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Annual Update in Intensive Care and Emergency Medicine 2011

Edited by J.-L.Vincent

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Common Abbreviations

AKI	Acute kidney injury
ALI	Acute lung injury
ARDS	Acute respiratory distress syndrome
AUC	Area under the curve
BAL	Bronchoalveolar lavage
CABG	Coronary artery bypass graft
CNS	Central nervous system
COPD	Chronic obstructive pulmonary disease
CPB	Cardiopulmonary bypass
CRP	C-reactive protein
CSF	Cerebral spinal fluid
CT	Computed tomography
CVP	Central venous pressure
DO_2	Oxygen delivery
ECMO	Extracorporeal membrane oxygenation
EKG	Electrocardiogram
GFR	Glomerular filtration rate
ICAM	Intercellular adhesion molecule
ICU	Intensