystallizable region; *IgG*, immunoglobulin G; *NH2*, amino; *RES*, reticuloendothelial system

20.2 Structures and Function of Immunoglobulins

The ultimate mission of the immune system is to recognise and to destroy extraneous molecules invading the host. To be inactivated, a foreign substance must react with fixed or circulating receptors, which trigger the final response. This task is accomplished by two distinct but strictly co-operating systems [6, 7]. The innate immune system includes cells of the reticuloendothelial system (RES) and the complement cascade. The number of receptors present on the surface of innate immune system cells is genetically determined and, albeit sufficient in number, cannot match the wide variability of microbial antigenic epitopes. Thus, a more flexible system is required in order to face the myriad of agents and/or substances that come into contact with the host. This second mechanism, known as adaptive immunity due to its capability to cope with continuously changing antigens, involves antibodies, which are encoded by genes that are able to undergo somatic recombination and hypermutation. Antibodies are secreted by plasma cells, which are derived from B lymphocytes, which are activated by trapping antigens on a cell-surface receptor and then stimulated with CD4+ T lymphocytes. Antibodies belong to five different classes of Ig (G, A, M, E, and D). The IgG class is considered the prototypical structure and consists of a Y-shaped molecule composed of two identical heavy (H) and light (L) peptide chains

Table 20.1 Possible mechanisms of action of immunoglobulins (adapted from [8, 9])

Toxin inactivation
Neutralise endotoxin and exotoxins
Increase clearance of endotoxin
Reduce bacterial cell adherence, invasion, and migration
Stimulation of leukocyte and serum bactericidal action
Enhance endotoxin-induced neutrophilic oxidative burst (7S-IvIgG); intact
Reduce endotoxin-induced neutrophilic oxidative burst (5S-IvIgG; Fab2 fragments and IgM)
Enhance serum opsonic activity
Modulation of cytokine effect
Modulate release of cytokines and their antagonists • Proinflammatory mediators • Antiinflammatory mediators
Infuse cytokines and antagonists contained in Ig preparations
Neutralise cytokines by anticytokine antibodies
Modulation of the complement cascade

IvIgG, intravenously administered immunoglobulin G; *IgM*, immunoglobulin M; *Fab*, fragment antigen binding

(Fig. 20.1). Both H and L chains are divided into a variable (V) domain that reacts with the antigen and a constant (C) region that activates the various components of the innate immune system, triggering a response (for example, phagocytosis, antibody-mediated and cell-mediated cytotoxicity and complement-mediated lysis). The region connecting the two functional parts can undergo conformational changes to reshape the molecule according to antigen variability. Therefore, Ig can be considered biochemical transducers that are able to:

- recognise invading micro-organisms and derived substances;
- opsonise bacteria;
- signal their presence directly or via the complement cascade to the cells of the innate immune system, which are ultimately responsible for their destruction;
- neutralise bacteria-derived toxins [1, 7] (Table 20.1).

Immunoglobulins are widely used as both therapeutic and diagnostic tools in many fields of medicine. On the basis of their specificity, IvIg preparations can be grouped into monoclonal – containing a single class of Ig directed against a single epitope of those present upon a target molecule (e.g. one epitope of TNF-α), or polyclonal – containing Ig directed against multiple epitopes of the target substance. The additional immunomodulatory effects attributed to the latter class are due to naturally occurring autoantibodies and some nonimmune proteins present in the preparation [1].

20.3 Rationale for Using IvIg in Sepsis

Both monoclonal and polyclonal Ig preparations have been used in septic patients, with different results [2, 8, 9]. Indeed, the recent history of critical care medicine has been marked by a number of RCTs studying the effects of monoclonal IvIg targeted against endotoxin and/or several different sepsis mediators or their cell-surface receptors. However, despite the sound biological bases and the results of preliminary trials performed in small numbers of patients, the results of larger RCTs using these "magic bullets" did not confirm these premises or even demonstrate a better outcome in the control arm [10]. Only post hoc analyses could identify, in some studies, small subsets of patients who benefited from this approach [5]. Various clinical reasons have been proposed as explanation for these contradictory results, including the role of coexisting disease in determining the outcome, the choice of 28- or 56-day survival as study endpoints, and the appropriateness of concomitant treatments [10]. Another possible reason may involve the treatment itself and the rationale behind monoclonal Ig therapy. As sepsis mediators are linked by multiple positive and negative feedback loops, the blockade of only one of the substances responsible for the initial phase (i.e. TNF-α) can be futile, as other mediators will maintain the septic response [11]. Despite the disappointing results of trials studying septic patients, antibodies directed against some of these substances are currently used to treat disorders such as Crohn's disease and rheumatoid arthritis, which, in contrast to sepsis, are characterised by a chronic and localised rather than acute and systemic inflammatory reaction [12]. However, the blockade per se of inflammatory mediators is not completely risk free; in fact, administration of anti-TNF-α antibodies in these clinical conditions has been associated with the occurrence of pulmonary and skin infections caused by intracellular agents and the activation or reactivation of tuberculosis [13].

Polyclonal preparations contain variable amounts of Ig directed against a variety of Gram-negative and Gram-positive epitopes and bacteria-derived substances, including endotoxin. Several preparations containing predominantly IgG with only traces of other Ig are available (Polyglobin®, Bayer, Germany), whereas only one product contains elevated concentrations of IgM (in addition to IgG) and minor amounts of IgA (Pentaglobin®, Biotest, Germany) (eIg). Aside from Ig concentration, the various preparations also differ with regard to the stabilisers used [1]. Unlike monoclonal IvIg, polyclonal IvIgs are widely used in septic patients despite the lack of very large, positive RCTs. Their popularity can be attributed to the widespread occurrence among critically ill patients of conditions associated with a downregulation of their immune capabilities, including postoperative status [14] and neoplasms [15]. Moreover, an ever-increasing number of atients survive an initial insult and face a prolonged length of stay (LOS) in the ICU, which make them prone to repeated infections [16].

20.4 Clinical Indications for IvIg in Sepsis

Polyclonal IvIg are used either to prevent sepsis in at-risk patients or to treat existing sepsis and its consequences. Several investigators have studied the effects of prophylactic IvIg

administration in different categories of patients prone to infections and sepsis, including premature infants and patients undergoing heart surgery. As far as the first category is concerned, a marginal reduction of early-onset neonatal sepsis has been demonstrated by a meta-analysis in premature newborns with a low birth weight [17]. However, this issue should continue to be considered as open, as other studies have failed to identify any survival benefit in this group of patients [18].

Patients undergoing heart surgery represent another group at elevated risk of sepsis due to different causes, including underlying conditions, presence of multiple invasive devices and prolonged ICU LOS; moreover, cardiopulmonary bypass (CPB) can trigger a systemic inflammatory reaction primarily ascribed to the interaction between the blood and the extracorporeal circuit and/or the absorption of endotoxin through the gut mucosa [19]. Using the Acute Physiology and Chronic Health Evaluation (APACHE), several investigations demonstrated a score ≥24 on the first postoperative day after CPB [20–22], indicating that IvIg or eIg administration could reduce disease morbidity and severity in such patients. Another study investigating the effects of eIg confirmed these results, demonstrating that the beneficial effect was limited to more seriously ill patients who developed severe postoperative sepsis [23].

According to recent guidelines for treating sepsis patients, which were issued under the auspices of the Surviving Sepsis Campaign (SSC), IvIg administration should be limited to paediatric sepsis [24]. This statement is rather surprising, as a previous meta-analysis based on the results of nine studies of >400 patients with sepsis and septic shock demonstrated that the risk of mortality in patients given IvIg was lower than that in control patients [relative risk (RR) = 0.60, 95% confidence interval (CI) = 0.47–0.76] [25]. This beneficial effect was significant in adult (n = 222; RR = 0.60 95% CI 0.47–0.77) but not in paediatric (n = 191; RR = 0.60; 95% CI 0.31–1.14) patients. These results have been confirmed by a more recent meta-analysis of a much larger number of patients, which demonstrated a better survival in adult septic patients given polyclonal IvIg compared with control patients (n = 2621; RR 0.74, 95% CI 0.62–0.89) [26].

The weakness of investigations concerning polyclonal IvIg use in sepsis – and therefore of the derived meta-analysis – lies in the relatively small number of patients studied and the heterogeneity of their underlying conditions [27]. The difficulties encountered in defining the exact role of IvIg according to evidence-based medicine (EBM) criteria can be imagined if one considers that only 20 of >4,000 studies were considered eligible for systematic review by Turgeon et al. [26]. A beneficial effect of polyclonal IvIg has also been demonstrated in less frequently encountered critically ill patients who have toxic shock syndrome secondary to severe streptococcal group A infections [28, 29]. With regard to the type of preparation of IvIg, different meta-analyses have demonstrated an increased survival rate in patients treated with eIg compared with preparations containing IgG alone [30, 31]. As the endotoxin molecule represents a target for IgM [14], this effect is particularly evident in patients who have Gram-negative infection [32].

A number of studies indicate that polyclonal IvIg administration is associated with either reduced morbidity or improved survival rate in different populations of patients with sepsis, severe sepsis and septic shock [33–36]. The improved survival rate is more marked in certain subsets of patients, such as those who have sepsis sustained by Gram-negative bacteria [2, 32]. However, it is important to stress that IvIg should be considered as an adjunctive treatment that integrates with, but does not replace, appropriate antibiotic therapy,

and may also be administered alongside the surgical drainage of the septic focus. This latter therapeutic approach could explain the contrasting results observed in different patient populations; a number of RCTs have actually demonstrated a more favourable outcome in surgical patients at risk of or with established sepsis who were given Ig compared with control patients [19–21, 33–36], whereas the effects in medical patients, including those with malignancies and neutropenia, appear to be less straightforward [37, 38]. These results can be ascribed to a number of factors, including sepsis source, different time intervals elapsing from diagnosis to treatment, exclusion of elderly patients and overall effect of other underlying diseases. In fact, administration timing appears to play a pivotal role, as demonstrated by Berlot et al., who observed that patients given eIg early in the course of severe sepsis had a significantly better survival rate than patients treated in a more advanced phase [39].

20.5 Conclusions

Sepsis treatment is multifaceted and typically requires multidisciplinary competencies. In recent years, the immunological therapeutic approach has been extensively studied, but the results of both experimental and clinical investigations have been puzzling, as the administration of monoclonal antibodies directed against specific sepsis mediators produced disappointing results, whereas the administration of the less specific IvIg was associated with better outcomes in different groups of patients. Despite these results, treatment with polyclonal IvIg is not recommended in current guidelines. On the basis of the published studies, it is possible to conclude that:

- some categories of patients, including premature newborns with low birth weight and patients undergoing heart surgery, can benefit from prophylactic IvIg administration;
- surgical patients treated with IvIg present a better outcome than control patients;
- effect on medical patients is less clear, probably due to the presence of other concomitant disorders that can influence the prognosis independently from the presence of sepsis;
- IgM-enriched IvIg preparations have been demonstrated to be more effective in reducing the mortality rate of patients with severe sepsis and septic shock than those containing IgG only;
- efficacy is probably time-dependent, being maximal in the early phases of severe sepsis and/or septic shock.

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Extracorporeal Endotoxin Removal in Sepsis 21

C. Ronco, D. Cruz, F. Nalesso and P. Piccinni

21.1 Background

Despite the relevant improvements in knowledge and care, the incidence of death in intensive care units (ICU) due to sepsis is still very high [1]. About 30% of septic patients die as a consequence of the progression of sepsis to septic shock and multiorgan failure [2]. Specific care protocols were introduced into clinical practice to rapidly identify and treat septic patients [Surviving Sepsis Campaign (SSC) guidelines] [3]. In fact, early diagnosis of sepsis could first result in reduced mortality rates, and second, the cost associated with sepsis could be lowered. A better understanding of the biological mechanisms involved in sepsis trigger and progression is fundamental for choosing appropriate treatment. The septic syndrome arises from the activation of innate host response, leading to a variety of clinical symptoms not specifically related to the presence of an infection. Moreover, microbial products, i.e. endotoxin [lipopolysaccharide (LPS)], and host-derived molecules can evoke the immune response. It is thus useful to rapidly recognise an abnormal immune response and specifically identify the presence of organisms and molecules able to trigger that response. The role of a specific diagnostic procedure could be profitably represented by quantifying circulating endotoxin and its interaction with the immune system. As the presence of small amounts of endotoxin can operate as an alarm molecule aiding the immune system to perform its antimicrobial action, the presence of large amounts of endotoxin could trigger an abnormal immune response itself. In the latter case, the endotoxin could represent the therapeutic target during sepsis.

21.2 Endotoxin as Therapeutic Target

Endotoxin originates from the outer wall of Gram-negative bacteria. Its recognition by the host's immune system involves its binding to the acute-phase protein called LPS binding protein (LBP), its docking to the membrane of myeloid cells via CD14 and the activation

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of an immune reaction – i.e. cytokine release, complement activation or nitric oxide syntheses – by means of toll-like receptor 4 (TLR-4) transcription [4]. A massive endotoxic invasion and/or a favourable genetic liability could enhance that immune response into a systemic inflammation, altered cardiovascular function, lung dysfunction and acute kidney injury [5, 6]. Critical patients seem likely to be exposed to abnormal endotoxaemia, even in the absence of proven Gram-negative infection, probably due to direct translocation from the gut as a consequence of hypoxaemia and hypoperfusion. Moreover, one third of patients with severe sepsis show a high immunological activation mediated by endotoxin and associated with an elevated risk of death [7, 8]. This subpopulation of septic patients could benefit of targeted antiendotoxin therapies.

21.3 Use of Polymyxin-B Based Haemoperfusion in Abdominal Septic Shock

In 1994, a haemoperfusion cartridge containing polymyxin-B (PMX-DHP) was introduced in Japan. This therapeutic approach allowed exploitation of the unique antiendotoxin properties of PMX, avoiding its toxic effect if used as a common antibiotic. PMX binds to endotoxin by means of ionic and hydrophobic forces, thus neutralising its pathogenicity. The PMX-based cartridge showed a high capacity of endotoxin removal and an endotoxin-mediated effect on activated monocytes [9]. The clinical effectiveness of this treatment was evaluated in several studies mainly carried out in Japan and Europe. Cruz and colleagues [10] carried out a systematic analysis of those results, showing the positive effects of the treatment on haemodynamics, pulmonary function and mortality. In 2009, the Journal of the American Medical Association (JAMA) published the "Early Use of Polymyxin B Hemoperfusion in Abdominal Septic Shock: the EUPHAS Randomized Controlled Trial." (www.clinicaltrials.gov with identifier: NCT00629382) [11]. This multicentric, randomised clinical trial enrolled 64 patients with abdominal septic shock between 2004 and 2007 in ten Italian ICUs. The improvement of mean arterial pressure (MAP) and the lower requirements of vasopressors in patients with septic shock presumed to be caused by abdominal infections were the primary endpoint of the trial. In the group of patients treated by PMX-DHP, MAP increased from 76 to 84 mmHg ($P = 0.001$) and the vasopressor requirement decreased (inotropic score from 29.9 to 6.8; $P = 0.001$) over 72 h. The conventional therapy group did not show the same improvements (MAP 74–77 mmHg, $P = 0.37$; inotropic score 28.6–22.4, $P = 0.14$). Pulmonary function, Sequential Organ Failure Assessment (SOFA) score and 28-day mortality were also evaluated. The partial pressure of oxygen in arterial blood/fractional inspiratory oxygen PaO_2/FiO_2 ratio slightly increased (235–264; $P = 0.049$) in the PMX group but not in the conventional therapy group (217–228; $P = 0.79$). SOFA score improved in the PMX group but not in the conventional therapy group (change in SOFA –3.4 vs. –0.1; $P = 0.001$). The 28-day mortality rate was 32% (11/34 patients) in the PMX group compared with 53% (16/30 patients) in the conventional therapy group [unadjusted hazard ratio (HR) 0.43, 95% confidence interval (CI) 0.20–0.94; adjusted HR 0.36, 95% CI 0.16–0.80). In conclusion, the EUPHAS study results confirmed an effect of rapid improvement in overall organ function, particularly within the cardiovascular system.

Although since 1994 >75,000 PMX-DHP cartridges have been used and several studies

carried out to assess the safety and effectiveness of this treatment for sepsis, the international scientific community remains sceptical regarding the effectiveness of extracorporeal endotoxin removal therapy in clinical practice. One criticism is related to the small sample size used in the majority of those studies. Italy is the primary country regularly using PMX-DHP to treat sepsis. Thus, the most established Italian investigators and users of PMX haemoperfusion are designing a new prospective, multicentre, open-label, collaborative data collection project. This study, EUPHAS 2, attempts to determine the effects of PMX-DHP on a large, diverse sample size. The project is coordinated by a scientific steering committee composed of two researchers participating in the EUPHAS trial and two experienced PMX-DHP users not involved in the trial. The aim of the EUPHAS 2 project is to collect a large quantity of data regarding PMX-DHP treatments to better evaluate the efficacy and biological significance of endotoxin removal in clinical practice. Additionally, this study aims to verify the reproducibility of data available in literature, evaluate the patient population chosen for treatment and identify subpopulations of patients who may benefit from this treatment more than others. To address these objectives, patients affected by severe sepsis or septic shock of any origin and dysfunction of one or more organs and treated with PMX-DHP will be included. All patient data will be recorded, including demographics, date of diagnosis of septic shock and endotoxin activity value, results of biological cultures, underlying diseases, main treatments and concomitant treatments with other medical devices and patient severity scores. All data prior to and after PMX-DHP treatments will be traced (vital signs, vasoactive pharmaceuticals, diuresis, SOFA score, haemodynamic variables, blood gas analysis, adverse events, concomitant care. Follow-up data will include ICU and hospital length of stay, and outcome.

Considering the overall number of patients treated by PMX-DHP per year in Italy, we modestly estimate that the database could collect one third of these patients, resulting in a minimum sample size of approximately 100 patients per year. The treatment will be considered as effective on the basis of the same criteria used in the EUPHAS study:

- 20% decrease of the vasopressor dependency index at 72 h;
- reduction of 3.5 points of delta SOFA score at 72 h;
- renal function: significant improvement of urine output and/or frequency of continuous renal replacement therapy (CRRT);
- respiratory function: significant improvement in oxygen metabolism, blood gases and/or mechanical ventilation-free days;
- improvement in ICU length of stay and/or ICU-free days (indicating the actual need for days of intensive care);
- patient prognosis.

This analysed data will be presented to all project participants during the annual user-group meeting (UGM) and upon agreement by the scientific steering committee will be submitted for publication.

21.4 Endotoxin Measurement in Human Blood

Thus far, treatment with PMX-DHP demonstrates its efficacy on patients enrolled only on the basis of the suspected presence of endotoxin. Nevertheless, abdominal sources of sep-

tic shock, due to the relevant amount of LPS contained in the gut, quite ensures its involvement. In 2003, the US Food and Drug Administration (FDA) cleared the Endotoxin Activity Assay (EAATM), K021885, as the first specific method for endotoxin measurement in human blood. This assay measures the neutrophil-dependent respiratory burst activity in the presence of a specific LPS reaction. Respiratory burst activity is detected as a light release using a chemiluminometer. The endotoxin activity of the test specimen (antibody only) is calculated after measuring basal (no antibody) and maximally stimulated (4,600 pg/ml of LPS plus antibody) responses in the same blood sample. Marshall and colleagues [7] carried out a multicentre trial using this new assay and enrolling a great number of patients. The incidence of endotoxaemia among critical patients was evaluated and the correlation existing between high levels of endotoxin activity and the worsening of clinical parameters and outcome of patients was confirmed. Moreover, the study reported the increase in endotoxin activity to be independent from the presence and type of infection. This assay can now be used to identify high levels of endotoxin in patients with sepsis.

Recently, two Italian studies confirmed the ability of the EAA to select patients eligible for PMX-DHP treatment. Monti and colleagues [12], in a retrospective study, evaluated the effect of PMX-DHP treatment after a 48-h follow-up on patients showing a high endotoxin activity at enrolment compared with the effect of standard care only on patients also showing high values of endotoxin activity. Despite a higher severity of illness, the PMX-HP treatment group at 48 h showed a significant and fast reduction in vasopressor requirements, which was not observed in the conventional group. The treated group also showed a significant improvement in SOFA score (13.23 ± 2.17 to 10.97 ± 3.63 points, $P < 0.05$) in comparison with the conventional group (not significant). Moreover, even if not significant, the crude mortality rates were 15% and 32%, respectively, in the PMX-DHP and conventional groups ($P = 0.614$, χ^2 test). Novelli and colleagues [13] also used the EAA as the enrolment criteria for treatment with PMX-DHP, showing both reduced endotoxin activity as a consequence of the treatment and improved clinical parameters of treated patients.

21.5 EUPHRATES

Among major criticisms of previous trials are small sample size, absence of endotoxin measurement and lack of blinding. As all studies were open label, there was the risk of introducing a bias that could have artificially prolonged survival in treated patients. Blinding has been a challenge due to the ethical problems of using a sham control. During 2011 and 2012, a new clinical trial, “Evaluating the Use of Polymyxin B Hemoperfusion in a Randomized Controlled Trial of Adults Treated for Endotoxemia and Septic Shock” (EUPHRATES) (www.clinicaltrials.gov, with identifier:NCT01046669) will be carried out in the United States. To overcome criticism of previous, single-centre, trials, EUPHRATES is designed to enrol 360 patients, which will make it the largest multicentre trial for an extracorporeal sepsis therapy.

One of the clinical challenges preventing verification of successful antiendotoxin strategies has been ensuring that patients enrolled in trials targeting endotoxin neutralisation or removal have endotoxaemia. No endotoxin measurements were included in any of the

previous studies, either as inclusion or monitoring criteria, as the assay was not widely available at the time the trials were conducted. EUPHRATES will use the EAA to screen eligible patients, and patients with no or low endotoxin levels will not be enrolled. Moreover, EUPHRATES will attempt to blind the study for those in charge of management decisions by using an innovative procedure without the use of a sham control. EUPHRATES, although powered for 28-day mortality as the primary outcome, will also track mortality for up to 1 year.

21.6 Conclusions

The clinical effects of PMX-based haemoperfusion in patients with severe sepsis are reported in several studies, demonstrating mitigation of the septic cascade in the early phases, with an improved prognosis and outcome. Recent clinical trials seem to confirm the expectations, having shown a reduction in mortality in patients with early signs of abdominal sepsis due to recent surgery

The new EUPHAS 2 study will provide more evidence regarding the use of PMX-DHP collecting, as it will collect a large quantity of data from several different centres and from a wide population range of septic shock patients, enrolling any patient with high endotoxin activity. It is therefore our aim that the EUPHAS 2 study will provide a definitive statement regarding the use of PMX haemoperfusion for treating endotoxic septic shock, provide a comparison between results from the FDA-cleared EUPHRATES scheduled to begin in the USA and those tracked in European clinical practice, and ultimately determine the role of PMX-DHP in sepsis therapy.

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Part IX
Perioperative Medicine

Perioperative Medicine: An Introduction

22

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22.1 Introduction

The term perioperative medicine describes the consultation, care, or co-management of a patient undergoing surgery (the patient preparing for, having and recuperating from surgery and at risk of complications [1]; the patient with specific risks; methods of risk reduction and medical management by healthcare professionals during this time period) provided by a team thanks to the cooperation among anaesthesiologist, surgeon and internal medicine physician. Evidence supporting best practices in perioperative medicine is expanding, though historically, this field has been directed by common practice and experience [2]. Perioperative medical practices represent a true challenge among specialties, among practitioners of a specific specialty and even among specialist in the same category. A wide range of differences exists among practitioners of perioperative medicine in their approach to diagnosing and treating otherwise healthy people who need treatment due to pathology in a specific organ. Given the increasing complexity of care required for hospitalised patients, there is greater reliance on the healthcare system for preoperative assessment. Several institutions have developed surgical/medical co-management teams that jointly care for patients in the perioperative setting. Perioperative medical care is widely recognised as an integral component of overall surgical case management [3, 4].

The perioperative period generally includes ward admission, anaesthesia, surgery, and recovery room (RR), thus covering preoperative, intraoperative, and postoperative patient care. The goal of perioperative care is to prepare patients both physically and psychologically for surgery and postsurgery and provide them with better care and conditions throughout the entire process.

Anaesthesiologists are highly skilled physicians. An anaesthesiology department should provide care extending from preoperative evaluation and the intraoperative procedure to postoperative critical care and pain management. Information obtained during preoperative assessment consists of:

- evaluating and optimising a patients' medical condition prior to anaesthesia or sedation;

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- prescribing and implementing a plan for anaesthesia;
- ensuring adequate pain control and resolving all anaesthetic side effects after the procedure is complete.

It is the anaesthesiologist's responsibility towards the surgical patient to ensure high-quality perioperative anaesthesia management, decrease adverse events that may occur following anaesthesia administration and assisting in the patient's return to daily life as soon as possible. Crucial components of realising this goal are risk assessment, and obtaining informed consent after providing the patient with reliable outcome predictions and preparing and implementing an effective management plan to cover the entire perioperative period based on patient assessment.

The preoperative clinic efforts are intended to:

- improve operating room efficiency;
- identify potential complications related to anaesthesia or surgical procedure;
- inform patients about what to expect on the day of their procedure.

The intraoperative period begins when the patient is transferred to the operating room bed and ends when the patient is transferred to the postanaesthesia care unit (PACU). During this period, the patient is monitored, anaesthetised, prepped and draped, and the operation is performed. Medical activities during this period focus on safety, infection prevention and physiological response to anaesthesia. The postoperative period begins after patient transfer to the PACU and terminates with the resolution of surgical sequelae. At the end of surgical procedure, irrespective of whether a regional or general anaesthesia was used, it is unacceptable to return patient to a general ward; the patient must enter the recovery room, a transition point between the operating theatre and the general ward (Table 22.1).

Best-practice patterns in modern medical care aim to integrate evidence from the medical literature with the clinician's personal and institutional expertise. Integrating evidence-based medicine into perioperative care is an important component of modern anaesthesiology, surgery, pharmacy, and nursing practice. Because evidence is continually evolving, perioperative patient care is ever changing. Our mission is thus to improve patient outcomes by promoting perioperative care among all professionals [6].

Table 22.1 Recovery room discharge criteria

Parameter	Value
Level of consciousness	Awake or immediately awakens to command
Airway obstruction	Can cough effectively and shallow secretions
Breathing	Respiratory rate >10/min
Circulation	Mean arterial pressure >65 mmHg
Temperature	36.5–37.5°C
Pain	Little or no discomfort
Nausea	No nausea

Henrik Kehlet termed such a principle the “fast-track concept”, which encompasses the entire perioperative phase beginning with preoperative preparation, covering atraumatic surgical and anaesthesiological techniques, reducing the neuroendocrine stress response and encompassing postoperative treatment. This strategy has been shown to positively influence organ function, homeostasis, morbidity rates, the need for hospitalisation and convalescence and, therefore, to reduce costs [7]. Additionally, various external funding and oversight organisations, including the Joint Commission, have begun to affect physician and hospital reimbursements and accreditation by tracking hospital and physician performance on certain “core measures” and their reported incidence of so-called “never events” (conditions or complications that should occur with a very low incidence) when providing ideal or perfect clinical care.

The objective of this review is to consider the most relevant aspects of perioperative medicine by focusing on some critical points, such as preoperative clinical decision making, the importance of monitoring vital parameters and organ function and anaesthesia safety [8].

22.2 Coexisting Diseases

The perioperative care patient with coexisting disease (high-risk patient) has the most pressing medical need. Higher-risk surgical patients represent a major challenge for healthcare resource utilisation. Identifying patients at the highest risk of perioperative morbidity may permit further clinic-to-bench translational understanding of the pathophysiologic mechanisms underlying postoperative organ dysfunction. Defining the high-risk surgical patient population is as critically important for global public health planning as it is for the perioperative team [9]. There are several factors during the perioperative period that may worsen coexisting disease or precipitate life-threatening conditions: sedative drugs and anaesthesia relieve anxiety, reduce blood pressure and decrease cardiac load. Risk factors may be stratified into high, medium, or low according to coexisting disease: respiratory disorders, diabetes, hypertension, heart disease, obesity and smoking are cardinal points that place a patient at higher risk for complications during surgery and the postoperative period [10–18]. The anaesthesiologist during the preoperative visit has six goals: assessing the patient’s condition (medical history and physical examination), discussing anaesthesia options and postoperative pain management, reducing patient anxiety, obtaining informed consent and coordinating patient care among medical professionals to improve outcomes [19]. The American Society of Anesthesiologists (ASA) classification system [20] correlates a patient’s preoperative status with the risk of postoperative morbidity (Table 22.2).

Approximately 2.5% of patients undergoing noncardiac surgery suffer from perioperative cardiac complications [21]. The risk factors for perioperative cardiac complications are: high-risk surgery, ischaemic heart disease, history of congestive heart failure, cerebrovascular disease, diabetes and renal failure (Tables 22.3 and 22.4). Preventing cardiac problems consists of identifying patients at risk; optimising preoperative condition by modifying underlying risk factors; optimising perioperative medication with adrenergic beta-antagonists, statins and acetylsalicylic acid; providing adequate perioperative monitoring; and implementing measures to prevent myocardial ischaemia (adequate sedation

Table 22.2 American Society of Anesthesiologists (ASA) preoperative physical status classification system

Classification	Patient's preoperative condition
Class I	Fit and healthy
Class II	Mild systemic disease
Class III	Severe systemic disease that is not incapacitating
Class IV	Incapacitating systemic disease that is constantly life threatening
Class V	Moribund; not expected to survive more than 24 h with or without surgery

Table 22.3 Risk factors for perioperative cardiac complications

Cardiac risk index			
Risk factor	Criteria	Number of factors	Cardiac risk (%)
Cerebrovascular disease	Stroke, transient ischaemic attack	0	0.4
Ischaemic heart disease	Myocardial infarction, angina	1	1.1
Congestive heart failure	History, examination	2	4.6
High-risk surgery	Thoracic, abdominal, vascular	≥ 3	9.7
Insulin-treated diabetes	-		
Serum creatinine >177 μmol/L	-		

Table 22.4 Cardiac risk stratification for noncardiac surgery

High (>5%)	Intermediate (1–5%)	Low (<1%)
Emergency surgery	Intraperitoneal surgery	Endoscopic procedures
Aortic and other vascular surgery	Intrathoracic surgery	Cataract surgery
Prolonged surgery associated with large fluid shifts and/or blood loss	Orthopaedic surgery	Breast surgery
Peripheral vascular surgery	Carotid endarterectomy	Superficial surgery

and analgesia; adequate oxygenation, oxygen transport and ventilation; and, if necessary, additional cardiac medication).

High-risk patients have a poor outcome prediction due to their inability to meet the oxygen transport demands imposed on them by the nature of the surgical response during the perioperative period. It has been shown that by targeting specific haemodynamic and oxygen transport goals at any point during the perioperative period, the outcomes of these patients can be improved [22]. This goal-directed therapy includes using fluid loading and inotropes in order to optimise preload, contractility and afterload of the heart whilst maintaining an adequate coronary perfusion pressure. Strategies include approaches that both increase tissue oxygen delivery and reduce metabolic demand [23].

22.3 Improving Outcome after Major Surgery

22.3.1 Perioperative Oxygen Transport

Oxygen delivery is dependent upon cardiac output and carriage by haemoglobin. Hypoxia is one of the major causes of morbidity and mortality following surgery and may be classified according to the cause of hypoxic hypoxia, stagnant hypoxia, anaemic hypoxia or isotoxic hypoxia. Oxygen therapy is effective and should be administered to all patients following major surgery. Oxygen transport balances should be assessed in critically ill perioperative patients. The balance between oxygen consumption and oxygen delivery is assessed by measuring the mixed venous oxygen saturation (SvO_2) or the oxygen utilisation coefficient (extraction ratio, VO_2/DO_2). A decrease in SvO_2 is a sensitive but not specific indicator of global oxygen transport balance and indicates an increase in the oxygen utilisation coefficient (oxygen extraction ratio). The balance between oxygen demand and consumption is reflected by the arterial lactate level: when oxygen demand exceeds consumption, excess lactate appears [24]. A reduced preload may be responsible for impaired oxygen transport. The fluid challenge may be an important diagnostic and therapeutic manoeuvre in patient with lactic acidosis unexplained by other reasons [25].

22.3.2 Fluid Management

There is a significant fluid flux in the perioperative period. Patients presenting for surgery have a fluid deficit (nil by mouth for at least 4-6 h). Some patients are at risk for dehydration, hypervolaemia, hypovolaemia, and fluid therapy should be administered to replace fluid deficit [26]. Regular hydration status and compensated vascular filling are targets of perioperative fluid and fluid-volume management and, in parallel, represent precautions for sufficient cardiac output and stroke volume to maintain tissue oxygenation [27].

The physiological and pathophysiological effects of fluid and volume replacement mainly depend on the pharmacological properties of the solutions used, the magnitude of

the applied volume and timing of volume replacement during surgery. In the perioperative setting, surgical stress induces physiological and hormonal adaptations in the body, which – in conjunction with an increased permeability of the vascular endothelial layer – influence fluid and volume management. A goal-directed volume management aiming at preventing hypovolaemia may improve patient outcome after surgery [28].

22.3.3 Glucose Control

The following steps are recommended to provide glucose control [29]:

- intraoperative and postoperative blood glucose concentration should be monitored for all patients undergoing surgery;
- perioperative insulin therapy should be initiated for diabetic patients intraoperatively to maintain glucose concentrations at <180 mg/dl and be continued for the first 24 h postoperatively per an institutional protocol to maintain glucose concentrations at <180 mg/dl;
- patients without diabetes who develop persistent glucose concentrations >180 mg/dl during the perioperative period should have perioperative insulin therapy initiated and continued for at least the first 24 h postoperatively per an institutional protocol to maintain glucose concentrations <180 mg/dl;
- anaesthesiologists and other perioperative care providers, including postoperative nursing staff, should be vigilant with regard to detecting and treating severe hypoglycaemia, particularly in patients who remain anaesthetised or sedated or who have acute haemodynamic or mental status changes.

22.3.4 Infection Prevention and Treatment

More than two decades ago, the Institute of Medicine released its landmark article "To Err is Human", which argued for significant improvements in healthcare quality and safety [30]. Some of the identified areas for improvement included reducing incidences of surgical-site (SSI) and healthcare-associated (HAI) infections, such as SSI and, specifically, deep sternal-wound infection (DSWI) for cardiosurgery patients, ventilator-associated pneumonia (VAP), urinary tract infection (UTI) and catheter-associated bloodstream infection (CABSI) [31, 32]. Many interventions that affect these HAI in cardiosurgery patients start in the early perioperative period with the placement of devices by anaesthesiologists or the surgical team, and anaesthesiologists, therefore, may be in the best position to help reduce the incidence of these complications. Additionally, extensive institutional attention is now focused on preventing HAI in many Medicare-participating hospitals because public and regulatory reporting of these infections is now required and the associated costs of these HAI will not be reimbursed (if not present on hospital admission).

22.3.4.1 Recommendations

The following steps are recommended [33–35]:

- anaesthesiologists and other perioperative care providers should continue to provide support to institutional infection control practices as they relate to healthcare-associated infections;
- perioperative prophylactic antibiotics should be given per institutional protocol. These should be continued for up to 24–48 h postoperatively to decrease the risk of SSI and DSWI;
- published bundle practices to prevent CABSI should be followed for placing all central venous catheters (as appropriate for the clinical situation). These include appropriate hand hygiene, using maximum barrier precautions, a chlorhexidine-based skin preparation solution, accessing the internal jugular or subclavian veins (when possible), and removing catheters when no longer needed for patient care;
- published bundle practices to prevent VAP should be followed on all patients requiring prolonged mechanical ventilation. These include lifting the head of the bed to an angle higher than 30°, interrupting daily sedation and stress-ulcer and deep-vein-thrombosis prophylactic strategies. Additionally, using continuous subglottic suction or anti-infective endotracheal tubes should be considered in all patients requiring (or at risk for) prolonged mechanical ventilation;
- Foley catheters should be removed as soon as they are no longer needed, and consideration for removal should occur as soon as possible in patients at risk for UTI.

22.3.5 Perioperative Bleeding Prevention and Treatment

Prophylactic strategies to reduce bleeding are obviously the most effective therapy to decrease the risk of serious perioperative bleeding. Optimal preventative strategies include interrupting maintenance antithrombotic therapy when appropriate, optimising intraoperative haemostasis using electrocautery and other surgical-based techniques, and implementing conservative strategies when resuming antithrombotic therapies, including both anticoagulant and antiplatelet agents after surgery.

Treating severe intraoperative and postoperative bleeding should be guided by patient-specific circumstances and available laboratory data. When possible, the physical factors, including temperature and electrolyte concentrations, and preoperative factors should be empirically and prophylactically corrected. Additional laboratory monitoring consisting of haematocrit, platelet count, international normalised ratio, activated partial thromboplastin time and fibrinogen should guide the use of platelet transfusion to treat thrombocytopoenia and coagulation factor replacement using either fresh frozen plasma (FFP) or cryoprecipitate transfusion to improve haemostasis. In patients with continued refractory bleeding despite platelet, FFP, or cryoprecipitate transfusion, thromboelastography may be an important complementary test that was recently included by the ASA in the panel of laboratory monitoring recommended for assessing coagulopathy [36]. If ongoing, severe

haemorrhage continues despite aggressive therapeutic attempts to correct coagulopathy, hypofibrinogenaemia, and thrombocytopoenia, the use of recombinant clotting factor VII (rFVIIa) may be considered.

22.3.5.1 Recommendations

The following steps are recommended:

- perioperative use of antithrombotic therapies, including anticoagulants and antiplatelet therapies, should be individualised to each patient's clinical circumstances, with input from cardiology, surgery, and anaesthesiology. Additional expert consultants, including haematologists and transfusionists, may be warranted;
- prophylactic antifibrinolytic agents should be used in all patients at high risk for haemorrhagic complications and should be considered for all other patients;
- anaesthesiologists should be familiar with the most current dosing guidelines and potential complications related to the use of rFVIIa during surgery.

22.3.6 Neurological and Cognitive Dysfunction (Delirium)

Neurological complications in the postoperative period represent a rare but dangerous event. Some surgical procedures carry a high risk of neurological complications [delirium; postoperative cognitive dysfunction (POCD)]. It is unclear what preventive and treatment strategies are best to ameliorate these catastrophic complications that put the patient at risk of long-term debilitation. Risk factors for POCD include preoperative, intraoperative and postoperative factors are presented in Table 22.5.

Table 22.5 Potential risk factors for postoperative cognitive dysfunction (POCD)

Advanced age
Low educational level
Preoperative neurologic deficit
Diabetes
Preoperative atherosclerotic disease (particularly cerebrovascular and aortic disease)
Altered intraoperative neuroperfusion (because of nonpulsatile cardiopulmonary bypass with concomitant cerebrovascular microemboli)
Intraoperative hypotension and hypoxia
Postoperative use of medications with central nervous system side effects
Postoperative infection

22.3.6.1 Recommendations

The following steps are recommended:

- patients should be screened for POCD while in the intensive care unit (ICU) at least daily using an objective, validated screening tool such as the Confusion Assessment Method;
- patients with POCD should be treated aggressively with antipsychotic medications, such as haloperidol, olanzapine or quetiapine, to relieve symptoms and restore normal mentation;
- families of patients at risk for POCD should be educated about the signs and symptoms upon hospital discharge. Routine follow-up or treatment is not yet available, and further studies in this area are especially warranted [37–39].

22.4 Intraoperative Care

Conventional monitoring and minimally invasive approaches can be used for perioperative optimisation of low- to moderate-risk patients. The choice of perioperative haemodynamic monitoring for goal-directed therapy (GDT) depends on surgery- and patient-related risk, and GDT should be early, adequate and individualised for every patient. An important goal of perioperative haemodynamic therapy is to maintain cardiac function and organ perfusion, optimising the balance between oxygen delivery and consumption. Based on adequate monitoring, GDT algorithms facilitate early detection of pathophysiological changes and influence perioperative haemodynamic therapy, which can improve clinical outcome [40]. The importance of selecting appropriate monitoring should be a major focus. Pulse oximetry and capnography have become routine monitoring devices in the perioperative period and in intensive care. Both techniques are noninvasive. Knowledge of the operating principles of pulse oximetry and capnography is desirable for accurate data interpretation.

22.5 Postoperative Care and Pain Management

Complications, both intraoperative and postoperative, are a significant source of morbidity and mortality for all patients undergoing surgery and can be anaesthetically, surgically or medically related. Prevention of complications are the basis for avoiding critical incidents. Efforts to minimise these complications have resulted in the development of the field of perioperative medicine.

22.5.1
Neurological Complications

Some surgical procedures carry a high risk of neurological complications, which occur frequently in the elderly. Among the interventions recommended in the elderly to reduce the risk of delirium are:

- providing supplemental oxygen;
- restoring serum sodium, potassium, and glucose to normal limits;
- withdrawing high-risk medications (anticholinergic drugs, benzodiazepines, meperidine);
- assuring adequate nutritional intake;
- getting the patient out of bed on postoperative day 1;
- treating severe pain.

22.5.2
Cardiovascular Complications

Cardiovascular complications have a high incidence in patients with preoperative risk factors [41]. Cardiac events contribute significantly to postoperative morbidity [42]. There are few areas within perioperative medicine that are well studied beyond the area of predicting cardiac risk. The American Heart Association perioperative guidelines and the guidelines of the European Society of Cardiology highlight the paucity of studies on interventions to prevent postoperative cardiac events [43].

22.5.3
Pulmonary Complications

Airway obstruction, hypoventilation leading to atelectasis, secretions, pain, abdominal distension and supine position may affect lung function.

22.5.4
Postoperative Bleeding

Postoperative bleeding occurs in procedures such as major arterial surgery and those involving the liver and spleen. Appropriate early diagnosis and intervention influence outcomes. The best strategy remains treating underlying disease and managing shock.

22.6
Pain Management

Postoperative pain management is an important but seemingly undervalued component

Table 22.6 Patient-controlled analgesia (PCA)

Advantages	Disadvantages
Improved pain relief	Equipment cost
Improved patient satisfaction	Trained staff required
Improved mobility	Technique-related mishap
Eliminates possible dosing delay	Masking of postoperative complications
Obtains analgesia	Accumulation of metabolites

of perioperative care [44]. Over the past decade, medical societies, governmental agencies and accrediting bodies such as the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) have paid increasing attention to the management of all types of pain, including postoperative pain. Despite this increased focus, the literature suggests that many patients continue to experience significant postoperative pain. Inadequately controlled pain can cause postoperative morbidity, prolong recovery time, delay return to normal living and decrease satisfaction with care. Postoperative pain needs to be assessed for appropriate analgesic management. Acute pain has wide-spread effects on the body's physiological homeostasis and includes nociceptive, inflammatory, neurogenic and psychological components. It may also be a factor in the development of chronic pain.

Acute pain management incorporates pharmacological, physical and psychological modalities. Effective analgesia should provide maximal relief and have minimal side effects. Improved postoperative pain relief is important for patient comfort, may decrease hospital stay and may lead to reduced morbidity. There are three groups of pain management:

1. conventional therapies:
    - nonopioid analgesic [e.g. paracetamol, nonsteroidal anti-inflammatory drugs (NSAIDs)];
    - opioid analgesics;
    - adjuvant analgesics (e.g. antidepressants, anticonvulsants, alpha-2 agonists);
2. advanced options:
    - epidural analgesia;
    - peripheral nerve blocks;
3. patient-controlled analgesia (PCA) (Table 22.6). The key to successful use of PCA is:
    - careful patient selection, ensuring good understanding of its use;
    - meticulous programming with appropriate settings;
    - staff familiarity with the system;
    - frequent pain assessment and drug reappraisal.

22.7 Infants and Children; Elderly and Pregnant Patients

22.7.1 Infants and Children

There are marked differences between neonate (first month of life), infant (first year of life) and children (>1 year). These differences are anatomical and physiological and must be taken into account in the perioperative period. Fluid balance and thermoregulation must be rigorously observed. Parental presence is important during the procedure and should be encouraged where possible.

22.7.2 Elderly Patients

Older patients typically have longer hospital stays, greater care costs and greater risks of adverse health outcomes related to surgical or medical problems than younger patients do. Older patients often have multiple comorbidities that limit their functional capacity and recovery and increase the risk of mortality. This is why perioperative management is such an important topic in current geriatric medicine [45]. Successful perioperative care in the elderly requires:

- understanding effect of ageing;
- knowledge of the patient's medical history;
- close supervision and monitoring.

Physiologic function of the organ systems of older adults is impaired as a result of the ageing process. Polypharmacy, drug interaction and drug overdose are important causes of morbidity. Older patients may also present with poor nutrition from the presence of chronic diseases, from illness they have close to the time of surgery or both. Elderly patients tolerate fluid overload/deficit poorly, and postoperative cognitive dysfunction is a serious complication.

22.7.3 Pregnant Patients

There are special considerations in pregnant women scheduled for surgery. Physiological modifications of pregnancy influence the response to anaesthesia, stress and surgery [46]. Specific diseases are associated with or exacerbated by pregnancy. Intraoperative and postoperative complications are related to preeclampsia, eclampsia and bleeding. Involving a multidisciplinary team increases the chance of successful outcome in high-risk pregnancies [47].

22.8 Good Medical Practice, Checklist and the Helsinki Declaration

The European Board of Anaesthesiology (EBA), in cooperation with the European Society of Anaesthesiology (ESA), produced a blueprint for patient safety in anaesthesiology. This document, to be known as the Helsinki Declaration on Patient Safety in Anaesthesiology, was endorsed by these two bodies and the World Health Organization (WHO), the World Federation of Societies of Anaesthesiologists (WFSA) and the European Patients' Forum (EPF) at the Euroanaesthesia 2010 meeting in Helsinki. The declaration builds on earlier statements about safety and quality of care and represents a shared European view of that which is worthy, achievable and necessary to improve patient safety in anaesthesiology in 2010. It recommends practical steps that all anaesthesiologists who are not already using them can successfully include in their own clinical practice [48]. These are relatively straightforward and, where currently used, have a track record of improving patient safety. Safety can be improved by analysing errors and critical incidents, reporting, checklists, safe system design, communication protocols and systematic risk analysis [49, 50]. All European anaesthesiology institutions are expected to support the WHO Safe Surgery Saves Lives initiative [51] (Table 22.7).

Medical errors cause considerable death and disability [10, 11], and recently, a number of studies have attempted to quantify the scale of that problem. In a systematic review examining >70,000 records of a general patient population, the overall incidence of in-hospital adverse events was 9.2%, of which 43.5% were thought to be preventable [52]. Around 230 million patients undergo anaesthesia for major surgery worldwide every year. Seven million develop severe complications associated with these surgical procedures, from which 1 million die (200,000 in Europe). All involved in such procedures must try to significantly reduce this rate [53]. The Safe Surgery Saves Lives programme includes a 19-item surgical safety checklist designed to improve team communication and consistency of care that will reduce complications and deaths associated with surgery. Implementation of the checklist and the associated cultural changes reduced death and complication rates among patients after surgery in diverse settings. The checklist consists of an oral confirmation by surgical teams ensuring completion of the basic steps for safe delivery of anaesthesia, prophylaxis against infection, effective teamwork and other essential practices related to surgery. The checklist is used at three critical junctures in care: before anaesthesia is administered, immediately before incision and before the patient is taken out of the operating room. Use of the checklist involves changes in both systems and behaviour of individual surgical teams [54]

Surgery has become an integral part of global health care, and surgical complications are common and often preventable. Indeed, data suggest that at least half of all surgical complications are avoidable. A growing body of evidence also links teamwork in surgery to improved outcomes, with high-functioning teams achieving significantly reduced rates of adverse events [55, 56]. The WHO published guidelines identifying multiple recommended practices to ensure the safety of surgical patients worldwide [57]. Introduction of the Surgical Safety Checklist into operating rooms was associated with marked improvements in surgical outcomes. The reduction in the rates of death and complications suggests that the checklist program can improve the safety of surgical patients in diverse clinical and economic environments.

Table 22.7 Surgical safety checklist is based on the World Health Organization's Guidelines for Safe Surgery

Recommended practices of the Surgical Safety Checklist	
Sign in	Before induction of anaesthesia, members of the team orally confirm that: • The patient has verified his or her identity, the surgical site and procedure, and consent • The surgical site is marked or site marking is not applicable • The pulse oximeter is on the patient and functioning • All members of the team are aware of whether the patient has a known allergy • The patient's airway and risk of aspiration have been evaluated and appropriate equipment and assistance are available • If there is a risk of blood loss of at least 500 ml (or 7 ml/kg of body weight in children), appropriate access and fluids are available
Time out	Before skin incision, the entire team orally: • Confirms that all team members have been introduced by name and role • Confirms the patient's identity, surgical site and procedure • Reviews the anticipated critical events: - Surgeon reviews critical and unexpected steps, operative duration and anticipated blood loss - Anaesthesia staff reviews concerns specific to the patient - Nursing staff reviews confirmation of sterility, equipment availability and other concerns • Confirms that prophylactic antibiotics have been administered ≤60 min before incision is made or that antibiotics are not indicated • Confirms that all essential imaging results for the correct patient are displayed in the operating room
Sign out	Before the patient leaves the operating room: • Nurse reviews items aloud with the team: - Name of procedure as recorded - That needle, sponge and instrument counts are complete (or not applicable) - That specimen (if any) is correctly labeled, including the patient's name - Whether there are any equipment issues to be addressed • Surgeon, nurse and anaesthesiologist review aloud key concerns for patient's recovery and care

22.9 Conclusions

Providing a high standard of perioperative practice and care requires the involved health care professional team to [58]:

- keep professional knowledge and skills up to date;
- recognise, and work within, the limits of individual competence;
- work with colleagues in ways that best serve patients' interests.

The Merriam-Webster's Collegiate Directory defines a profession as "a calling requiring specialized knowledge and often long and intensive academic preparation". "Professional" is defined as "characterized by or conforming to the technical or ethical standards of a profession and exhibiting a courteous, conscientious, and generally businesslike manner in the workplace". "Professionalism" is characterized as "the conduct, aims, or qualities that characterize or mark a profession or a professional person" [59]. Obligations of professionals include trustworthiness, respect of human worth and protection of important values. Clinicians, managers, scientific societies and the like are challenged to address the perioperative medicine "problem" of high rates of morbidity and mortality by using novel – yet timely and comprehensive – strategies, for it appears that the problem will be unrelenting in its impact on quality and quantity of life, as well as healthcare expenditure, throughout the world.

Patient safety has received much attention in the past decade, and the first report produced by the Quality of Health Care in America project [30] more than two decades ago was appropriately titled: "To Err is Human: Building a Safer Health System" (Table 22.8). This paper shocked the world by claiming that medical error was among the leading causes of death in the United States. In contrast, anaesthesiology was cited as an area in which there were impressive gains in safety and quality. The mechanisms to which these remarkable gains are attributable include practice guidelines, anaesthesia simulators and benchmarking.

Table 22.8 Perioperative safety

Recommended practices of the Surgical Safety Checklist	
Perioperative safety	All surgery and anaesthesia is associated with some risk
	Risks are specific to individual patient
	Patient requires an honest appraisal of risks
	Informed consent is required from all patients (except in extreme conditions)
	Anaesthesia is a vulnerable state during which patients trust the anaesthetist entirely
	Everything possible must be done to ensure patient safety
	Healthcare professionals must take precautions to protect themselves

Anaesthesiology, which includes anaesthesia, perioperative care, intensive-care medicine, pain management and emergency medicine, has the opportunity to influence and to play a key role in improving safety and quality of patient care. Increasing numbers of older and sicker patients, more complex surgical interventions, more pressure on throughput, new drugs and devices and simple chance all pose hazards in the practice of anaesthesiologists. As interventional possibilities widen and become more powerful, thus introducing greater complexity into the healthcare process, the potential for harm increases. Physicians skilled in perioperative medicine will be increasingly called upon to assess and manage surgical patients with high medical risks, comorbidities and perioperative complications. Quality of care and patient outcomes will be enhanced if evidence-based recommendations for medical care of surgical patients are consistently implemented using systematic quality-improvement approaches.

Understanding perioperative pathophysiology and implementing care regimes to reduce the stress associated with surgery will continue to accelerate rehabilitation and be associated with decreased hospitalisation times and increased patient safety and satisfaction after hospital discharge. Developments and improvements of multimodal interventions within the context of "fast-track" surgery programmes represent major challenges for the medical professionals working to achieve a "pain- and risk-free" perioperative environment. A multidisciplinary, physician-instigated research agenda is needed to tackle the many unresolved issues in perioperative medicine. The mission is to improve patient outcomes by promoting education, research and collaboration among hospitalists and all professionals who participate in the care of the perioperative patient. Education plays a key role in improving patient safety and developing, disseminating and delivering patient-safety training. All institutions providing perioperative anaesthesiological care to patients should comply with the minimum standard of monitoring recommended by the EBA both in the operating theatre and recovery areas and should implement protocols and support the WHO checklist [60, 61]. The question we must ask ourselves is: Are we training the new generation of anaesthesiologists to be perioperative physicians and to be professionals? Perioperative care represents a very challenging field; high standards of care, patient satisfaction and monitoring cost of care represent real critical points for the physician and his or her patients, their relatives and the community at large. We are confident that the community will accept the challenge of promoting the best health system services available. We sincerely believe the mission of optimising perioperative medicine is entirely achievable.

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Neuraxial Analgesia for Caesarean and Vaginal Delivery and Childhood Learning Disabilities[1]

23

J. Sprung, R. Flick and D. Warner

23.1 Introduction

The short- and long-term effects of obstetric anaesthetic techniques on behaviour and development of the neonate, infant and child have been of long-standing interest. It is clear that these techniques may at least transiently affect some aspects of newborn behaviour [1–7]. However, the impact of obstetric analgesia and anaesthesia on long-term outcomes in the absence of concurrent events such as foetal asphyxia is not known. Studies evaluating the association between perinatal and environmental characteristics and childhood behavioural outcomes have suggested that operative or instrumented deliveries per se are not linked to childhood behavioural disorders or abnormalities in cognitive, verbal or reading functioning [8–12], but these studies do not specifically evaluate the impact of anaesthesia and analgesia.

In the peripartum period, children may be exposed to anaesthetic and analgesic drugs that are administered to the mother. Exposure of foetal or neonatal animals to anaesthetics can cause histopathological changes in their brains, even following single, relatively brief, administration [13–19]. These changes may be associated with a diminished capacity to retain learned behaviour [20]. However, the significance of these findings to humans is not clear. We recently showed that repeated, but not single, exposure to anaesthesia prior to the age of 4 years is associated with an increased incidence of learning disabilities (LD) [21]. Although the lack of effect of a single anaesthetic exposure on the incidence of LD in infants and young children is reassuring [21], it is still possible that even brief anaesthetic exposure in the perinatal period might have neurotoxic effects [22]. Using the same population-based birth cohort described in our previous report [21], we sought to determine whether an association exists between foetal exposure to anaesthesia during Caesarean delivery (CD) and the subsequent development of LD in a birth cohort of children.

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APICE 23. Antonino Gullo (Ed.)

Table 23.1 Effects of mode of delivery and anaesthetic exposure on risk for developing learning disabilities among children in the 1976–1982 Rochester, Minnesota, Birth Cohort[a]

	Unadjusted			Adjusted		
	HR	95% CI	P value	HR	95% CI	P value
Type of delivery			0.135			0.050
Vaginal	1.00			1.00		
CD (general anaesthetic)	0.97	0.68–1.37		0.88	0.59–1.31	
CD (regional anaesthetic)	0.73	0.53–0.99		0.64	0.44–0.92	
Gestational age						0.314
≥ 37 weeks				1.00		
32–36 weeks				0.86	0.62–1.20	
≤ 31 weeks				0.50	0.18–1.39	
Birth weight (g)						0.269
≥ 2,500				1.00		
< 2,500				1.24	0.85–1.81	
Gender						<0.001
Female				1.00		
Male				1.66	1.44–1.93	
Anaesthesia exposure < 4 years[b]						0.008
0				1.00		
1				1.04	0.82–1.34	
≥2				1.80	1.25–2.61	
Mother's education						<0.001
Any college education				1.00		
High school graduate				1.64	1.41–1.91	
Some high school				3.09	2.46–3.89	

[a]Analyses were performed using proportional hazards regression, with findings presented as hazard ratio (HR) and corresponding 95% confidence interval (CI)

[b]Number of exposures to anaesthesia under the age of 4 years (excluding exposure during labour and delivery)

The educational and medical records of all children born to mothers residing in five townships of Olmsted County, MN, USA, from 1976 to 1982 were reviewed to identify those with LDs. Of the 5,320 children in this cohort, 497 were delivered via CD (with general anaesthesia N = 193; with regional anaesthesia N = 304). LD incidence depended on delivery mode ($p = 0.050$; adjusted for sex, birth weight, gestational age, exposure to anaesthesia prior to age 4 and maternal education). LD risk was similar in children delivered vaginally or by CD with general anaesthesia but was reduced in children born by CD with regional anaesthesia [hazard ratio (HR) 0.64, 95% confidence interval (CI) 0.44–0.92; $p = 0.017$ for comparison of CD under regional anaesthesia compared with vaginal delivery]. Unadjusted and adjusted analyses are shown in Table 23.1. Children exposed to general or regional anaesthesia for CD are no more likely to develop LD compared with children delivered vaginally, regardless of the use of neuraxial blocks in 32% of mothers who delivered vaginally. An unexpected finding was evidence suggesting that the adjusted risk of LD was lower in children delivered by CD under regional anaesthesia compared with children delivered vaginally.

The potential long-term effects of anaesthesia on immature central nervous system structure and function have attracted considerable recent interest based on in vitro and animal data showing that these drugs can cause apoptosis and other degenerative changes when applied to the young brain [13–19]. We recently published the first evidence that repeated, but not single, exposure to anaesthesia and surgery in children (prior to age 4) is associated with an increased risk of LD [21].

It is clear that the newborn may be at least transiently affected by anaesthetics and analgesics administered during labour and delivery [3, 23–25]. In contrast to these short-term effects, there are few studies attempting to assess the effect of mode of delivery on long-term child neurodevelopment. The Collaborative Perinatal Project [8] found that school achievement of 26,760 children, measured by standardised test of intelligence, did not differ between children delivered vaginally or by CD; however this study did not examine the method used to provide anaesthesia and used standardised rather than individually administered tests of achievement. McGee et al. [9] compared “normal spontaneous delivery” vs. “other than normal spontaneous delivery” (rotation/CD/forceps, etc.) and found no effect on behavioural maturation at age 7 as defined by standardised test of intelligence and other behavioural domains. McBride et al. [11] found no deleterious effect of delivery mode (various types of forceps delivery vs. elective CD vs. spontaneous delivery) on developmental outcomes in children at age 5 years (compared by standardised IQ tests). Pasamanick et al. [10] found no difference in behavioural disorders between children delivered by “serious operative procedures” (CD, forceps, breech extraction, internal version and extraction) compared with children delivered vaginally, although there were only a few CDs in this study [10]. In all these studies, the type of anaesthesia used for CD was not reported.

There are very few animal studies that could provide insight into potential effects of obstetric anaesthesia and analgesia on neonatal outcome. Rizzi et al. [19] found that 4 h of maternal exposure to isoflurane caused neuroapoptosis of the foetal guinea pig brain; however, this is a much longer exposure than during typical CD. Therefore, this may not be an applicable model to a term human foetus. Golub et al. [26] examined the role of epidural anaesthesia administered to primates on long-term infant behaviour. Monkeys at term received either epidural bupivacaine or saline during induced vaginal delivery. At 1 year, infant monkeys born of mothers receiving bupivacaine did not exhibit abnormali-

ties or specific cognitive deficits in learning, memory or attention, although some earlier phases of behavioural development were affected [26]. Again, this study likely has limited applicability to our findings other than suggesting a lack of deleterious long-term effects attributable to absorbed bupivacaine on the term foetus.

The fact that CD in our study was not associated with an increased risk of LD is consistent with these prior findings and is reassuring regarding any concern that the brief exposure to general anaesthesia during CD could adversely affect learning. This lack of adverse effect occurred despite several potential risk factors present in the CD deliveries with general anaesthesia, including an increased frequency of prematurity and emergent delivery. What was not expected was the apparent decrease in risk associated with regional anaesthesia for CD, which persisted after adjustment for known risk factors for LD.

Given the lack of relevant animal data to suggest a potential mechanism, we can only speculate. One potential factor that could be relevant is the stress response to labour and delivery. The perinatal period is critical to subsequent behavioural development, and stress responses during that period play a significant factor in developmental outcomes [27]. Perinatal stress has been associated with synaptic loss resulting in learning abnormalities in animals [28] and maladaptive responses in humans and animals [27, 29–34]. Labour and vaginal delivery in humans is associated with a significant increase in the levels of stress hormones such as epinephrine, norepinephrine and cortisol [30]. Evidence is accumulating that exposure of the developing human brain to stress can produce lasting organisational changes that can lead to a variety of abnormal behaviours in later life (hyperactivity, hyperreactivity, decreased cognition, etc.) [27]. For example, an increased frequency of attention deficit hyperactivity disorder has been linked to the presence of peripartum stressors [35]. Anaesthesia and analgesia during labour and delivery may reduce the level of stress. CD performed under epidural anaesthesia decreases stress hormone levels in both the mother and foetus compared with vaginal delivery (both with and without labour epidural analgesia) [30, 36] and significantly decreases these levels compared with elective CD performed under general anaesthesia [37]. It is not known whether the stress response accompanying vaginal delivery and CD with general anaesthesia is of sufficient intensity and duration to affect subsequent neurodegeneration. If so, CD with regional anaesthesia could inhibit the stress response sufficiently to potentially affect long-term outcome. We emphasise that this speculation depends on several assumptions, and this result should be regarded as generating hypotheses that can be tested in future studies.

23.2 Conclusions

Children exposed to general or regional anaesthesia during CD are not more likely to develop LD compared with children delivered vaginally, suggesting that brief perinatal exposure to anaesthetic drugs does not adversely affect long-term neurodevelopmental outcomes. Rather, the risk of LD appears to be lower in children delivered by CD whose mothers received regional anaesthesia. Our results can only be viewed as hypothesis-generating and needs to be confirmed (or refuted), especially considering the possibility that undergoing CD with regional analgesia is simply a marker for unidentified confounders that may explain the differential risk for LD between groups. We propose the hypothesis

Table 18.2 Association between neuraxial labour analgesia for vaginal delivery and development of learning disabilities

Model	Hazard ratio	95% confidence interval	P value
Unadjusted	1.19	1.03 – 1.37	0.02
Adjusted[a]	1.15	0.98 – 1.35	0.08
Adjusted[b]	1.05	0.85 – 1.31	0.63

Three models were fit: (1) unadjusted; (2)[a] adjusted for covariates known to be associated with learning disabilities [gestational age (≤31 weeks, 32–36 weeks, ≥37 weeks), sex (male, female), birth weight (<2,500 g, ≥2,500 g), maternal education (some high school, high school graduate, any college), 5-min APGAR score, and number of anaesthesia exposures before the age of 4 years (0, 1, 2 or more)]; (3)[b] adjusted for all covariates listed in (2) as well as additional peripartum maternal and child variables (maternal age, use of forceps or vacuum extraction, foetal presentation, dystocia, prolonged labour, birth trauma, use of opioids, any inhalational anaesthetics and/or supplemental regional blocks during delivery, labour induction, postdelivery resuscitation or neonatal intensive care unit admission following delivery)

that regional anaesthesia for CD attenuates the neonatal stress response to vaginal delivery, which in turn has significant effects on later neural development.

The role of stress attenuation on LD pathogenesis was tested in a subsequent study[38]. We tested the hypothesis that stress attenuation with neuraxial analgesia during vaginal delivery may reduce LD rate in children compared with those whose mothers delivered vaginally but without analgesia. This study demonstrated that the use of neuraxial labour analgesia during labour and vaginal delivery was not an independent risk factor for subsequent development of childhood LD [in a fully adjusted model (Table 23.2), proportional hazards regression analysis, HR 1.05, 95% CI 0.85–1.31; p = 0.63]. Several factors could explain the lack of effect of neuraxial analgesia on LD incidence. Although neuraxial analgesia can attenuate some measures of maternal stress responses [30, 39], its effects on neonatal stress responses are less clear. Furthermore, neuraxial block for labour is typically established after the onset of labour. Therefore, significant stress could have already been present by the time of block initiation. The effects of epidural labour analgesia on neonatal cortisol levels is not well studied, with one small study finding no effect [30] and another larger study finding a decrease in cortisol levels [40]. We have no data regarding the quality of analgesia achieved by the neuraxial analgesia, and other analgesics were used in both groups. In addition, neuraxial analgesia does not prevent psychological stress associated with delivery, which may play a significant role in elevating stress hormones regardless of the level of pain control [41]. Thus, it is possible that there was little or no difference in the stress experienced by neonates in the two groups. Also, it is possible that the high frequency of assisted deliveries in the neuraxial group may have increased foetal stress [30, 40, 42], counterbalancing any beneficial stress-reducing effects of neuraxial analgesia that the mother might experience. Finally, it is possible that short but extreme neonatal stress during delivery plays no role in the development of LD and cannot explain our prior result observed with neuraxial anaesthesia during CD [43]. Future studies are needed to evalu-

ate potential mechanisms/explanation of our previous findings that the incidence of LD is lower in children born by CD under neuraxial anaesthesia compared with vaginal delivery.

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Off-label Drugs in Perioperative Medicine: Clonidine

24

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24.1 Introduction

Alpha-2 agonists produce diverse responses, including analgesia, anxiolysis, sedation–hypnosis and sympatholysis [1, 2]. Clonidine represents a valuable, and arguably still underexploited, resource in patient management, especially during the perioperative period. Clonidine has been widely used for >35 years to treat hypertension, and off-label for a variety of purposes, including withdrawal from long-term abuse of drugs or alcohol [1–5], as well as to reduce perioperative stress in patients who are at risk of perioperative ischaemia and are in chronic pain therapy [6].

24.2 Pharmacokinetics and Pharmacodynamics of Alpha-2 and Imidazoline Receptor Agonists and Effects on Different Organ Systems

Activation of alpha-2-receptors, which are G-protein-coupled receptors [7], results in reduced norepinephrine release, thus inducing sympatholysis [1]. Adrenergic receptors are classified as alpha-1, alpha-2, beta-1 or beta-2 and subsequently are further divided in three major subtypes: alpha-2a, 2b and 2c [8–10]. Alpha-2-receptors are widely distributed and are located presynaptically, postsynaptically and extrasynaptically, with the highest concentrations in the locus coeruleus, a modulator of wakefulness [11], and in the intermediolateral cell column and substantia gelatinosa of the spinal cord that are involved in pain modulation [12]. Alpha-2-adrenoceptors are also found on primary afferent terminals of peripheral nerve endings [13].

Clonidine has an imidazole ring in its structure and therefore interacts with the imidazoline receptor [2]. It has an alpha-2 to alpha-1 selectivity ratio of 200:1 and alpha-2 to imidazoline selectivity of 16:1 [14]. It is dependent on dose, administration route and the dosing regimen. The optimal dose remains unknown due to the variability of the haemodynamic response to different doses, rates and routes of administration and because many

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pharmacokinetic and pharmacodynamic studies have been performed in healthy volunteers [2]. The effects of clonidine may be different in the aged population, in high-risk patients and in patients treated with other drugs (additive or synergistic effect). Clonidine withdrawal may precipitate hypertensive crises after long-lasting continuous intravenous infusion. As a consequence, patients should be weaned off clonidine gradually. Clonidine has an elimination half-life of 8 h, and its redistribution half-life is 10 min. After oral administration, peak plasma concentration is reached in 1–2 h and duration of action lasts 6–12 h [15]. Due to its high lipid solubility, diffusion and redistribution in the central nervous system occur rapidly [16]. Activation of alpha-2a receptors leads to sedation and analgesia, whereas activation of alpha-2b receptors leads to haemodynamic effects [2, 8].

In the cardiovascular system, lower doses induce sympatholysis by blocking the sympathetic arm of the autonomic nervous system, which is mediated by the alpha-2a adrenoreceptor subtype [10]. Clonidine mainly decreases heart rate by increasing vagal tone [1, 17], inhibiting the cardioaccelerator nerve [18]. At higher doses, its hypertensive action dominates via activation of alpha-2b adrenoceptors due to alpha-2-mediated vasoconstriction and presynaptic inhibition of norepinephrine release [19], causing decreased cardiac output. When rapid intravenous administration is given before the onset of central alpha-2-adrenoceptor-mediated sympatholysis (leading to reduced systemic blood pressure), short-lasting hypertension may occur, which is mediated via peripheral alpha-2b adrenoceptor subtype. In the central nervous system alpha-2 agonists produce their sedative–hypnotic effect by acting on alpha-2a receptors in the locus coeruleus and produce their analgesic effect by acting on alpha-2a receptors within the locus coeruleus and spinal cord [2, 20].

Drugs such as clonidine acting via alpha-2c adrenoreceptors may also have therapeutic value in disorders associated with enhanced startle responses and sensorimotor gating deficits, such as posttraumatic stress disorder, and drug withdrawal states [1, 16]. Although clonidine has little effect on intracranial pressure, when administered as an intravenous infusion, it may induce a critical but transient increased intracranial pressure in some severe head-injury patients [21, 22]. This effect may result from cerebral autoregulatory vasodilatation and increased cerebral blood volume as a response to its hypotensive effects. In addition, direct activation of cerebral alpha2b receptors may result in cerebral vasoconstriction, which – combined with a reduction in mean arterial pressure – may reduce cerebral perfusion [23, 24]. However, there may be some outcome advantages in using clonidine under certain highly controlled circumstances [24, 25].

In the respiratory system, clonidine was demonstrated in pigs to relax the airway, even in the hyperreactive state [26]. In healthy human volunteers, it caused minimal minute ventilation depression and had no effect on hypercapnic and hypoxic ventilatory drive [27–29]. A lack of respiratory effect was seen when clonidine was used alone in healthy volunteers at the dosage of 4 $mcg^{-1}kg^{-1}h^{-1}$ [28]. Respiratory rate and oxygen saturation did not change compared with the placebo group. However, Ooi et al. suggested that clonidine had a respiratory depressant effect in adult volunteers, as it was found that ventilatory response to carbon dioxide was significantly attenuated [27]. Although the combination of an opioid and an alpha-2-adrenergic agonist may act synergistically for the analgesic response, there are conflicting results regarding this drug combination on respiratory depression [29, 30]. Koppert et al. found that coadministration of remifentanil (0.1 $mcg/kg^{-1}min^{-1}$ over 30 min) and clonidine 2 mcg/kg^{-1} for 5 min led to significantly decreased oxygen saturations, especially during the time of remifentanil infusion [30]. In the kidney,

alpha-2-adrenoceptor agonists promotes diuresis, increases the release of atrial natriuretic factor and decreases secretion of rennin and vasopressin [31]. Clonidine clinically insignificantly inhibits insulin release and decreases salivary and gastric secretions [32, 33]. It also produces mydriasis and decreases intraocular pressure [34]. Clonidine also has immunomodulating properties [35]. Clonidine is available for oral, transdermal, intramuscular, epidural and IV administration (outside the United States) [36].

24.3 Effects on Sedation

Through their action on the locus coeruleus, which is a wakefulness-promoting noradrenergic nucleus with one of the highest concentrations of alpha-2 receptors, alpha-2-adrenoceptor agonists induce rapidly reversible sedation while partially preserving cognitive brain function. Sedation-associated alpha-2 agonists seems to act through the endogenous sleep-promoting pathways [1, 11, 12]. Bonhomme et al., in a observational study, found that electroencephalogram (EEG) patterns and decreased regional cerebral blood flow of specific brain regions observed during clonidine-induced sedation are similar to those of early-stage non-rapid-eye-movement (REM) sleep [37]. Hall et al. evaluated the sedative, analgesic and cognitive effects of clonidine infusions in humans in a placebo-controlled, randomised study performed on separate days [28]. They evaluated the dose–response relationship for 1-h infusions of clonidine 1, 2 and 4 mcg/kg^{-1} h^{-1} in eight healthy volunteers aged 22–30 years. Clonidine infusions resulted in significant and progressive sedation, but all study participants were easily awoken to perform tests and evaluations. Statistically significant analgesia, memory impairment and reduced performance on the digit symbol substitution test occurred during 4 mcg/kg^{-1} h^{-1} infusions. There were no statistically significant changes in cardiorespiratory variables throughout the study.

In the clinical setting, clonidine is an efficient means of controling anxiety during conscious sedation, suggesting that preoperative clonidine administration could be a useful supplement to intravenous sedation for nonsurgical procedures [38–41]. Nascimento et al. performed a randomised, controlled, double-blind, prospective clinical study in 62 patients submitted to an elective cineangiocardiography [39]. The patients were divided in two groups: the clonidine group received 0.8 mcg/kg^{-1}, whereas the control group received a 0.9% saline solution. Parameters and sedation score were analysed every 5 min and at four different intervals. The clonidine group presented better mean arterial pressure and heart-rate stability and sedation efficacy, whereas the control group presented a significantly higher meperidine intake. Hall et al. found that orally administered clonidine pretreatment increased and prolonged sedation and amnesia and stabilised vital signs while significantly decreasing diazepam and postoperative analgesic usage [40]. Vital parameters remained unchanged. In another study, intravenously administered clonidine 0.5 mcg/kg^{-1} significantly increased the sedative effect of benzodiazepine [41].

Enhanced noradrenergic activity is also a major factor in the pathophysiology of stress-induced mental disorders. Clonidine could play a useful role in treating sleep disturbance and hyperarousal in posttraumatic stress disorder, with minimal adverse effects and low financial cost [42, 43].

24.4 Clonidine in the Treatment of Acute and Chronic Pain

The antinociceptive effect of alpha-2-adrenoceptor (alpha-2a) agonists is mediated by activation of descending inhibiting noradrenergic systems, which modulates wide-dynamic-range neurones. Furthermore, they inhibit the liberation of substance P and endorphins and activate serotoninergic neurones [2, 13, 20]. Mu-opioid receptors, which coexist with alpha-2 adrenoceptors in the spinal cord, may act in synergy with alpha-2-adrenoceptor agonists [2, 36, 44–46]. In a double-blind, placebo-controlled study, Tamsen et al. found that intravenously administered clonidine (200 mcg) matched the analgesic effect of meperidine (50 mg) in postoperative pain, as assessed by the time interval between drug administration and subsequent dosing [47]. In another study, during the postoperative period after spinal fusion, patients blindly received either clonidine (5 mcg/kg^{-1} infused the first hour and then 0.3 mcg^{-1} kg^{-1} h^{-1} during 11 h or a placebo. Clonidine IV reduced total morphine requirements, delayed pain onset and decreased pain scores compared with placebo [48]. Clonidine significantly reduces morphine delivered mainly during the first 12 h [49, 50]. Marinangeli et al., in a double-blind, randomised study, evaluated the optimal intravenous dose of clonidine and found that when sedation and analgesic effect of clonidine is required, 3 mcg/kg^{-1} bolus dose followed by a continuous infusion of 0.3/mcg kg^{-1} per hour should be considered the optimal dose [51].

As is well known, hyperalgesia is a common adverse effects after using powerful short-acting opioids [52]. Koppert et al., in an experimental study on healthy volunteers, investigated the time course of analgesic and hyperalgesic effects of the mu-receptor agonist remifentanil alone or in combination with the N-methyl-D-aspartate-receptor antagonist S-ketamine or clonidine [30]. Opioid-induced postinfusion hyperalgesia was abolished by S-ketamine. In contrast, elevated pain ratings after infusion were not reduced by ketamine but were alleviated by the alpha-2-receptor agonist clonidine. Clonidine has also been used for managing opioid withdrawal [53]. In health, the nervous system exists in a balance between inhibitory and excitatory influences. This balance may be upset if neural tissue is damaged or irritated and may give rise to neuropathic pain. Such neuropathic pain does not respond consistently to opioid analgesics or non-steroidal anti-inflammatory drugs, and it may therefore be necessary to utilise other therapeutic agents (i.e. tricyclic antidepressants and anticonvulsant drugs) with known activity on either the excitatory or inhibitory components of the pain pathway. The neuropathic pain is mediated by low-threshold mechanoreceptors, sympathetically dependent, and sensitive to both alpha-2-agonists and N-methyl-D-aspartate antagonists. As a consequence, clonidine may also have a potential role in treating neuropathic pain [54, 55]. Studies in animals and patients have shown that transdermal, epidural and intravenous administration of the alpha-2-adrenoceptor agonist clonidine reduces pain intensity in neuropathic pain syndromes for periods varying from some hours to 1 month [56, 57]. Despite clonidine's use for treating neuropathic, neuralgic and deafferentiating pain, a large meta-analysis found that the beneficial effects of systematically administered clonidine were expected only in pain states with increased sympathetic nervous system activity (e.g. hyperalgesia caused by sympathetically maintained pain was relieved by transdermal application of clonidine) [58]. Based on this evaluation, a grade C recommendation was given. Clonidine was also used to avoid the development

of complex regional pain syndrome. Frade et al. found that parecoxib (5 mg) administered IV combined 1 mg/kg^{-1} lidocaine + 30 mcg clonidine once a week for 3 weeks was an effective locoregional intravenous block [59].

24.5 Clonidine in Neuraxial Blocks, Locoregional and Intra-articular Anaesthesia

The spinal cord is a site of significant alpha-2-adrenoceptor-agonist activity [60, 61]. Clonidine has been administered in neuraxial blocks to improve analgesia by increasing the duration of sensory and motor block and to decrease complications associated with a high dose of a single drug. A recent systematic review of data from 22 randomised trials (1,445 patients) testing a large variety of doses of clonidine added to intrathecal bupivacaine, mepivacaine, prilocaine or tetracaine found that clonidine 15–150 mcg prolonged in a linear, dose-dependent manner the time to two-segment regression (range of means, 14–75 min) and the time to regression to L2 (range of means, 11–128 min) [62]. The time to first analgesic request (median 101 min, range 35–310) and of motor block was prolonged, and there were fewer episodes of intraoperative pain with clonidine, without evidence of dose responsiveness. Time to achieve complete sensory or motor block and extent of cephalic spread remained unchanged. The risk of bradycardia was unchanged. The optimal dose of clonidine, however, remained unknown. Although neuraxial clonidine prolongs anaesthesia, it can cause hypotension and bradycardia [60, 62], and although it prolongs analgesia in central neuraxial blocks, its use in peripheral nerve blocks remains controversial. A systematic, qualitative review of double-blind, randomised, controlled trials (27 studies from July 1991 to October 2006 of 1,385 patients) found that 15 studies supported the use of clonidine as an adjunct to peripheral nerve blocks, whereas 12 studies failed to show any benefit. The authors concluded that clonidine improves analgesia and anaesthesia duration when used as an adjunct to intermediate-acting local anaesthetics for some peripheral nerve blocks. Evidence is lacking for the use of clonidine as an adjunct to local anaesthetics for continuous catheter techniques [63]. Axillary block or regional anaesthesia with clonidine IV for Dupuytren's surgery offered a significant advantage for decreasing the incidence of complex regional pain syndrome compared with either locoregional intravenous block with lidocaine alone or general anaesthesia [64]. Partial sciatic nerve ligation produces axonal damage, a local inflammatory response, and wallerian degeneration. Romero-Sandoval et al. tested the hypothesis that clonidine would have a similar effect in established nerve injury [65]. Their results suggest that perineural clonidine acts on alpha-2-adrenoceptors to reduce hypersensitivity in established nerve injury, most likely by an immunomodulatory mechanism, and may be effective in patients in the weeks after nerve injury. Side effects of clonidine may also be found with regional analgesia [66]. Intra-articular administration of clonidine in arthroscopic knee surgery has also been described with contradictory results [67, 68].

24.6 Clonidine as Preanaesthetic Drug and Intraoperative Anaesthetic/Analgesic-sparing Effect

Substantial reductions in the need for various anaesthetics while providing haemodynamic stability have been demonstrated with clonidine administration [69–79]. Clonidine has also been used as a preanaesthetic because of its anxiolytic properties without having respiratory depressant activity and therefore may be potentially useful during that period [15, 80–89]. Premedication with clonidine reduced the requirement for volatile agents during general anaesthesia [84], whereas clonidine 2.5 and 5.0 mcg/kg^{-1} given orally as premedication decreases the propofol concentration required for loss of consciousness [85]. However, 5 mcg/kg^{-1} clonidine orally was associated with prolonged recovery from propofol/fentanyl anaesthesia [86, 87].

After oral premedication with either clonidine 3 mcg/kg^{-1} or placebo in patients undergoing vascular surgery, Morris et al. found that clonidine reduced the requirement for propofol, which is a pharmacokinetic effect and not a pharmacodynamic central sedative effect [88]. However, the authors did not measure cardiac output or hepatic blood flow. Interestingly, Ghosh et al. found that clonidine treatment groups demonstrated reduced heart rate and mean arterial pressure [89]. Therefore, it is possible that the reduced cardiac output of these patients resulted in altered propofol disposition so that slower infusion rates were required to achieve the same blood concentrations. Ghignone et al., in a double-blind study in patients undergoing aortocoronary bypass surgery, found a 45% reduction in fentanyl requirement after pretreatment with clonidine orally (5 mcg/kg^{-1}), morphine intramuscularly (0.15 mg/kg^{-1}) and lorazepam orally (0.003 mg/kg^{-1}) [73]. Flacke et al. determined that patients given clonidine pre- and intraoperatively required 40% less sufentanil during coronary artery bypass graft surgery, as determined by strict haemodynamic criteria [77]. Fehr et al. found that clonidine administration (4 mcg/kg^{-1}) after anaesthesia induction resulted in a significant decrease in the bispectral index value with a contemporary significant reduction of propofol target concentration [76].

24.7 Preventing Perioperative Haemodynamic Stress Response

Surgical trauma results in diffuse sympathoadrenal activation, which is thought to contribute to perioperative cardiovascular complications in high-risk patients. Induction of anaesthesia, tracheal intubation, surgical incision and surgery under regional anaesthesia and mergence from anaesthesia are associated with dramatically increased sympathetic activity. Alpha-2-adrenoceptor agonists at appropriate doses reliably control heart rate and blood pressure in patients undergoing surgery [3, 4, 69, 75, 78, 81, 90–101], including neurosurgery [24, 70, 81, 93, 102–104]. Wijeysundera et al. found that in cardiac patients, treatment with an alpha-2 agonist reduced the risk of myocardial ischaemia [0.71, 95% confidence interval (CI) 0.54–0.92; $p < 0.01$) [5]. In a systematic review, Nishina et al. found that clonidine reduced the incidence of myocardial ischaemia in patients undergoing cardiac and noncardiac surgery [96]. Those results were confirmed by Stevens et al. in

another quantitative systematic review [97]. Wallace et al. [98] conducted a prospective, randomised, controlled trial in which they studied 190 patients with or at risk for coronary artery disease comparing clonidine or placebo. The incidence of perioperative myocardial ischaemia was significantly reduced with clonidine. In addition, clonidine reduced the incidence of postoperative mortality for up to 2 years. However, these patients were disproportionately present in the placebo group, and the mortality difference was thus considered to be due to the presence of a subset of high-risk patients in the placebo group [4].

24.8 Other Clinical Uses of Clonidine

Other postoperative benefits offered by alpha-2 agonists and clonidine include prevention of shivering as well as the use as premedication drugs in patients with obstructive sleep apnoea syndrome [42, 87, 105–107].

24.9 Conclusions

Clonidine has several clinically beneficial properties, including:

1. sympatholysis, anxiolysis and sedative effect;
2. maintaining haemodynamic stability;
3. opioid- and anaesthetic-sparing effects.

The lack of widespread use of clonidine by anaesthesiologists probably reflects [108, 109]:

1. off-label use;
2. absence of an intravenous form of the drug in the United States and lack of precise intravenous dose–effect relationship in different fields of application;
3. possible systemic side effects, especially in patients at risk for bradycardia or atrioventricular nodal block, or with severe head trauma with high intracranial pressure.

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Part X
Spinal Cord Stimulation

Cost Effectiveness of Spinal Cord Stimulation in the Management of Severe Angina

25

M. Börjesson, C. Mannheimer

25.1 Refractory Angina Pectoris

The majority of patients with angina pectoris often experience satisfactory pain relief through pharmacological treatment and/or surgery. Conventional medical management includes short-acting nitrates, beta-blockers, anticoagulants, angiotensin-converting enzyme inhibitors, long-acting nitrates, calcium-channel blockers and aspirin, whereas surgery includes coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI). However, there is a group of patients that continues to suffer from lasting and severe and disabling angina pectoris despite optimum drug treatment and who are not suitable candidates for surgery. This condition has been defined as refractory angina pectoris [1].

Patients with refractory angina generally have poor quality of life due to inadequate symptom relief, frequent hospitalisations, and limited physical activity with negative consequences for their quality of life. Due to the challenging pain problem, refractory angina is clinically important not only for the cardiologist, but also for other specialists, such as those in acute medicine, anesthesiology, and pain treatment [1].

Additional treatment modalities for severe angina pectoris, including refractory angina, are therefore needed. Only a few of the additional treatment modalities, which include transcutaneous electrical nerve stimulation (TENS), spinal cord stimulation (SCS), endoscopic thoracoscopic sympathectomy (ETS), thoracic epidural anesthesia (TEDA), transmyocardial and percutaneous myocardial laser revascularisation (TMR and PMR), stem cell therapy, and enhanced external counterpulsation (EECP), available for refractory angina, have been extensively analysed in high-quality studies [1].

Based on available data, SCS is considered by the European Society of Cardiology (ESC) as the first-line treatment, with a level A recommendation, for refractory angina [1]. The American Heart Association (AHA)/American College of Cardiology (ACC) updated guidelines on managing patients with chronic stable angina pectoris gives SCS a level B recommendation, based on grade IIb evidence [2].

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25.1.1 SCS in Angina Pectoris

SCS and TENS have been developed directly on the basis of experimental animal findings and are theoretically based on the gate-control theory [3] and its general principles of segmental pain inhibition. The first spinal cord stimulator was implanted in 1967 [4], and toward the end of the 1970s, the method was tried in patients with severe peripheral arterial circulatory insufficiency of the lower extremities, with favourable effects, both on peripheral arterial circulation and pain [5]. Subsequently, TENS was also tried in patients with refractory angina pectoris with good clinical results [6–8]. As 10–15% of patients developed troublesome skin irritation after a period of TENS use, treatment with implanted spinal cord stimulators was introduced for patients with severe angina pectoris in the late 1980s [9, 10].

Local anaesthesia is used during SCS implantation. Via an incision at the T 6–8 level, an electrode is inserted into the epidural space and guided via X-ray monitoring up to the T 1–2 vertebrae level. Its location is adjusted until the patient experiences paraesthesia within the area of the individual anginal pain localisation. An extension wire is then tunnelled subcutaneously via an incision to the left flank, where it is connected to a subcutaneous pulse generator below the left costal arch. The stimulation intensity is then fine-tuned postoperatively. The patient can regulate the strength of the actual stimulation using a remote control [5].

25.1.2 SCS Efficacy in Refractory Angina Pectoris

In recent years, a systematic review [11] and a meta-analysis [12] on the efficacy of SCS in severe angina pectoris have been published. The systematic literature research, 1966–2003, carried out as part of the Swedish Board of Health and Welfare (SBU), report on long-standing pain and an additional research covering the years 2003–2007 was performed by Börjesson et al. [11]. Acute studies, case reports, mechanistic studies and reviews were excluded, and the remaining 44 studies were graded for quality according to a modified Jadad score. The eight medium- to high-score studies formed the basis for conclusions regarding scientific evidence (strong, moderately strong, or limited) for SCS efficacy. The authors found strong evidence that SCS gives rise to symptomatic benefits (decrease in anginal attacks) and improved quality of life in patients with severe angina pectoris [11]. There is also strong evidence that SCS can improve the functional status of these patients, as illustrated by improved exercise time on treadmill or longer walking distance without anginal pain. In addition, there was limited scientific evidence, saying that SCS have no negative effects on mortality, and that the complication rate was low [11].

The systematic review and meta-analysis of the same studies by Taylor et al. [12], published the same year, concluded that SCS appears to be an effective and safe treatment option for managing refractory angina pectoris patients. In addition, SCS was found to be of similar efficacy and safety to the treatment alternative of PMR. The authors concluded that the results of the meta-analysis supports the current treatment recommendations (AHA/

ACC) regarding SCS in severe angina pectoris and also supports a more widespread use of SCS for managing refractory angina [12].

A third, and recent, UK review, of the SCS cost-effectiveness in, among other conditions, severe angina pectoris, was published in 2009 [13]. It concluded that for severe angina pectoris, SCS was more effective than PMR at 3 months but not at 12 months in increasing time to angina, whereas the effects on quality-of-life data were similar. Short-term follow-up suggests that SCS is more effective than no SCS/inactive device in symptom relief (delaying time to angina and reducing nitrate consumption).

25.1.3 SCS Cost-Effectiveness in Severe Angina Pectoris Patients

In addition to treatment efficacy, the widespread use of SCS for managing severe angina pectoris is dependent on favorable cost-effectiveness data. The first such study published was a retrospective analysis of efficacy and cost–benefit ratio, by Yu et al. in 2004 [14]. Eighteen months after SCS implantation, the effects on Canadian Cardiovascular Society (CCS) functional level and symptom relief were analysed (n = 24). In the year postimplantation, the duration of hospitalisation decreased significantly, and the total cost of the SCS implantation was recovered within 16 months after the procedure, which is well under the expected half-life of the device. The conclusion was that SCS treatment was effective in preventing hospitalisation and saving costs in hospital care [14].

The Electrical Stimulation versus Coronary Artery Bypass Surgery study (ESBY) in severe angina pectoris was a randomised, prospective study including patients with increased surgical risk and no prognostic benefit from revascularisation [15]. The main result was that SCS was equally effective compared to CABG in relieving symptoms of these heavily-symptomatic patients, at a lower complication rate, at 6 months. In a 2-year follow-up study, the cost-effectiveness of SCS was compared with CABG in these patients [16]. Costs of hospital care, morbidity, and causes of death after both treatments were assessed, together with SCS complications. The results showed that the patients randomised to SCS had fewer hospitalisation days, both related to the primary intervention (mean 5 days compared with 11 days; $p < 0.0001$) and due to cardiac events ($p < 0.05$) compared with patients randomised to CABG. When taking into account the cost of the primary intervention (SCS/CABG), hospital days, and follow-up treatments, as well as follow-up visits, the total cost was lower per patient with SCS compared to those with CABG (16,400 euros per patient vs. 18,800 euros per patient). Thus, SCS was a less expensive symptomatic treatment option than CABG for patients with severe angina pectoris ($p < 0.01$) [16].

In the SPiRiT trial, SCS was compared with PMR for patients with refractory angina pectoris in a randomised, controlled, single-center study (n = 68) and found to be equally effective and safe [17]. A clinical and cost-effectiveness analysis of the SPiRiT trial was published in 2008 [18] showing that the mean incremental cost per cost per quality-adjusted life-years (QALY) of using the SCS over 24 months was £46,000 (compared with the maximum acceptable of £30,000 per QALY, suggested by the National Institute for Clinical Excellence (NICE) [19]. Patients had a nonsignificant improvement in exercise and quality-of-life outcomes, but the costs of SCS were higher. The probability of SCS being cost effective compared with PMR in this study over a 2-year period was calculated to

be 30%. The authors concluded that more and longer studies are needed to select patients suitable for SCS, i.e., those who would benefit the most and therefore potentially make SCS more cost effective.

A comprehensive cost-effectiveness analysis of SCS for neuropathic and ischaemic pain, including severe angina pectoris, was recently performed by the School of Health and Related Research (ScHARR) in Sheffield, UK [13]. The authors reviewed studies on efficacy, listed all health care and costs of the procedure in a UK setting. In addition, they used a model for their economic evaluation based on a prospective observational study comparing the cost-effectiveness of CABG, PCI, or conventional medical management (CMM) [20]. Consecutive, unselected patients who had undergone coronary angiography in the UK were recruited. A subgroup of 1,740 of the original 4,121 patients followed up for 6 years were found suitable for CABG, PCI, or both, 70% having a CCS class of III-IV (severe angina). The model then explores the costs and benefits added through pain relief over a 6-year period. All costs (medication, SCS implantation, PCI, CABG, follow-up, side-effects) were added, and the health economic outcomes, cost per life-year gained (LYG), and cost per QALY gained were calculated for each treatment modality. The results of the study regarding SCS efficacy in patients with severe angina is summarised above [13]. Regarding the cost-effectiveness of SCS treatment, the authors' conclusions are limited by the low number of available studies on clinical effectiveness. However, the conclusions suggest that the most favourable economic profile for SCS treatment is when it is compared to CABG in patients clinically appropriate to receive PCI and/or CABG [13]. The threshold analysis suggests that the incremental cost-effectiveness ratio of SCS + CMM is likely to be better than £30,000 per QALY gained for additional survival benefits of 6–83 days, depending on the patient's suitability for different treatment modalities [13].

25.2 Conclusions

To summarise, the efficacy of SCS in managing severe angina has been shown in several recent reviews [11–13]. For SCS to be regarded as a routine treatment modality for severe angina pectoris, more and longer studies, especially on its long-term efficacy, are needed. Health-related quality-of-life measures using validated instruments could improve future cost-effectiveness analyses, which are also needed for SCS to be accepted as part of the routine management of severe angina pectoris.

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Part XI
Neurotrauma

Clinical Assessment and Diagnostic Procedures in Neurotrauma

26

M. Zanello, M. Vincenzi and M. Bandini

26.1 Introduction

Much has been learned over the past 20 years about traumatic brain injury (TBI). The surgical management of TBI has changed little during this period and continues to concentrate on early evacuation of significant space-occupying lesions. In contrast, there have been major changes in our approach to the critical care management of TBI during this period, and this is reflected in the progressive and significant reduction in severe TBI mortality from 50% to 10% over the last 30 years. This trend in reduced mortality and improved outcomes has, for the most part, been subsequent to the use of evidence-based critical care management protocols that emphasise assessment and monitoring [1].

The main reasons for clinical assessment and monitoring neurocritical and neurotrauma patients could be summarised as follows:

1. detect the severity of trauma and recognise early neurological worsening before irreversible brain damage occurs;
2. individualise patient care decisions;
3. guide patient management;
4. monitor therapeutic response of some interventions and avoid any consequent adverse effects;
5. assist clinicians to understand the pathophysiology of complex disorders;
6. design and implement management protocols;
7. improve neurological outcome and quality of life in survivors of severe brain injuries.

TBI remains a major cause of death, disability and economic costs to our society, with an estimated annual mean incidence between 180 and 245 per 100,000 population and >200 hospital admissions per 100,000 in Europe each year [2]. The mortality rate for deaths outside of the hospital is approximately 17 per 100,000 people; it is approximately 6 per 100,000 for hospitalized patients. Approximately 52,000 deaths per year in Europe result from TBI. TBI rates among men are approximately twice those of women, though death rates for males are 3.4 times as high as they are for females. Rates are highest among adolescents, young adults, and seniors, with a characteristic bimodal distribution. The av-

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erage cost per inpatient care associated with severe TBI in the most developed European countries is around 6,000 euro, with the costs due to initial hospitalisation being only a small part of total costs [3].

26.2 Clinical Assessment

One widely used scheme in head injury relating to pathophysiologic processes is that which differentiates primary from secondary injury. Primary injury refers to the unavoidable, immediate parenchyma damage occurring at the time of injury. The consequences of the initial mechanical injury include physical disruption of cell membranes and infrastructure and disturbance of ionic homeostasis secondary to increased membrane permeability. This, in turn, may lead to astrocytic and neuronal swelling, relative hypoperfusion, and a cascade of biochemical neurotoxic events. Mechanical lesions can consist either of focal injuries (scalp laceration and contusion, skull fracture, epidural haemorrhage, subdural haemorrhage, subarachnoid haemorrhage, brain contusion and laceration, intraparenchymal hemorrhaege, intraventricular hemorrhaege) or diffuse patterns of axonal injury. That pathoanatomic type of injury influences outcome has long been recognised, particularly once imaging of patients with neurotrauma became routine. Secondary injury refers to potentially avoidable damage that occurs to at-risk brain areas at variable times after injury as the consequence of further physiological insults, such as cerebral oedema, increased intracranial pressure (ICP) with its complications (i.e., transtentorial herniation, brain death), hypoxia, reperfusion, ischaemia due to vasospasm, vascular/brain compression, hypercarbia, hyponatraemia, hyperthermia, infection, and seizures. The term secondary injury has also been used to encompass the multitude of complex neurobiological cascades altered or initiated at a cellular level following primary injury. Trauma can trigger exceptionally complex changes in cellular physiology that may involve inflammatory pathways, lipid peroxidation, neurotransmitter changes, ionic fluxes, and accumulation of potentially neurotoxic proteins. The importance of these secondary insults has gained widespread recognition.

Among the numerous barriers to finding effective interventions to improve outcomes after TBI, the heterogeneity of the injury and identification and classification of patients most likely to benefit from the treatments are considered some of the most significant challenges. Many bedside physical assessment tools are available for use in the critical care setting to help differentiate the multiple types of TBI and variety of host factors and other confounders that might influence the clinical course. In addition, newer advances in neuroimaging, biomarkers, and neuromonitoring tools may increase the effectiveness of clinical evaluation, helping classify patients into groups most likely to benefit from specific treatments.

26.2.1 Severity and Early Prognostic Factors

A reliable outcome predictor on admission after TBI is of great clinical relevance to sup-

port early clinical decision making. A large body of evidence supports the relation between a number of early detectable factors and outcome after TBI, including Glasgow Coma Scale and single-component scores, age, pupillary response and size, previous and concomitant hypotensive events, and computed tomography (CT) scan characteristics [4]. For other predictors, the relation is less well established. Information obtained during the subsequent clinical course may further contribute to outcome prediction.

The prognostic value of the different characteristics was recently quantified in the International Mission for Prognosis And Clinical Trial Design in TBI (IMPACT) study data [5]. Clinical severity had the highest prognostic value, followed by CT characteristics. The IMPACT study also highlights the importance of laboratory examinations as confident predictors. Meta-analysis studies like this show that predictions can be made on admission and result in the development of valid, increasingly complex, prognostic models [6, 7].

26.2.1.1 Glasgow Coma Scale

The presenting neurological condition of patients with head injuries is the primary factor in determining initial management and prognosis. The clinical severity of TBI is indicated by the level of consciousness, as assessed by the Glasgow Coma Scale (GCS), a score widely used because of its high interobserver reliability and generally good prognostic capabilities [8]. This scale corresponds to the definition of coma as no eye opening (E <2), no verbal utterances (V <3), and not following commands (M <6). Many studies have shown an association between a low score on the GCS and poorer outcome [9]. TBI is stratified according to GCS score into the broad categories of mild (scores 14, 15), moderate (9–13), or severe (3–8). The latter group has the highest mortality and morbidity rates. The three components of the GCS assess the function of the cerebral cortex and upper brainstem, the reticular activating system: the eye-opening response measure, the arousal mechanism of brainstem; the verbal response, the integration of cerebral cortex and brainstem; and the motor response, the integrity of cerebral cortex and spinal cord. Asymmetric motor responses (spontaneous or stimulus induced) have localising value. In patients with more severe injuries, the motor component of the GCS has the greatest predictive value, because eye and verbal response in these patients is often absent. The prognostic value of the eye and verbal components of the GCS becomes more relevant in patients with less severe injuries who can obey commands.

Reporting each GCS component (GC Score) in the subscore E-V-M sequence (as it follows the sequence of a systematic clinical investigation of the patient) instead of the GCS sum score is preferable. Providing only the total GCS score results is significant information loss and may diminish predictive validity [10], whereas reporting each component may also allow a better comparison of patient populations among different studies. From a prognostic perspective, GCS assessment should therefore be done at a fixed time period, usually on admission after primary respiratory and haemodynamic stabilisation. To obtain the most reliable information, GCS assessment should be performed repeatedly within the first 24 h and include data from the prehospital setting. All assessment should be reported. This proposition is based on the observation that GCS scores of up to 30% of all TBI patients fluctuate early after injury, deteriorating or improving secondarily when

compared with initial values. However, reliable GCS assessment may be obscured in the acute setting by medical sedation, endotracheal intubation, and neuromuscular blockade. These procedures are the cornerstones of severe TBI management but may contribute to an underestimation of the severity of cerebral injuries upon hospital admission. It has been suggested that GCS may overestimate brain injuries in 13% of TBI [11].

The GCS has some other limitations; for example, brainstem reflexes and eye movements are not considered. Moreover, whereas the GCS has proved to be extremely useful in TBI clinical management and prognosis, it does not provide specific information about the pathophysiologic mechanisms responsible for the neurological deficits. In the acute phase (0–4 h), there is consensus that, despite the limitations noted, the GCS score remains the standard and most well-validated index of overall neurologic injury severity. However, it is most helpful on the more severe end of the injury spectrum. Moving beyond the acute phase evaluation and into the intensive care unit (ICU) phase (approximately 4–12 h postinjury), additional parameters may be incorporated into the early clinical evaluation and characterisation of injury. Appropriate tools might serve to better define specific injury type, extent, pathophysiology, and evolution over time. Where appropriate, ICP monitoring, microdialysis sampling, brain tissue partial pressure of arterial oxygen (pO_2) measurements, and electroencephalogram (EEG) may have a role. The GCS is still an important instrument for decision making when used in combination with these other diagnostics.

26.2.1.2 Physical Assessment and Neurological Evaluation

Complete neurologic examination should be done as soon as the patient is sufficiently stable. When possible, it is essential to ascertain the mechanism of trauma and the time injury occurred. An accurate neurological examination could help to determine the type and position of the pathological process: haemotympanum, postauricular haematoma, periorbital haematoma, and cerebrospinal otorrhoea/rhinorrhoea are indicative of basilar skull fracture. Facial-nerve function may be impaired immediately or after a delay. Other fractures of the cranial vault are sometimes palpable, particularly through a scalp laceration, as a depression or stepoff deformity. However, blood under the galea aponeurotica may mimic such a stepoff deformity.

Moreover, clinical evaluation should focus on occurrence of lucid intervals, amnesia, headache, nausea and vomiting, transient visual obscurations, lack of motor coordination, dizziness, difficulty balancing, fatigue, or lethargy. Progressive decrease in consciousness may result from increased ICP, which classically manifests as Cushing's triad, a combination of hypertension, bradycardia, and respiratory irregularity. Funduscopic examination may disclose traumatic retinal detachment and absence of retinal venous pulsations due to elevated ICP, but examination may be normal despite brain injury. Severe diffuse brain injury or markedly increased ICP may produce decorticate or decerebrate posturing. Both are poor prognostic signs. Transtentorial herniation may result in coma, unilaterally or bilaterally dilated and unreactive pupils, hemiplegia, and Cushing's triad. Failure to recognise herniation signs will cause irreversible brain damage and death. Although a full neurological examination should always be undertaken, special emphasis besides conscious state and GCS should be given to pupillary size and reaction and to focal neuro-

logical signs in the limbs. Abnormalities in pupillary reactivity indicate brainstem damage or compression and are strongly associated with poorer outcome; pupillary reactivity is a more stable variable in the early phase after injury than is the GCS, because it is less prone to influences of sedation and paralysis [12]. Unfortunately, clinical examinations have low sensitivity and specificity for diagnosing high ICP.

Following clinical evaluation, radiological assessment is essential. As CT technology improved and became more widespread, utilisation also increased – providing a wealth of information not incorporated into physiological classification systems such as GCS – to enhance classification of severity of injury. CT scan clearly shows the macroscopic intracerebral or extracerebral haematoma, as well as cerebral contusion, oedema and infarction, sulcal effacement, ventricular and cisternal compression, and midline shift. The prognostic value of CT characteristics has been well documented, including the status of basal cisterns, midline shift, presence and type of intracranial lesions, and traumatic subarachnoid haemorrhage. Small "slit" ventricles and absence of the basal cisterns, according to the Marshall score [13], are signs of mass effect and indicate generalised brain swelling. These signs, together with the presence of subarachnoid haemorrhage, are the strongest CT predictors of outcome [4]. Absence of these findings does not exclude increased ICP, and mass effect may be present with normal ICP. MRI may be useful later in the clinical course to detect more subtle contusions and diffuse axonal injury.

26.2.1.3 Neurological Worsening

Some patients with initially moderate TBI and a few with initially mild TBI deteriorate over time. It has been estimated that 10–20% of moderate brain injury patients further deteriorates and may require more aggressive monitoring and treatment. Deterioration in neurological function is a dire prognostic sign that generally indicates progressive brain damage. Early prognosis studies showed that the worst GCS recorded over a given time period is especially predictive of poorer outcome. Deterioration in neurological function has been defined more objectively as neuroworsening and includes the following criteria highly predictive for poor outcome: spontaneous decrease in GCS motor score ≥2 points compared with previous examination, new loss of pupil reactivity, development of pupil asymmetry of ≥2 mm as well as other deterioration in neurological status sufficient to warrant immediate medical or surgical intervention, and diagnostic procedures (CT) [14]. Secondary insults can occur in the clinical setting despite clinicians' best attempts to avoid them. Patients are particularly at risk for secondary insults during transport within and between hospitals. Severity, duration, and number of secondary insults contribute to a poorer outcome.

26.2.1.4 Extracranial Organ Dysfunction

Patients with an isolated head injury do not simply have a problem with the brain but are typically also critically ill, with major extracranial organ dysfunction that may not be relat-

ed directly to trauma. Clinical severity relates to extracranial and intracranial injuries. The overall severity of extracranial injuries and physiologic instability are often assessed with the Abbreviated Injury Score or the Injury Severity Score (AIS/ISS) [15, 16]. The Trauma Score is a simplified scale that includes the GCS and multiple vital signs to provide an overall score to assess injury severity [17]. The coexistence of TBI and extracranial injury is associated with high mortality and morbidity rates. By contrast, there is no consensus on the prognostic value of major extracranial injury in patients with TBI. For patients with more severe brain injuries, the effect of extracranial injury on functional outcome is small, whereas in those with milder brain injuries, extracranial injuries have a more pronounced effect. For example, the prevalence of respiratory failure and ICU-acquired sepsis was higher in this group of ICU patients than in those with nonneurologic causes of admission to the ICU [18, 19].

26.2.2 Diagnostic Procedures: Neuromonitoring

Neurologic monitoring can be classified broadly into four types:

1. pressure, e.g., ICP from which cerebral perfusion pressure (CPP) is estimated;
2. blood flow, e.g., thermal diffusion or blood flow velocity, e.g., transcranial Doppler;
3. electrophysiology, e.g., EEG;
4. metabolic measures such as jugular venous oximetry, cerebral microdialysis, and direct brain tissue oxygen (BtO_2).

It is believed that with effective neuromonitoring, secondary brain injury can be recognised early and better managed before irreversible injury occurs, thereby improving patient outcome. Current Guidelines for the Management of Severe Head Injury emphasise the use of ICP monitoring [4].

26.2.2.1 Pressure: ICP and CPP

Raised ICP is the most important "secondary insult" in brain-injured patients and a predictor of poor outcome after TBI. ICP is also used to calculate CPP, which represents the pressure gradient across the cerebral vascular bed and is used as a therapeutic target for brain-injured patients. However, it is important to realise that there has never been a randomised controlled trial showing an outcome benefit for patients with ICP monitoring and ICP-guided treatment compared with patients without ICP monitoring.

ICP is a reflection of the relationship between alterations in craniospinal volume and the ability of the craniospinal axis to accommodate added volume. It cannot be estimated without directly measuring it. There are several different, but related, factors that have to be taken into consideration when a mass lesion within the cranial cavity starts to expand. One is brain distortion. The sequence of events is, therefore, local deformity with displacement of cerebrospinal fluid (CSF), shift and distortion of the brain, and eventually the appearance of internal hernia in the intact cranium. These are the displacement of brain tissue from one intracranial compartment to another or the spinal canal. These herniae, in turn, lead to the de-

velopment of pressure gradients because of obliteration of subarachnoid space and cisterns and secondary vascular complications, such as haemorrhage and ischaemic brain damage.

Almost from the time of the first attempt to monitor ICP in acute intracranial pathology, researchers have tried to determine whether the prognosis of a patient can be obtained from ICP. Data from large prospective trials have provided the most convincing evidence for a direct relationship between ICP and outcome. A strong relationship exists with survival, and a recent analysis of the same data set by regression tree methodology shows a strong relationship between ICP and functional recovery. Narayan et al., in a prospective study in 133 severely head-injured patients, demonstrated that the outcome prediction rate was increased when the standard clinical data such as age, GCS on admission, and pupillary response with extraocular and motor activity were combined with ICP monitoring data [20]. Marmarou et al., reporting on data from 428 patients that were recorded in the National Institute of Health's Traumatic Coma Data Bank, showed that, following the usual clinical descriptors of age, admission motor score, and abnormal pupils, the proportion of hourly ICP recordings >20 mmHg was the next most significant predictor of outcome [21]. In a prospective study of 124 head-injured adult patients in ICU, using a computerised data collection system capable of minute-by-minute monitoring, Jones et al. found that ICP >30 mmHg, arterial pressure <90 mmHg, and CPP <50 mmHg significantly affected patient outcome [22–24].

In summary ICP is a complex parameter that contains combined information about cerebral compensatory and cerebral blood flow (CBF) regulation mechanisms. The dynamics of ICP, its waveform, and secondarily derived indices portray useful information about brain homeostasis. There is circumstantial evidence that this information can be used to modify and optimise patient treatment. Secondary variables, such as pulse amplitude and the magnitude of slow waves, index of compensatory reserve, and pressure–reactivity index (PRx), look promising in clinical practice. The optimal CPP derived using PRx is a new concept that may help to avoid excessive use of vasopressors in CPP-oriented therapy [25]. However, the use of secondary ICP indices remains to be confirmed in clinical trials.

Even if there are insufficient data to recommend ICP monitoring and management as standard care in all brain-injury patients, the evidence is "good enough" to recommend ICP monitoring of patients with severe injuries who are at increased risk of intracranial hypertension. Which patients are at high risk of ICP elevation is a matter of controversy. ICP should be monitored in all salvageable patients with a severe TBI (i.e., GCS ≤8) and an abnormal CT scan. [4]

26.2.2.2 Cerebral Blood Flow: CBF

Cerebral ischaemia is a frequent complication after traumatic brain injury [26, 27]. Posttraumatic cerebral ischaemia (PTCI) is present in 90% of fatal cases, and in some is the only cause of death or poor outcome [26]. CPP is a major determinant of cerebral perfusion in the injured brain, and targeted CPP management is widely advocated for TBI patients [28]. However, the optimal CPP target remains elusive and may vary substantially in different patients or in the same patient over time [28]. Hence, direct measurement of CBF plays a crucial role in PTCI diagnosis [29].

Cerebral pressure autoregulation is the specific intrinsic ability to maintain constant CBF over a range of blood pressures and is generally observed in mean arterial blood pressure of between ~ 50 and 150 mmHg. Pressure autoregulation mechanisms protect against cerebral ischaemia due to hypotension and against excessive flow (malignant hyperaemia) during hypertension, when capillary damage, oedema, diffuse haemorrhage, and intracranial hypertension might otherwise result. The loss of or impairment in cerebral pressure autoregulation carries important consequences for patients with TBI. Across multiple studies, 50–85% of patients with severe TBI have demonstrated an absence of or impairment in autoregulation [30, 31]. Impaired cerebral pressure autoregulation may be a significant risk factor for secondary injury in the first few hours after severe TBI, when CBF is reduced in up to 60% of patients and when patients are most likely to be hemodynamically unstable [32]. However, in 30% of patients with severe TBI and CBF as low as 18 ml/100 g/min, arteriojugular differences of ($AVDO_2$) measurements have indicated that CBF does not meet the metabolic demands of the injured brain [33].

At present, no single method can be regarded as a gold-standard measure of cerebral autoregulation. The most frequently used and the most convenient technique in the neurointensive care unit for estimating changes in cerebral perfusion is transcranial Doppler ultrasonography insonation of the main carotid artery (MCA) given that the MCA is most likely to be "visible" to the ultrasound through the thin part of the temporal bone [34].

26.2.2.3 Brain Oxygenation Monitoring and Cerebral Metabolism

Brain oxygen may be assessed using imaging (e.g., positron emission tomography or magnetic resonance spectroscopy), jugular venous oximetry, near-infrared spectroscopy (NIRS), or with direct BtO_2 monitors. Jugular bulb oximetry ($SjVO_2$) provides information about the adequacy of global CBF in relation to metabolic demands. The clinical usefulness of $SjvO_2$ monitoring is debatable. Although a publication earlier this decade found that $SjvO_2$ monitoring does not substantially influence the management of head-injured patients, other studies indicate a clear and practical benefit [35, 36]. There are difficulties in establishing the relationship between flow and metabolism in injured brain regions from the global venous drainage of the brain. NIRS measures the chromophore level of oxygenated and deoxygenated haemoglobin via photon scattering, although in a target volume that cannot be clearly defined. New models of NIRS monitors can estimate percent oxygen saturation of mixed cortical blood and provide information with faster resolution, probably allowing continuous monitoring of CBF autoregulation. More clinical studies need to be conducted to unequivocally prove the utility of this interesting noninvasive technology [37]. BtO_2 has been used as an estimator of local perfusion adequacy. The method is promising because of its good temporal resolution. BtO_2 differs from $SjvO_2$ in that it monitors oxygen metabolism in a small, focal volume of brain. This is important from a therapeutic perspective, as the debate is centered primarily on whether BtO_2 reflects CBF or oxygen extraction. Several studies demonstrate that BtO_2 is influenced by a wide range of parameters [38]. In conclusion, BtO_2 may be a predictor of patient outcome, and specifically, BtO_2 <10 mmHg is associated with a greater risk of poor outcome. However, several questions remain.

26.2.2.4 Neuroelectrophysiological Tests

Clinical neurophysiology (CN) provides functional evaluation of the nervous system. There are two main advantages of CN with respect to clinical examination: it can be employed in sedated and/or curarised patients, and it provides quantitative data for comparison with follow-up studies [39]. Over recent decades, there has been interest in EEG and evoked potentials (EP) as predictors of outcome [40]. However, some have suggested that the predictive ability of EEG is limited because TBI has a greater effect on subcortical axonal fibers than on cortical grey matter, which generates most of the EEG signal [41].

Many studies have shown that somatosensory evoked potentials (SSEPs) are useful predictors of outcome after TBI [42]. A meta-analysis showed that bilaterally negative SSEPs had a 98.5% positive likelihood ratio for an unfavourable outcome [43]. SSEPs have been used to determine whether the neurologic deficits are from an injury to the brain, spinal cord, or peripheral nerve. When injury to the nervous system is confined to the brain, SSEP testing within the first week after injury is the best single predictor of outcome when compared with clinical examination, CT, age, ICP, and EEG recordings. Many studies have shown that absent cortical SSEP waveforms in the early stage after TBI predict unfavourable outcome (death, persistent vegetative state, severe disability) in adults, whereas normal cortical SSEPs usually predict a good recovery.

Continuous neuromonitoring is indicated in selected TBI patients. The major reversible events, which can be picked up by continuous neuromonitoring, are: nonconvulsive seizures, neurological consequences of increased ICP, EEG changes consecutive to modifications in the degree of metabolic encephalopathy and/or drug influences, EEG and/or EP changes induced by the ischaemic penumbra [44, 45].

26.2.2.5 Neuronal Biomarkers

Interest in the use of biomarkers, including laboratory variables, has been increasing in recent years. Biomarkers should be traceable in blood and should be proportional to the mechanical impact and extent of the injury, and their specificity is as important as their sensitivity. The appearance of markers in the blood and/or in the CSF may indicate which cell population or which domain of the cells has been affected by the injury.

Several putative serum, CSF, and microdialysate biomarkers have been evaluated in clinical studies of TBI: S-100 protein and neuron-specific enolase (NSE) are among the most widely investigated [46–51]. S-100 proteins are brain-specific calcium-binding proteins with small molecular weight (20 kDa) and can be found in the cytoplasm of astroglia and Schwann cells. A correlation between S-100B and primary end points (GCS, CT) in patients with severe head injury has been reported in several studies. Strong evidence has been accumulated in severe TBI, showing that S-100B also correlates well with outcome. There is a correlation between the peak value of S-100B, the lowest CPP, the highest ICP scores, and patient age. NSE is a glycolytic enzyme specific for neurons with a molecular weight of 78 kDa and a biological half-life of 48 h. NSE in serum peaks within 12 h after injury

and decreases during the subsequent hours. Secondary increases of NSE have been seen in a few patients with poor or fatal outcomes. A significant correlation between serum NSE and GCS and 3-month outcome has also been reported. Although an association between several biomarkers and outcome has been established, the prognostic value of biomarkers is unclear owing to relatively small numbers analysed in univariate analyses [52].

The prognostic value of routinely measured laboratory variables has been more widely investigated. High glucose concentrations, low haemoglobin, low platelets, and coagulation disturbances are the strongest predictors of outcome and are independently related to poorer outcome [53–56]. On the basis of the observed association between higher glucose concentration and poorer outcome, two randomised trials were recently done to assess the effect of intensive insulin therapy to reduce glucose concentrations. The risks of tight glucose control in TBI have been illustrated in microdialysis studies in the brain and show that normalisation of blood glucose could lead to a depletion of glucose in the extracellular fluid of the brain, thus compromising cerebral metabolism [57–59].

26.3 Conclusions

After traumatic brain injury, clinical manifestations vary. Hence, large numbers of observations are required before significant data convergence is achieved providing a consistent picture. The injury usually triggers a variety of pathophysiological mechanisms that in turn create a highly heterogeneous pattern of changes within the brain. The monitoring of comatose head-injured patients in neurointensive care provides information regarding the fluctuations in cerebral haemodynamic and metabolic function. Following brain trauma, the system of cerebrovascular circulation usually works without feedback information. Moreover, physiologically negative feedback loops are converted to positive vicious cycles. The aim of clinical assessment and diagnostic monitoring is to provide missing data, closing the disrupted control loop by an appropriate therapy managed by doctors' decisions.

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Part XII
Disaster Medicine

Disaster Preparedness

27

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27.1 Introduction

Disasters have always been part of the history of humankind and have been described in ancient texts [1]. Historically, they have been considered as punishments by the god(s) or were associated with the movement of celestial bodies, the stars, influencing human affairs and determining the course of events. The word disaster in fact stems from the Latin *dis astro*, and implies an unfavourable position of the planets (stars), thus linking them to fate.

It is generally accepted that the first historical report of a disaster is that of Plinius the Junior: On 25 August 79 AD, the volcano Vesuvius, which the ancient Romans considered a place frequented by the god Bacchus because of the good wine produced in its vicinity, suddenly awoke. From its summit, a huge cloud of lapillus and lava obscured the sun and fell to the areas surrounding the volcano, destroying towns such as Pompeii, Ercolano, Stabia and Naples.

Likewise, the history of emergency aid is as old as catastrophes. The pottery of classical Greece depicts hunters helping dress each others' wounds. From this instinctive life-saving motivated assistance, the more organised and structured military medicine derives. The categorisation of treatment priority according to the lower grade of injury severity, promoted by Sir Jean-Dominique Larrey in the eighteenth century, historically represents the first attempt of medical management optimisation in order to save those soldiers who could battle the following day [2]. From frontline care, we gradually proceeded to transnational and subsidiary action of the modern world witnessed by the founding of the International Red Cross, the later Red Crescent and the subsequent federation into the league following World War I. The birth of the World Health Organisation (WHO) is a more recent momentous event that significantly drove the development of medicine specifically applied to disasters. Those events can be considered as the starting point of the development of disaster medicine as a health discipline. A strong impetus further in this direction was the foundation of the Mainz Club by Professor Rudolf Frey in 1976. Five years later, this group of motivated medical experts converted the club into the World Association for Emergency and Disaster Medicine (WAEDM) and in 1985 published the

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first copy of the Journal of the WAEDM, now called Prehospital and Disaster Medicine.

With disasters and the number of people affected by them on the increase, the importance of disasters as medical management problems must be widely recognised [3]. Moreover, there is high expectation that due to many different factors, such as climate change, population growth, environmental degradation, deforestation, emerging or re-emerging infectious diseases, hazardous materials, economic imbalance and other factors, we will witness an increase in extreme events and weather-related disasters [4, 5].

Any health provider can be forced by situations to face events that overwhelm local medical resources, and this requires specific knowledge and training. The disaster environment is complicated and stressful. It is characterised by situational uncertainty, time compression and high demand for qualified carers. To cope with such events, today's medical doctors must have absolute command of a vast and varied knowledge base. Health decision makers must be familiar with those principles that lead disaster and mass casualty incident (MCI) management. Disaster planning and preparedness may now represent a prominent part of health care policy and practice. If health is "a state of complete physical, mental, and social well-being and not merely the absence of disease or infirmity" (WHO 1946), the art of care has the responsibility to recover it when it is lost and to protect it when it is present. Disaster medicine can no longer be considered an act of some brave and valiant health care provider but a medical discipline with its own academic rank.

27.2 Definitions and Modern Background

In the literature, there have been many attempts to define disaster. Gunn [6] defined it as the result of a vast ecological breakdown in the relations between humans and their environment, a serious and sudden event (or slow, as in drought) on such a scale that the stricken community needs extraordinary efforts to cope with it, often with outside help or international aid. Likewise, a disaster can be defined as a destructive event that results in the need for a wide range of emergency resources to assist and ensure the survival of the stricken population [7]. Similarly, disasters are events that overwhelm community, destroy property and damage populations [8]. These definitions are closely aligned with that of the WHO: "A disaster is a severe psychological and psychosocial disruption that largely exceeds the ability to cope of the affected community" [9]. These definitions imply situations or events that overwhelm local capacity, necessitating a request for external assistance. This suggests that disasters are the consequence of disequilibrium between various phenomena or hazards encountered by human populations and the visceral resistance and reaction of those populations.

In recent years, the response to disaster situations has undergone a constant process of improvement and strengthening that provides this kind of humanitarian, but yet unorganised, assistance an imprinting of organisation and high technological development. Now days, many professional and voluntary organisations exist to provide care for populations affected by disasters and the scientific and more systematic approach to disaster medicine is directed towards its recognition as an academic medical discipline.

27.3 A New Philosophy of Actions

The objective of all disaster efforts is to reduce the occurrence and/or the impact of catastrophic situations on life, environment and property. In regard to health care, the medical response must be conducted to provide assistance to the maximum number of victims and to reduce the physical sequelae and mental traumas. In that effort, the goal should be to maintain the quality of assistance provided by the health system before the tragic event [10]. Nevertheless, it is obvious that this laudable and admirable desire is impossible to achieve in most cases. Disaster implies a situation in which the available resources are not sufficient to meet the needs of immediate aid and the severity of health damage is too high to be faced without an unavoidable decrease in quality standards of health care. It is implicit in the term disaster that disequilibrium between needs and available resources exists.

Medical response in disaster situations differs radically from the routine. The behavioural philosophy no longer focuses on individuals: the objective is to serve the greatest number of saveable victims, thus creating a condition of passive euthanasia of those whose injuries require great amounts of time and resource-consuming treatment. Physicians must understand that the natural desire to save lives with heroic devotion and perseverance must be put aside.

The rapidity of the interventional operation remains a main objective of disaster planning. Experience gained in recent years has taught us that emergency responses with the best outcomes are those carried out by the emergency teams on site rather than international equips and field hospitals. In fact, the probabilities that victims will be rescued alive decrease abruptly after 24–48 h after the event [11]. This critical time limit is based on pathophysiologic reasons. To simplify, a complete airway obstruction, common in unconscious victims, or a postmyocardial arrest causes asphyxia within 5–10 min; a partial airway obstruction can result in cerebral damage; hypovolaemic shock can cause multiple organ failure or death if not treated within 1 h; an intracranial haematoma can determine cerebral function impairment or death if not drained within the “golden hour”; very severe injuries as well as intestinal perforations can cause septic shock or death if not treated within 6 h; compartmental or crush syndrome can bring about death when the victim is released from entrapment [12]. Retrospective studies about earthquakes in Italy [13] and Armenia and a terrorist attack of similar impact in New York City [14] acknowledged the key role of early intervention. If teams trained in advanced life support had reached the disaster site within 6 h, from 25% to 40% of the victims could have been saved. The expression “the golden 24 hours” refers to that which is summed up above and described in Figure 27.1, showing the correlation between time and percentage of survivors according to data from the earthquake in Kobe, Japan, in 1985 [15]. During the first 24 h, a considerable number of people buried in rubble were still alive. After 24 h, the percentage of survivors decreased rapidly, and after 5 days, all who were dug out were dead.

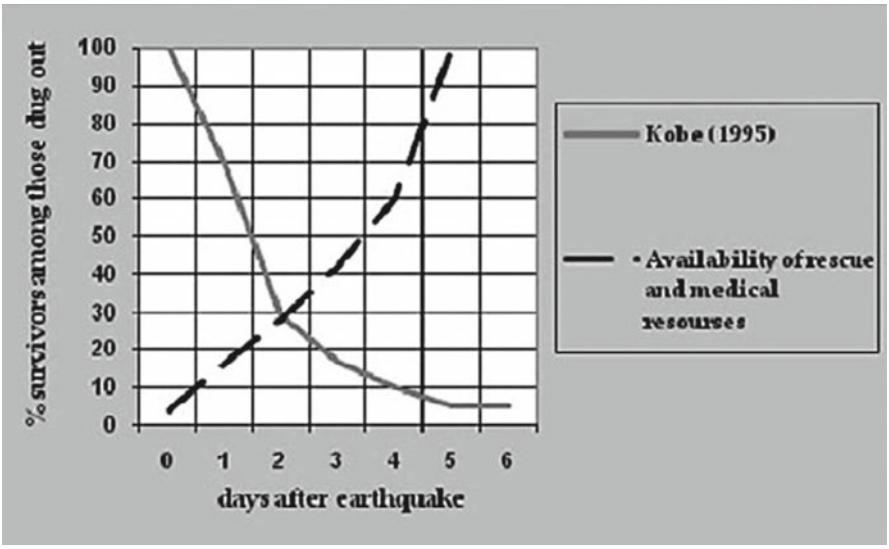

Fig. 27.1 Percentage of survivors in Kobe earthquake (source [15])

27.4 Disaster Classification

There are also no universally available criteria by which to classify a disaster in terms of consequences, such as casualties and the cost of damage. The most important classification is based on the triggering factors that allow us to evaluate the evolutive risk, i.e. the possibility that the event might repeat itself or continue to cause damage to things and persons, among whom are the rescuers. Natural disaster refers to any event that reaches the definition of a disaster, which results from natural forces and in which human intervention is not the primary cause of those forces. Man-made disaster is considered any event that reaches the definition of disaster as a result of significant human action [16]. The common distinction between natural and man-made or anthropic disasters is progressively decreasing in meaning. Many natural disasters are triggered by the environmental devastation produced by humans. Likewise, many man-made events are the results of human error and can be complicated by secondary effects on the natural environment. Very often, disasters have peculiarities of both man-made and natural events [17].

Scientists have been attempting to delimit the taxonomy of disasters, but it appears from the literature that there is no generally accepted classification of disasters [18–21]. Other classifying factors are important for making decisions regarding the type and extent of rescues to initiate, both outside and inside the hospital.

The geographic configuration (urban or rural suburban area) and social configuration (industrialised or developing countries) will determine the type of disaster and the relative physical consequences on persons, as well as the number of victims and the rapidity of rescues. Geographical extension (<1 km, between 1 and 100 km, >100 km) essentially depends on the type of event that has occurred, considering that technological accidents

are usually circumscribed, whereas large-scale natural disaster generally extent over entire regions. According to the number of victims, meaning persons involved in the event, we can distinguish between small disasters (<100 victims), medium-sized disasters (100–1,000 victims) and large-scale disasters (>1,000 victims). When speaking of the effects on the community, we must consider alterations to the social organisation due to damage to communications, telephone systems, public facilities and aid facilities. Depending on the extent of damages, we speak of a disaster as being simple or complex.

27.5 Disaster Management Phases

Emergency management activities can be categorised into a series of phases [22] (Fig. 27.2). Each management phase is unique.

27.5.1 Preparedness

27.5.1.1 Day to Day

The preparedness phase involves activities undertaken in advance of an emergency. These activities develop operational capabilities and improve effective disaster response. Disaster plans are developed and revised to guide disaster response and increase available

Fig. 27.2 Disaster cycle

resources. Planning activities include developing hazard analyses, writing mutual aid operational plans, training response personnel and improving public information and communications systems.

27.5.1.2 Increased Readiness

As a crisis begins to develop, government takes action to increase its readiness. Actions taken during the build-up of a crisis situation are designed to increase an organisation's ability to respond effectively. Increased readiness actions include briefing government officials, reviewing plans, preparing information for release to the public, updating resource lists and testing warning and communications systems.

27.5.2 Response

27.5.2.1 Preimpact

When emergency managers are able to recognise the approach of a potential disaster, actions are taken to save lives and protect property. The response phase is activated to coordinate emergency response activities. During this phase, warning systems may be activated, resources may be mobilised, emergency operation centres (EOC) may be activated and evacuation may begin.

27.5.2.2 Immediate Impact

During this phase, emphasis is placed on saving lives, controlling the situation and minimising the effects.

27.5.2.3 Sustained

As the emergency continues, assistance is provided to victims of the disaster and efforts are made to reduce secondary damage. Regional or state-wide mutual aid may be provided to assist with these efforts. Response support facilities may be established. The incidents' resource requirements continually change to meet the needs of the incident.

27.5.3 Recovery

At the onset of an emergency, actions are taken to enhance the effectiveness of recovery operations. Recovery is both short-term activity, intended to return vital life-support systems to operation, and long-term activity, designed to return infrastructure systems to predisaster conditions. Recovery also includes cost-recovery activities.

27.5.4 Mitigation

Mitigation planning includes a review of ways to eliminate or reduce the impact of future disasters. Specific hazard mitigation plans are prepared following a federally declared disaster. They reflect the current risk analysis and mitigation priorities specific to the declared disaster.

27.6 Disaster Plan and Education

The disaster plan is the written document or map for disaster management generated by any given political jurisdiction or private organisation. Written plans may vary widely in scope, detail, structure, purpose and elaborateness. In every case, the disaster plan is the product of the planning process, thereby becoming the principal connection between the disaster planning activity and the disaster response. Construction of the plan is such that it addresses issues relevant to response. The focus is upon writing down a description and analysis of needs that arise and actions that can be undertaken and resources that should be assembled to support the actions. Put another way, the planning process anticipates demands and devises strategies and tactics, linked with resources, for meeting them. Thus, plans address all aspects of the response, including personnel, equipment, contingency issues, policy issues and interorganisational and intergovernmental relations. Once a plan is created, its implementation revolves around the logistics and protocol needed to execute the specified series of tasks. Subsequently, a variety of training needs may be identified. These include both training and education of personnel regarding the threats, the response processes and procedures and the use of the equipment called for under the plan.

Training is the activity that translates information defined as needed by the plan into a coherent programme that can be imparted to responders. Then, simulations represent the constructed opportunities to test the protocols and equipment specified under a plan and taught in the training phase. Moreover they provide the “experience” needed to reduce errors and that cannot be gained in a real situation due to ethical and practical aspects, as the disaster involves a multitude of victims. The main feature of a simulation is that it is used to reproduce reality in a simplified way, so that learners can better understand why things happen and how. Participatory simulations are learning games in which players play an active role in the simulation of a system or process. They create a scenario, medi-

ated by a set of underlying rules that enable enquiry and experimentation [23]. The major idea of participatory simulation is the concept of "learning by doing". Learners actively participate, analyse information, make decisions and see the outcome of their actions. This should improve learning success [24]. Advantages in training over real operational systems include: elimination of catastrophic consequences of error; reduction of physical danger; cost containment; elimination of nonsalient attributes; "replay" possibilities; compression or expansion of time; and iterative manipulation of variables for evolving design and data collection [25].

The use of simulations in medical education, in general, and in disaster medicine education, in particular, is well documented [26–30]. When considering simulations, we distinguish two different kinds: virtual and live. In the former, real people use simulated equipment in a simulated world (or virtual environment); in the latter, real people use simulated (or dummy) equipment in the real world. Computer technology is being used increasingly in simulation [31]. Interactive simulation systems fit the requirement of allowing social interaction, which is the key element in those scenarios where users are expected to cooperate in order to solve a particular problem, such as in response to disasters. Live simulations are major enterprises that demand many resources, a full staff of evaluators and controllers, a complement of actors (victims and other event-impacted personnel) and realistic simulations of the physical damage and other consequences of the event. Participants at all levels must literally execute their tasks under the disaster plan on the operational field in real time.

Unfortunately, there is no strong evidence to support firm conclusions about the effectiveness of specific training methods. An interesting review conducted by Hsu et al. [32] indicated that live hospital disaster simulation can help identify problems with incident command, communications, triage, patient flow, security and other issues; and computer simulations, tabletop and other exercises may help train key decision makers in disaster response. The authors conclude that different types of training exercises may have different roles to play in educating hospital staff in disaster response.

27.7 Conclusions

Until a few decades ago, disasters were viewed as one-off events and responded to by populations and governments without taking into account all implications and causes of these events, including social and economic. Gradually, this attitude changed to an emphasis on preparedness measures, such as stockpiling of relief goods, preparedness plans and a growing role of education and training. Disasters might no longer be considered as extreme events created entirely by natural forces but as unresolved problems of development. This disaster preparedness and planning approach is the only key to improving the efficiency of relief and response actions and reducing the impact of such inevitable events.

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Medical Emergency Response in Toxicological Mass Casualty

28

P.L. Ingrassia, L. Ragazzoni and F. Della Corte

28.1 Introduction

Emergencies and disasters can occur anywhere in the world, affecting human health and lives and the infrastructure built to support them. Chemical releases arising from technological incidents, natural disasters, and conflict and terrorism are common [1]. The International Federation of Red Cross and Red Crescent Societies has estimated that between 1998 and 2007, there were nearly 3,200 technological disasters with approximately 100,000 people killed and nearly 2 million people affected. Unfortunately, the threat of major events involving chemicals is predicted to increase worldwide for three main reasons. First, the chemical industry is rapidly growing, and the number of chemicals available in the market is increasing [2]. Second, chemical incidents may have an impact beyond their original location, in some cases crossing national borders. Third, there is concern regarding the deliberate use of chemicals for terrorist purposes [3].

Many facilities that work with hazardous materials are located in urban areas. Thus, emergency involving exposure to chemicals could represent one of the most common disasters that occur in the community setting. To minimise these negative impacts, and because chemical incidents often involve acute releases and health risks with a very dynamic time course (as a result of changing conditions, e.g. weather, exposure routes, secondary emissions), it is critical to ensure that (plant) operators, authorities, emergency responders and hospitals work together in a rapid, comprehensive and effective response to chemical incidents. It might be taken into consideration that a single patient exposed to a hazardous material may overwhelm even a modern, high-volume facility [4].

Preparation begins with a thorough understanding of the threat and with the development of simple and efficient countermeasures. When a chemical incident occurs, rapid and effective response is dependent on detailed prevention planning, appropriate medical treatment and subsequent postevent analysis to improve the quality of future response operations.

APICE 23. Antonino Gullo (Ed.)

28.2 Types of Incidents and Epidemiology

A chemical incident is defined as the uncontrolled release of a toxic substance resulting in (potential) harm to public health and the environment [5]. Therefore, the term chemical incident might refer to events caused by humans, such as the explosion of a factory that stores or uses chemicals, contamination of food or water supply with a chemical, an oil spill, a leak in a storage unit during transportation or an outbreak of disease that is (likely to be) associated with chemical exposure. There is increasing awareness that natural disasters can trigger technological disasters and that these conjoint events may pose tremendous threats to regions, particularly those unprepared for such events. In fact, natural causes, such as volcanoes, earthquakes and forest fires, can cause chemical incidents. Natural disasters may disrupt chemical containment systems and cause secondary anthropogenic chemical incidents (e.g. tank rupture after flooding). The term natech disasters (natural-disaster-triggered technological disasters) refer to this type of incident [6].

Chemical disasters caused by humans are the result of significant human action, either intentional or unintentional. However, this distinction is becoming weak. Incidents involving the use of commercial or industrial chemicals have the potential to cause a major public health disaster comparable to that of known agents used for deliberate releases, such as vesicants or nerve gases. Chemical terrorism may actually occur as an intentional toxic chemical spill or release involving industrial and/or commercial products. In some cases, industrial agents are more likely to be used as weapons of choice by terrorists due to their

Table 28.1 The ten most important industrial disasters for the period 1900–2010. Results are sorted by total number of affected people at the country level

Country	Date	Total people affected
Mexico, explosion	19 Nov1984	708,248
Brazil, poisoning	01 Apr 2003	550,000
Soviet Union, radiation	29 Sep1957	400,935
Japan, radiation	30 Sep1999	320,600
India, gas leak	03 Dec 1984	300,000
Canada, chemical spill	1979	220,000
United States, radiation	28 Mar 1979	200,000
Italy, explosion	10 Jul 1976	190,893
PR China, gas leak	16 Apr 2004	150,000
Soviet Union, radiation	26 Apr 1986	135,000

Source: EM-DAT: The OFDA/CRED International Disaster Database. Université Catholique de Louvain, Brussels, Belgium. Available at: www.em-dat.net

ready availability, toxicity and low cost. In effect, the main difference between unintentional industrial accidents and intentional chemical sabotage or terrorism may only be the distinction of malicious intent [7].

In principle, chemical emergencies are more likely to occur where there are situations combining both high hazard and high vulnerability. There is mounting concern, for example, that heavy industrialisation in some parts of the world is proceeding faster than appropriate regulatory and surveillance measures [8]. At the same time, many of the most devastating chemical incidents have occurred in countries with a long industrial history [9]. Table 28.1 shows the ten most important industrial disasters in the twentieth century.

Recently the frequency of chemical incidents increased by at least an order of magnitude. On the contrary, due to improved ability to manage chemical emergencies in many developed nations, impact severity of such disasters decreased over the same period [1]. In 1976, Italy witnessed one of the greatest accidents involving chemical agents. In the Industrie Chimiche Meda Società Azionaria (ICMESA) chemical plant near the town of Seveso, an exothermic reaction that raised the temperature and pressure in a vessel caused a safety valve to rupture and a fluid mixture to be released into the air. The toxic vapour cloud, containing sodium hydroxide, ethylene glycol and sodium trichlorophenate dispersed over an area 6-km long and 1-km wide, covering a densely populated area. The incident did not cause any immediate casualties, but 37,000 people were exposed to the chemical and approximately 80,000 animals died from the exposure [10]. Results of morbidity and mortality follow-up studies showed an increased occurrence of cancer, cardiovascular and respiratory diseases and diabetes in the affected population [11].

Little data are available to assess the frequency and intensity of natech releases. Most data in the scientific literature are anecdotal and collected for a specific natural disaster [12, 13]. Hurricane Katrina caused 504 chemical releases in six US states, including 183 releases from oil platforms and vessels, primarily in the Gulf of Mexico. These included oil spills and hexane, ammonia and sulphuric-acid release. Flooding in the summer of 2002 in the Czech Republic resulted in multiple chlorine releases from the Spolana chemical facility situated on the River Labe in Neratovice, north of Prague. There, 400 kg of chlorine gas was released, causing environmental contamination of water supplies and damage to waste-treatment plants [14]. Italy is concerned with possible natech disasters as a result of flooding on the Arno River, and prototype plan to protect against such accidents has been completed [15].

28.3 Medical Management

Casualties of chemical incidents often seek medical assessment and care in hospital emergency departments. Typically, these patients arrive with little or no warning or information regarding the responsible agent. Within 90 min of an event, 50–80% of the acute victims arrive at the closest hospital or medical facility (Fig. 28.1) [16]. It is unlikely that toxicant identification will occur prior to casualties presenting to health-care institutions. Therefore, the ability of prehospital and hospital providers to recognise symptoms and signs related to chemical exposure is essential. This initial recognition can be lifesaving for patients as well as their health-care providers.

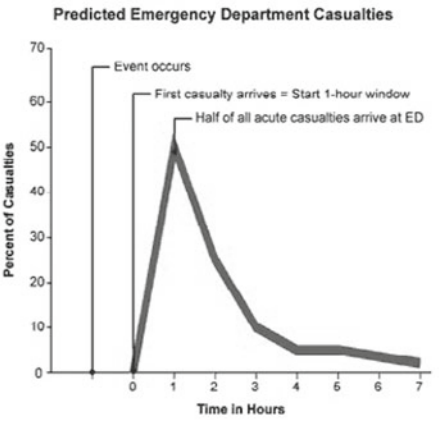

Fig. 28.1 Predicted emergency department casualties (source: CDC 2006 [16])

28.3.1 Identifying the Event

There are several key suspicious findings that can alert health-care responders to the possibility of a chemical event. They include unusual environmental signs, such as atypical smoke or coloured residue, atypical smell, ill or dead animals and visible active sources. Very important findings also include fewer trauma injuries than expected, the appearance of similar clusters of signs and symptoms in otherwise healthy people (toxidrome) and the appearance of the same group of symptoms amongst first responders arriving at the disaster site unprotected. Emergency medical responders, either in the field or in the hospital, need to rapidly see the overall picture. A rapid systematic approach is recommended for evaluating a chemical incident and its victims. Memorised mnemonic devices can help in this stressful and time-compressed situation (Table 28.2). After determining that an ongoing incident is a chemical event, it is recommended by some authors to ascertain whether the chemical is an organophosphate or not, as organophosphates are highly toxic agents for which there are effective and available antidotes that could be implemented immediately at the site of the incident, and any delay in administration results in grave health consequences [17–19].

28.3.2 Identification of Priorities: Triage

A system used at mass casualty incidents involving chemical agents is needed to help emergency responders detect exposure to or the involvement of chemicals, protect themselves from secondary contamination and provide accurate and rapid categorisation of victims according to the severity of their clinical conditions. Currently, no mass-casualty triage scheme has become accepted as a gold standard [20]. Cone and Koenig developed, through expert opinion, a system for triaging injured patients who are or may be contaminated by chemical, biological, radiological or nuclear material and piloted it at an airport

Table 28.2 ASBESTOS: acronym for the mnemonic systematic approach to the evaluation of chemical casualties

Agent(s)	Type(s) and estimated dose
State(s)	Solid? Liquid? Gas? Vapour? Aerosol? Combination?
Body site(s)	Exposed/route(s) of entry
Effects	Local? Systemic?
Severity	Mild? Moderate? Severe?
Time course	Onset? Latent period? Getting better/worse? Prognosis
Other diagnoses	Instead of? In addition to?
Synergism	Combined effect of multiple exposures or insults?

disaster drill (Fig. 28.2) [21, 22]. The purpose of this system is to decide which patients need immediate, life-saving care before and during decontamination and to determine the order in which patients are decontaminate. They used the Simple Triage And Rapid Treatment (START) system as a basic template and modified it [23]. In general terms, the assessment of respiratory rate was eliminated and replaced with a subjective assessment of the overall respiratory status (breathing well/breathing with difficulty/not breathing); and the assessment of radial pulse was eliminated and replaced with assessment using the Glasgow motor score. The only manoeuvres that can be performed before and during

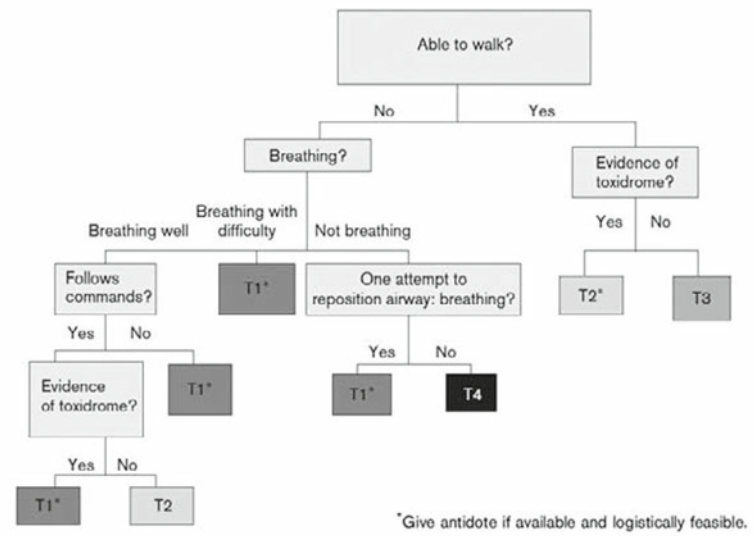

Fig. 28.2 Trauma and chemical triage (source: Cone and Koenig 2005 [21])

decontamination are airway opening, manual cervical spine immobilisation, bag–valve–mask ventilation and direct pressure on bleeding wounds. Following decontamination, patients are re-triaged for additional care and transport. The proposed chemical algorithm includes the use of antidotes and recommends their administration as soon as practical.

28.3.3 Decontamination and Evacuation

Decontamination is the process of removing or reducing the concentration of harmful substances. It should be performed whenever there is a likelihood of contamination or risk of secondary exposure. Different methods and techniques are used in decontamination of toxicological mass casualties, such as clothing removal, reducing absorption, water showering or chemical neutralisation [24]. As the most common chemical incidents involve gases and vapours, evacuation from the source and removal of clothing typically is all that is needed to prevent further exposure or injury [25]. However, the cornerstone of chemical-injury management and victim decontamination is considered copious skin lavage and wound irrigation with water, both for liquid and solid substances [26]. The practical implication of this is that decontamination showers should have a relatively high flow rate. The effect of water temperature also should be noted: relatively lower temperatures may reduce vasodilatation of skin vessels (thereby inhibiting absorption), but the use of cold water increases the risk of hypothermia [27].

The decision regarding whether or not to decontaminate is matter of debate. Okumura et al. recommend using a simple scheme based on whether patients are able to walk or the visibility of the suspected materials (Fig. 28.3) [28]. Also, the appropriate place for

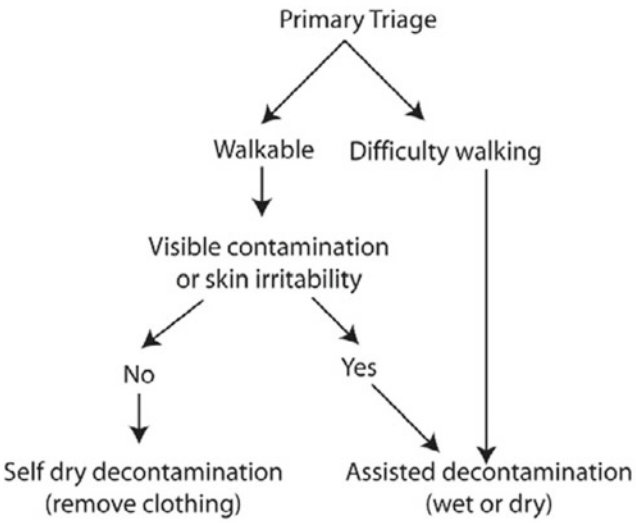

Fig. 28.3 Algorithm for selecting decontamination method (source: Okumura et al. 2007 [28])

victim decontamination is currently controversial. Decontamination at the scene would be too time consuming and would not improve the outcome. In Israel, decontamination is performed directly at the door of health-care facilities. This approach comes from the fact that every hospital in Israel has infrastructure (water shower) at the entrance and evacuation distances are short.

Toxic-agent-release incidents are no different from others in the importance of establishing a safety site. Routinely, Israeli responders isolate a circle around the source of 100 m from the margins of the building in an indoor event and 200 m from the source in an outdoor event, based on risk analysis. This circle defines an area in which rescue personnel should enter only with appropriate protection measures [29]. There are four levels for personal protective equipment (PPE):

1. Level A provides the highest degree of respiratory and skin protection by means of a totally encapsulating, chemical-protective suit with a self-contained breathing apparatus;
2. Level B provides the same high degree of respiratory protection but less skin protection, with the self-contained breathing apparatus being worn on the outside of the chemical-resistant suit;
3. Level C is worn in the warm zone and utilizes an air-purifying respirator and chemical-resistant suit;
4. Level D is a work uniform affording minimal protection and typically would be worn in the cold zone [30].

There is no strong evidence about which level is appropriate for health personnel. Nevertheless, there is a consensus that Level C can be appropriate for emergency medical services caregivers and health providers in the emergency room [31]. Unfortunately, there is a common lack of training regarding the use of PPE and the performance of medical procedures while wearing PPE [32, 33]. The problem of secondary contamination may be present right through the entire chain of care, including in intensive care units, which may receive severely injured patients from the emergency department in rapid succession. Therefore, staff should be aware of the dangers and should be trained to take appropriate precautions [34].

28.3.4 Medical Treatment

Depending on the chemicals released, the way they are disseminated and the properties of each agent, various physical effects and degrees of symptoms and signs can result. In general, the adverse effects caused by toxic exposure may be classified as follow [35]:

1. local: effects that arise at the site of contact with the agent, such as bronchoconstriction from respiratory irritants or irritation of the skin and eyes by irritant gases;
2. systemic: effects that affect organ systems remote from the absorption site, such as central nervous system depression due to solvents absorbed through the skin;
3. mental: effects on mental health arising from real or even perceived releases, caused by psychological stress associated with the event.

The term toxidrome refer to similar clusters of signs and symptoms. Toxidromes are essential for successfully recognising poisoning patterns. Based on the potential offending

Table 28.3 Major toxidromes caused by chemical agents

Toxidrome	Chemical	Characteristics	Clinical signs and symptoms
Cholinesterase inhibition	Organophosphates, carbamates	Cholinergic syndrome with miosis, increased exocrine secretions (muscarinic effects), fasciculations & paralysis (nicotinic effects) and central nervous system effects	Miosis, dim vision, eye pain, headache, rhinorrhoea, salivation, lacrimation, urination, defecation, sweating, chest tightness, wheezing, fasciculations, paralysis, cognitive impairment, seizures, coma
Irritants	Chlorine, ammonia, phosgene, CS (riot-control agent)	Respiratory tract, skin and ocular irritation	Nose irritation, sore throat, cough, chest tightness, eye irritation, wheezing, stridor, acute lung injury
Asphyxiants	Cyanide, carbon monoxide	Tissue hypoxia resulting in cardiovascular and central nervous system depression	Headache, fatigue, dizziness, nausea, anxiety, dyspnoea, altered mental status, cardiac ischaemia, syncope, coma, seizures
Vesicants and skin caustics	Sulfur mustard, lewisite, phosgene oxime	Skin burns, respiratory irritation & acute lung injury, ocular injury	Conjunctivitis, erythema, sore throat, cough, corneal damage, vesicles & bullae, nausea, wheezing, stridor, laryngeal oedema, acute lung injury

Source: Markel et al. 2008 [29]

agents, four major toxidromes can be identified (Table 28.3) [29]. Some author considered immediate identification of respiratory victims in chemical emergencies as the key factor in medical management of those victims. This approach comes from the fact that the respiratory system is the bodily system most frequently and severely compromised. Also, immediate and near-term toxic respiratory illness caused by chemical events is very amenable to intervention with relatively simple and inexpensive technology, and minimal training is required to identify airway victims [36]. In general, resuscitation might be based upon the essential ABCs of basic and advanced life support and can be summarised as follows [37]:

A Assessment and Airway: Assessment must be made of the environment and the patient as a whole, remembering that traumatic injury may be present along with toxic injury, particularly if the release was accompanied by an explosion or fire. The nature

of the hazard must be determined in conjunction with members of fire and rescue services, who will retain overall control of the chemical incident. If reliable information is not available, a persistent, transmissible threat must be assumed. In this active threat situation, protected entry to the decontamination zone is mandatory and must be affected in conjunction with the site controller.

B Breathing: This assessment relies on rate, form and depth of breathing. Because of the need for personal protection, normal ventilatory assessment by auscultation usually will not be available.

C Circulatory support: This includes control of haemorrhage and management of dysrhythmias when appropriate.

D Decontamination and Disability: Decontamination depends upon the persistency of the toxic hazard and must be integrated with necessary life-support measures. Disability from both toxic and traumatic causes must be assessed in a primary survey.

E Evacuation: Initially, this will be to the decontamination zone surrounding the contaminated area. Patient triage is required before their evacuation into the decontamination zone. After decontamination is completed, transfer will be possible to the clean zone and then to hospital care.

28.3.4.1 The Role of Anaesthesiologist

Although emergency medical service providers and emergency department staff would, in most cases, be in the front line in a major chemical incident, they would soon be overwhelmed, and anaesthesiologists would certainly be the next in line because of their ability to respond to the need for life support [38]. Moreover, as respiratory distress is the most common symptom in a mass casualty chemical release, anaesthesiologists may have a major role in treating casualties brought to the health services [39].

28.3.5 Psychological Care

Exposure to a complex emergency has a substantial psychological component [40]. Previous studies found that people exposed directly or indirectly showed posttraumatic disorders, depression, elevated levels of distress and lowered sense of security, especially in cases of deliberate release of chemicals [41–43]. Considering previous experiences, it is reasonable to assume that following a toxicological mass casualty incident, hospitals will rapidly overflow with victims manifesting symptoms related to stress reaction. The spectrum of stress-related disorders will probably include mainly acute stress reaction, anxiety with or without somatisation and concern for relatives. The number of stress-related casualties may even exceed the number of physical injury casualties [44]. This would impair the capability of health-care facilities to provide sufficient care, as well as increase the risk of posttraumatic stress disorder developing among both physically injured and stressed victims.

28.4 Conclusions

Victims of toxicological mass casualty incidents depend on the ability of emergency providers and hospital personnel to think of the possibility of chemical exposure, to recognise and manage toxidromes and injuries and to prevent secondary contamination. For responders, comfort and confidence with everyday practices might include preparedness for all hazard types, including chemical exposure. Thus, achieving effective management of toxicological incidents requires a coordinated educational approach. The definition of core competencies for chemical education and training and their inclusion with disaster medicine in the basic curriculum of medical professional schools must be considered a key factor for improving the degree of preparedness and response to accidental or intentional mass-casualty incidents [45].

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Part XIII
Quality of Care

Telemedicine to Improve Care in the Critically Ill

29

G. Murias, B. Sales and L. Blanch

29.1 Introduction

In critical care medicine, physicians must constantly make both general and specific decisions. Critical care patients are nearly always undergoing several different treatments and procedures. Although timely decisions are required for both decisions and procedures in critical care, the type of training that enables the physician to reach them is different in each case. Specific training enables staff to perform procedures; however, the clinical skills and judgment required for decision making can only be acquired with years of experience.

Closed intensive care units (ICUs), i.e. those in which critical care specialists take charge of patients, have better outcomes than open units [1]. Thus, one might expect closed units to gradually replace open units. However, a survey of ICU chiefs in Canada revealed that no specialists were present in about 50% of the units and that specialists were only present a few hours each day in another 25%. In fact, 90% of the units did not meet the staffing standards recommended by the Society of Critical Care Medicine [2]. This situation is apparently worse in the United States [3, 4].

Medical emergencies are a growing need. Statistics from the Department of Health of the United Kingdom show that emergency consultations have increased at an annual rate of 6% since 1994. In a scenario with limited resources, faster attention to emergencies leads to delays in attending the remaining patients. Another compounding problem is that emergency departments suffer from a shortage of qualified staff, so that the number of units staffed by physicians has slowly decreased. In June 2006, after 3 years of investigation, a commission designated by the United States Institute of Medicine presented its conclusions about the future of medical emergencies [5–7]. Their principal recommendations can be summarised in four points: (1) integrate the different stages in patient care; (2) institute proper channelling; (3) guarantee best practice according to current knowledge; (4) evaluate the results of the system.

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29.2 Costs in the Critical Care Setting

Studies show that the main reason people give up medical coverage is the high cost involved [8], and economists have found a good correlation between increases in health care costs and decreases in medical coverage in the population [9]. To explain these disproportionate health care costs [10], numerous arguments have been put forth: inefficiency, excessive administrative costs, poor administration, inadequate care (with an enormous increase in costs due to medical error), waste of resources, and fraud. In the analysis of avoidable expenditures, apart from the need to develop a more efficient system with lower administrative costs, one point that stands out is the need to reduce medical error. A bed in the ICU costs eight times as much as a bed in a general ward [11], and personnel costs account for 64% of those costs [12]. It is therefore evident that with the current paradigm, the shortage of specialists is not the only reason ICU staffing often fails to meet the standards proposed in international recommendations: even if enough specialists were available, the system probably would not be able to pay them.

29.3 Telemedicine

Care and monitoring of patients in critical care units (ICU), operating rooms and emergency departments have evolved within the framework of the model in which the specialist is present in the same place as the patient. The specialist must be physically near the patient not only to perform medical acts and procedures but also to monitor the patient's evolution, deal with monitor alarms, access the clinical history, see the medical images and finally make the appropriate decisions. Whereas a physician must be physically present to perform procedures such as placing a central venous line or intubating a patient, there is no reason the rest of the physician's responsibilities cannot be fulfilled from a remote location. Moreover, considering that the level of skills and training necessary for these two types of tasks are clearly different, there is no reason the same person should be in charge of carrying out both kinds of tasks. Intelligent aggregating (using automatic processes and intelligent alarms) could alert the specialist to potentially dangerous changes in the patient's status, even when less experienced staff would not be able to detect a problem. In addition to the direct advantages discussed above, telemedicine can bring indirect benefits to this scenario. The most refined telemedicine systems should integrate information from the hospital information system, including data from monitoring devices. Acquiring and standardising these signals would dramatically increase the semantic value of medical registers. More importantly, this information could be used for other purposes.

29.4 Integrated Telemedicine and E-Learning

At least nowadays, one part of staff training – the part centred on skill acquisition – re-

quires the physical presence of both teacher and pupil. However, much training involves acquiring theoretical knowledge that makes up most of the curriculum, and this objective can be accomplished equally through either traditional or e-learning arrangements.

Given the potential consequences of medical errors, health care professionals receive extensive training and are expected to maintain errors to a minimum. Case-based learning systems (medical residency programmes, for example) yield the best results. However, these systems are labour intensive and consume enormous amounts of resources and time. Furthermore, this kind of learning can increase patient morbidity and mortality. This is where e-learning can help most. Computer simulations can replicate the intellectual processes involved in case-based learning.

E-learning comprises many different strategies with very different levels of technological development. At one end of the spectrum, e-learning is nothing more than the delivery of electronic documents for office applications (text files, electronic forms, slide presentations). In this approach, computers merely change the way contents reach students; the characteristics of the learning process remain unchanged. At the other end of the spectrum, sophisticated simulation systems allow the rules of the process to be changed, facilitating case-based learning. Unfortunately, in most simulation systems, the number of cases that can be introduced is limited during the programming stage.

Integrating telemedicine and e-learning systems could be highly advantageous. The system would make it possible to save interesting cases and to construct a teaching library. Cases in the library might include information about the problem and the solutions tested to enable posterior analysis of the actions undertaken and the effects brought about by different manoeuvres or changes. Thus, rather than simulations, this approach would enable learning based on real cases as well as on the mistakes made.

Telemedicine systems handle sensitive data that must operate on channels that can guarantee security and privacy of the information. There are diverse methods to maintain the security of a system, among them being the use of virtual private networks (VPN), encryption techniques and certificates and digital signatures. In any system for the practice of telemedicine, the value of the information transmitted depends on its quality, representation and reliability. In these critical systems, all data with questionable quality, representation or reliability are worse than worthless because they could lead to medical errors and consequent risks.

Communications among different systems can be ensured through standards for data storage and communication. Although its implementation is far from complete, HL7 (Health Level 7) is a set of standards for electronic exchange of medical information that will probably become the standard in telemedicine. HL7 encompasses clinical and administrative information; its most commonly used specification is a messaging standard for electronic interchange of health care data between systems and subsystems on the one hand, and between these and the hospital information system (HIS) on the other [13, 14].

29.5 Conclusions

Telemedicine has obvious advantages: it enables specialists to attend patients that need them in situations where human resources are unavailable or economically unviable. Nev-

ertheless, these direct advantages can even be surpassed by the indirect advantages related to the possibility of acquiring, normalising, synchronising and storing medical signals. In the very near future, it will be possible to amplify the reach of alarm systems, improve their specificity and enable the triggering of qualitatively different alarms: in addition to emitting sounds at the patient's bedside, alarms will consist of e-mails, short message services (SMS) or pager messages that can be sent immediately or according to a predefined scaling system when problems are not satisfactorily resolved. Not only will this change the way medical knowledge is applied, it will also change the way that knowledge itself is produced. Applying data-mining techniques to large databases of medical signals can generate huge amounts of information and lead to a new strategy for formulating hypotheses to be tested with the scientific method. It is even reasonable to expect that these analyses might reveal systematic alterations in one or more signals before the onset of an event [15].

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Professionalism, Quality of Care and Pay-for-Performance Services

30

A. Gullo, C. Santonocito, P. Murabito and M. Astuto

30.1 Professionalism Promotes Health Care Systems

There is an ongoing, heated debate concerning the best model possible for health care systems to respond to public expectations. Our society requires changes – radical changes – that place the organisational apparatus of the health care system in a critical position. Public opinion, as well as the opinion of medical professionals, reflects doubts concerning the ability of physicians to preserve their current role in serving patients. The term professionalism is frequently found in the medical literature and in debates about how to obtain the best organisation of health care systems. Although there is no consensus regarding the definition of professionalism, the term is closely related to the moral principles and standards of care, handed down from generation to generation, that make up the foundations of the medical profession [1, 2].

Renewal of the medical profession entails improvements in the quality of professional attributes related to ethics and morality, to clinical practice based on evidence and to standards for medical care and the use of new technologies. It also involves improvements in monitoring the quality of outcome, acquisition of knowledge and use of such knowledge through the observance of the Hippocratic Oath. Along the same line, it involves improvements in monitoring clinical research conducted for the sole purpose of helping patients. The correct application of all these elements and the presence of a solid and dynamic process of continuing medical education and specialisation represent the one way of renewing the medical profession. As John D. Lubahan defined it, the term professionalism is "the image of the ethical and moral conduct of those who practice the medical profession" [3].

In medicine, the term professionalism implies "good medical practice", which derives from the long and demanding training process that the profession requires. The demand for a better definition of professionalism in medicine is a result of significant changes within our society and a growing need to guarantee improved quality in community-based health care services. Thus, the term professionalism is being identified as the essence of humanisation, competence and specialisation [3].

APICE 23. Antonino Gullo (Ed.)

Table 30.1 The human element of professionalism. Modified from [5]

Definition	That part of the system represented by healthcare professionals
Role	To pause; to allow for critical-thinking skills
Goal	To do the best for patients; patient safety; professional performance

Bion and co-workers recently focused on the importance of human factors in managing critically ill patients [4]. The analysis of human factors provides a useful framework in which to understand and rectify unreliability and causes of errors, in particular, in complex systems such as the critical care setting. This makes human factors a particular area of research. Human factors influence performance as concerns the task, the individual and the organisation or system. By definition, professionalism indicates a crucial concept concerning the contract between medicine and society (Table 30.1). However, medical integrity may be influenced by political considerations. In this scenario we express our personal point of view on medical professionalism according to physicians' specialty, practice setting and pay-for-performance trials [5].

Professionalism, which is fundamental to medical practice, must be thought of explicitly. It is the basis of the relationship between medicine and society, which most observers call a social contract. The social contract serves as the basis for society's expectations of medicine and medicine's expectations of society. It therefore directly influences professionalism, considering that we live in the era of commercialism, consumerism, bureaucratisation and industrialisation [6]. The role of the healer is universal; however, how professionalism is manifested differs among countries and cultures owing to differences in their social contracts (USA vs. Europe vs. Italy, and so on). When we think of professionalism, it should be related to different cultures and their social contracts, respecting local customs and values [7].

A decreased public trust in all professions has brought increased attention to medical professionalism; it relates to those skills, attitudes and behaviours that people have come to expect from individuals during the practice of a profession and includes several concepts, such as maintenance of competence, ethical behaviour, integrity, honesty, relationships, responsibility, reliability, altruism, caring and compassion, service to others, adherence to professional codes, justice, respect for others, self-regulation, scientific knowledge, excellence, scholarship and leadership. There are no codes in the physician charter of medical professionalism [7] concerning pay-for-performance service.

Health care systems are regulated to support the health care needs to a target population. There is a multifaceted variety of health care organisations around the world. In some countries, health care system planning is delivered among market participants, whereas in others, planning is made more centrally among governments, trade unions, charities, religious or other coordinated bodies to delivery planned health care services targeted to the populations they serve. It seems a very difficult task comparing different organisations of health care systems, resource allocation and the modality to assure a horizontal and extra salary to improve the quality of care and outcome while reducing costs at the same

time. However, health care planning has often been evolutionary rather than revolutionary. The goals set by health care systems, according to the World Health Organization [8], are good health responsiveness to the expectations of the population and fair financial contribution.

Duckett proposed a two-dimensional approach to evaluation of health care systems: quality, effectiveness and acceptability on one dimension, and equity on the other [9]. Health care providers are trained professionals, working as self-employed individuals or as employees within an organisation – either a for-profit corporation, a nonprofit company, a government entity or a charitable organisation. Examples of health care providers are doctors and nurses, paramedics, dentists, medical laboratory personnel, specialist therapists, psychologists, pharmacists, chiropractors and optometrists. There are generally five primary methods of funding health care systems [10–12]:

1. direct, or out-of-pocket payments;
2. general taxation by the state, county or municipality;
3. social health insurances;
4. voluntary or private health insurances;
5. donations or community health insurances.

Advances towards improving the standard of care represent a real challenge in health care system management. Escalating costs and the growing imbalance between primary and specialty care have increased the urgency of calls for a fundamental reform of the health care payment system. This is a very critical point of controversy, and strong disparities persist in different area such as continental, national, regional and local environments [13]. At the core of the problem is the fact that the dominant fee-for-service models reward volume and intensity rather than value. However, although faults in the way we pay for health care are obvious, it is much less clear what feasible approach would yield better results. Avoiding disparity of care delivery and the capacity of high-quality care while lowering costs [14] and protecting patient safety are the cardinal points in a period of recession caused by a broken economy.

30.2 Patient Safety, Quality of Care and Evidence-Based Medicine

The focus on safety and quality of medical care is increasing because of the high cost of health care services and of the potential for harm [15]. Poor quality of care is not only costly but also produces errors and increased human suffering; in other words, poor quality of care results in an increase in morbidity and mortality. Patient safety is a new health care discipline that emphasises the reporting, analysis and prevention of medical errors that often lead to adverse health care events. The frequency and magnitude of avoidable adverse patient events was not well known until the 1990s, when several countries reported staggering numbers of patients harmed and killed by medical errors. Recognising that health care errors affect one of ten patients around the world, the World Health Organization (WHO) defines patient safety as an endemic concern [16]. In the USA, the public, as well as medical specialists in anaesthesia, were shocked in 1982 by the ABC television programme titled “The Deep Sleep”. Presenting accounts of anaesthesia-related accidents, the producer stated that every year, 6,000 Americans die or suffer brain damage related

to these mishaps [17]. In 1999, the Institute of Medicine (IOM) of the National Academy of Sciences released a report: "To Err is Human: Building a Safer Health System" [18]. The IOM called for a broad national effort to include the establishment of a Center for Patient Safety, to promote reporting of adverse events, to develop safety programmes in health care organisations and to raise the attention of regulators, health care purchasers and professional societies. Media attention, however, mainly focused on staggering statistics: from 44,000 to 98,000 preventable in-hospital deaths annually, and 7,000 preventable deaths related to medication errors. The experience was similar in other countries [19–25]. Although anaesthesiologists represent only about 5% of physicians in the USA, anaesthesiology has become the leading medical specialty addressing issues of patient safety [26].

Quality improvement (QI) initiatives in the intensive care unit (ICU) aimed at decreasing infections and maintaining normoglycaemia levels have been shown to improve outcomes as well as to decrease costs [27]. According to Hendrickson [28], the concept of using financial incentives to support and improve quality of care within the context of a professional endeavour such as medicine is not without moral and practical risks: damaging professionalism, increasing patient dissatisfaction with the low quality of care delivered, threatening the ongoing physician–patient relationship and, last but not least, the negative trend for access to care for all patients are the main negative elements empowering medicine as a mission. More than two decades marked a decisive improvement in life-sustaining technologies (LST), which resulted in an increased number of ICUs. ICU patient care is resource-consuming, as approximately 20% of the hospital budget is spent in the ICU.

Anaesthesiologists, intensivists, critical care physicians and nurses have a broad expertise in hospital organisation and the expanding area of quality and safety management by increased adherence to evidence-based guidelines, monitoring processes and improving quality of care [27]. Evidence-based medicine (EBM) integrates an individual doctor's exam and diagnostic skill targeted to a specific patient with the best evidence available from medical research. The doctor's expertise includes both diagnostic skills and consideration of each patient's rights and preferences in making decisions about patient care. Clinicians use relevant clinical research based on the accuracy of diagnostic tests and the efficacy and safety of therapy, rehabilitation and prevention to develop an individual treatment plan [29]. The development of evidence-based recommendations for specific medical conditions, termed clinical practice guidelines, or "best practices", has improved in the last decade. In the USA, >1,700 guidelines have been developed as a resource for physicians to apply to specific patient presentations [30]. The National Institute for Health Clinical Excellence (NICE) in the UK provides detailed clinical guidance for both health care professionals and the public about specific medical conditions [31].

30.3 Definition and the Reason for Measuring and Improving Performance

The definition of performance is the process whereby an organisation establishes the parameters within which programmes, investments and acquisition are reaching the desired results [27]. The process of measuring performance often requires the use of statistical evidence to determine progress towards specific organisational objectives. Performance may

Table 30.2 Different aspects of outcome

1. Medical outcome
- Survival rate: ICU, hospital, long-term
- Complication rate related to care
- Medical errors
- Adequacy of symptom control
2. Economic outcome
- Resource consumption: ICU, hospital, posthospital
- Cost-effectiveness of care
3. Psychosocial and ethical outcome
- Long-term functioning and quality of life
- Patient satisfaction
- Family satisfaction
- Concordance on desired end-of-life decisions
- Appropriateness of medical interventions provided
4. Institutional outcome
- Staff satisfaction and turnover rate
- Effectiveness of ICU bed utilisation
- Effectiveness of processes/procedures/functions involved in ICU care

ICU, intensive care unit

be measured using benchmarks or relative comparisons. There are three ways of evaluating performance: structure, process and outcome (Table 30.2). Structural measures are used to track and pay for resources that help improve care delivery (e.g. personnel such as diabetes educators or nutritionists, and specific infrastructures such as an electronic medical records system). Process measuring evaluates clinical services demonstrated to be necessary to facilitate positive health outcome, such as testing haemoglobin A1c levels in patients with diabetes or prescribing aspirin to heart attack patients upon hospitalisation. Outcome measurement typically evaluates clinical outcomes, such as whether blood pressure of diabetic or hypertensive patients is under control or whether hospital patients are readmitted to the emergency department, the ICU or the ward for potentially avoidable conditions [32]. Initially limited to small pilot programmes for improving performance, the use of outcomes measurement rapidly expanded over recent decades; more than half of all health maintenance organizations (HMOs) have now implemented some form of it and plans are underway to introduce pay-for-performance measures into Medicare and Medicaid in the United States [33].

Table 30.3 briefly reports several reasons for adapting performance measurements [34]. Measures that are not directly connected to improving performance (such as those directed to improving communication with the public to build trust) are measures that are means to achieving the ultimate purpose. Pay-for-performance trials in health care remain a controversial grey zone. Every reimbursement system creates some sort of potential conflict of interest. As defined by Radwin, what is needed to reduce the clash between “medicine, money and morals” are policies that hold doctors accountable to patients for fulfilling the profession’s ideals [35]. Pay-for-performance programmes have been developed by

Table 30.3 Reasons for measuring performance

1. To evaluate how well a public agency is performing: formulate a clear, coherent mission, strategy and objectives; then based on this information, choose how those activities will be measured;
2. To control how managers can ensure their subordinates are doing the right thing;
3. To budget: budgets are crude tools in improving performance;
4. To motivate: give staff significant goals to achieve and then use performance measures, including interim targets, to focus their thinking and work and to provide a periodic sense of accomplishment; performance targets may also encourage creativity in developing better ways to achieve the goal; measures to motivate improvements may also motivate learning;
5. To celebrate: commemorate accomplishments – such rituals bond staff, give them a sense of individual and collective relevance; moreover, by achieving specific goals, people gain sense of personal accomplishment; celebration helps improve performance because it must work through one of the likes – motivation, learning, etc.;
6. To produce: how public manager convinces political superiors, legislators, stakeholders, journalists and citizens that the agency is doing a good job;
7. To learn: learning is involved with a process – of analysis information provided by evaluating corporate performance (identifying what works and what does not);
8. To improve: what exactly should who do differently to improve performance; for a corporation to measure what needs to improve, it first needs to identify what it will improve and develop processes to accomplish that

United States and United Kingdom policy makers and payers (those who pay for health care services) as a means of improving the quality of health care. In fact, the Institute of Medicine's 2001 report, "Crossing the Quality Chasm", suggested realigning incentives to improve care [32]. However, USA health care quality falls short of established benchmarks based on the best available evidence. National Health Service (NHS) in the United Kingdom introduced pay-for-performance (P4P) contracts for all family practitioners. In the USA, more than half the commercial HMOs have started using such contracts, and recent legislation requires the Centres for Medicare and Medicaid Services do the same for Medicare [33].

Compensation is a core function of human resource management, one that has important direct and indirect implication, appraisal, training, retention and labour relations. At the centre of competency, cost and productivity issues in government, pay for performance is a key methodology in the compensation field and a central component of contemporary civil service reform [36]. As such, this controversial technique is a fitting topic. In light of expectations, the success of pay-for-performance programmes, by most accounts, is at best disappointing; indeed, the consequences are often counterproductive. Based on a previous experience in recent decades, the strategy may or may not be good in principle but is certainly difficult to do in practice. Starting from this critical point, pay-for-performance initiatives were defined by Bowman: The Success of Failure: The Paradox of Performance Pay [37].

In this context, we try to explore the most relevant aspects useful for selecting the priorities for better understanding the true meaning of the definition of medical professionalism, as well as the importance of monitoring safety, validating improved performance

and quality of care. Most organisations, furthermore, recognise merit, and most personnel believe that remuneration should be tied to contribution. On the other hand, managers see pay for performance as a basis for control, and employees embrace its intuitive appeal. It is not surprising, then, that public and private organisations claim to give great deference to merit, which needs clear explanation regarding meaning and value; particularly in the management of the health care system.

30.4 Pay for Performance: Definition and Examples of Impact

Pay for performance is the broadly encompassing term used to describe recent efforts to restructure payment to physicians and all allied members of the health care system so that rewards are commensurate to performance. Pay for performance is a term that describes health care payment systems that offer financial rewards to providers who achieve, improve or exceed their performance on specified quality, safety, costs and other benchmarks (Tables 30.4–30.6) [38, 39]. Initially limited to small programmes, pay for performance has rapidly expanded over the past decade. Hospitals that achieve quality improvements through their pay-for-performance programmes also stand to benefit from improved efficiencies. Higher-quality care not only has better outcomes but is also more efficient and cost effective. For example, as quality of care increase, length of hospital stay decreases, entailing lower costs and providing the opportunity to treat more patients.

There are various versions of pay for performance, and each presents its own advantages and disadvantages. The traditional version is also the most intuitive: compensate

Table 30.4 Pay-for-performance reimbursement strategy. Modified from [37]

Financial rewarding system	Insurance carriers pay money to hospitals based on how hospital stay is characterised by disease-related groups (DRGs)
Has the quality of care improved?	Yes: hospitals will receive financial rewards No: hospitals will receive financial penalty

Table 30.5 Pay-for-performance: three "WH" questions. Modified from [37]

What is it? (rationale)	US health care system reimbursement structure promoted by insurance carriers and federal government to motivate health care workers to deliver the best care for patients
Who is it for?	Hospitals, health care practitioner groups, individual physicians
What is its target?	Improve quality of care and control costs

Table 30.6 Pay-for-performance and different alternative programs that ensure extra payments for containing avoidable hospitalisations in Italy. Modified from [38]

• Pay-for-performance programs
• Pay-for-participation in improvement activities
• Pay-for-compliance with clinical guidelines

providers who keep costs down. One of the most common ways this is done is to give providers monetary rewards for limiting referrals to specialty providers. However, many physicians feel that such incentives can compromise patient care by placing selective pressure on providers; they thus prefer a system that rewards for satisfaction instead [40].

Competencies are characteristics of a person that cause superior performance of resource allocation and rationing. Problems to pay for performance include internal inequality and the potential for misuse. People bitterly experienced that competence was often not in tune with performance [6]. Most approaches adjust aggregate payments to physicians and hospitals on the basis of performance on a number of different measures. Payments may be made at the individual, group or institutional level. Pay for performance represents a radical departure from traditional-pay methods in which providers receive the same payment regardless of differences in quality of service. Incentives include positive and negative financial rewards, as well as nonfinancial rewards such as a premium network designation (e.g. preferred providers) and public recognition and reporting of high-quality performers. The programme is intended to drive lasting and meaningful improvements in health care parameters such as financial, clinical and patient satisfaction. It offers the greatest potential yet for balancing the autonomy that is critical to the practice of medicine with the provider's accountability, which is equally critical to patients who must receive safe and high-quality care.

However, such a programme is not a panacea, and implementation challenges abound. Neither is it just a report card for a hospital's internal use: public reporting of performance based on pay-for-performance metrics can affect a hospital's reputation. Even hospitals that deliver high-quality care can pale in the public spotlight if they do not accurately and diligently comply with pay-for-performance reporting requirements. Therefore, the use of this payment system promises to change the way patients select their hospitals. To this end, such programmes generally use measures that can be grouped into five categories:

1. evidence-based clinical performance;
2. patient safety;
3. patient satisfaction;
4. efficiency;
5. infrastructure.

Often, other definitions of pay for performance emphasise one of two drivers and evidence its multiple origins and difficult politics. The Council of Medical Specialty Societies (CMSS) in the United States, a group that includes many national health care agencies, states: "P4P means enhancing or reducing payments through the schedules, bonuses or

other initiatives, based on performance on certain measures of quality and value" [41]. The American Medical Association (AMA) states: "P4P programs are designed to improve the effectiveness and safety of patients care" [42]. An anaesthesiologist observes: "P4P represents the most recent step in managed care" [43]. A working group of the Committee on Economics of the American Society of Anesthesiologists states: "P4P programs propose to link payment rate to evidence of achievements of specific quality indicators" [44]. However, a question remains: can pay-for-performance programmes improve health quality and reduce disparities? In fact, despite growing enthusiasm for such programmes in the policy and commercial sectors, the evidence to support their effectiveness is weak [45]. Generally, studies show that modest improvement can be achieved in measures explicitly incentivised, at least over the short term [46]. However, it is unclear whether the improvements are a result of the financial incentives themselves or simply the increased focus on services resulting from performance measurement and publication data [47].

Another version of pay for performance is more correctly thought of as pay for participation. Instead of direct individual rewards for individual performance, providers are compensated for participation in larger collaborative activities designed to improve performance outcome. Providers receive regular feedback on their performance from peers and then work collaboratively to improve efficiency and collective patient morbidity and mortality rates: a highly effective programme in interventional cardiology is currently in place, with resultant improvements in mortality and postprocedure complication rates [48].

For surgical procedures, pay for performance presents unique challenges, as surgical outcomes are often more difficult to quantify and compare fairly. In response, a model based on Centres for Excellence has been developed at locations throughout the United States. The model involves identifying and funnelling patients towards hospitals and providers with proven track records of high-quality care. One example is the Leapfrog Group, a consortium based in Washington, DC, which has developed evidence-based referral practices for five surgical procedures based on risk-adjusted mortality rates, process measures and minimum-procedure volume [49].

30.4.1 Conclusive Remarks and Looking to the Future

Introduction of the pay-for-performance programme has been associated with a general trend in the UK National Health Service (NHS) away from placing implicit trust in health care professionals towards more active monitoring of their performance [50]. Financial incentives are most likely to be the most effective means of influencing professional behaviour when performance-target rewards are aligned to the values of the staff being rewarded [51, 52]. Professional motivation alone may not be sufficient to improve quality of patient care, especially when physicians have to make financial investment in their practices – for example, by employing more staff to achieve gains in quality. Sustained improvement in quality of care – which involves a range of health care providers (e.g. physicians, nurses, administrative staff) – requires a combination of other factors, including clear goals, good teamwork and effective leadership [53]. Ultimately, the most important question is whether pay for performance is actually effective in improving quality and/or efficiency. This remains an area of controversy (Table 30.7).

Table 30.7 Pay-for-performance programs: concerns

• Economic incentives become an organising model that can be turned into an obligation under pressure from some group
• An infinite cost escalation in the time of finite resources
• Internal inequality and potential for misuse
• Competence often is not in line with performance
• Set or increased amount of work time is not often useful to improve performance

For example, an analysis of the Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the ACC/AHA Guidelines (CRUSADE) registry examined the effects of pay for performance on treatment of myocardial infarction and found that pay for performance resulted in only limited improvement in quality of care and outcomes [54]. A more recent analysis of various pay-for-performance plans found mixed results, with no consistent improvement in quality in all plans [55]. Some fundamental problems included the fact that many of these programmes seemed to permit adverse selection by allowing providers or hospitals to exclude the sickest patients. The remaining patients only appeared to have improvements in quality; in reality, many improvements were simply due to improved documentation. Much depends on the details of the plan, as all pay-for-performance plans present structural questions that must be correctly addressed prior to implementation. Several questions remain unsolved: should benefits be given to individual physicians or to organisations that will then distribute the benefits collectively? What is the correct compensation amount? How should performance be measured? Who should be rewarded for performance: all high performers or only the top performers [56]?

To date, there are no decisive answers as to whether pay-for-performance programmes work definitively respecting professionalism recommendations; the linking of physician reimbursement to measures of clinical performance is growing in popularity among payers, including local health authorities and manager, including national and federal governments. Although a body of literature is developing on the anticipated positive results of such programmes – and we applaud innovations that improve care – little evidence exists on the effectiveness of such programmes [57–59]. Pay for performance focuses attention on ethical conflicts because it rewards good quality care by improving the physician's income, but conflict of interest exists with nonfinancial incentives to improve quality – only the incentives differ. Similarly, financial conflicts exist in every payment system, such as incentives in fee-for-service payment to increase care or the incentive under capitation to do less rather than more. In all of these conflict-of-interest situations, the ethical imperative is the same: clinicians must ensure that provision of medically appropriate levels of care take precedence over personal considerations [60, 61]. According to Snyder and Neubauer, pay for performance programmes and other strong incentives can increase the quality of care if they purposely promote the ethical obligation of the physician to deliver the best-quality care for their patients [59]. Proposed methods for assuring quality processes

Table 30.8 Initiatives to improve quality processes and clinical performance. Modified from [59]

• Use of chronic care management processes (CMPs)
• Electronic medical record (EMR) capabilities
• Participation in external quality improvement (QI)

and improving clinical performance are suggested by Damberg et al. in Table 30.8 [61]. Lagasse and Johnstone – in a thoughtful review – define pay for performance, or value purchasing, as "the use of incentives to encourage and reinforce the delivery of evidence-based practice and health care systems' transformation that promotes better outcomes as efficiently possible" [61]. This definition provides some insight into the current status of pay for performance by describing its driving force more clearly than it does any particular incentives. In other words, the driving forces pay for performance are quality improvement and cost reduction.

In conclusion, the American College of Emergency Physicians (ACEP) removed the assumptions that pay for performance can improve patient-centred care, but only if we learn how to measure it. As pay-for-performance programmes evolve, ACEP hopes to move forward the debate on incentives for quality by insisting on a patient-centred focus – one that puts the needs and interest of the patients first [62, 63].

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Subject Index

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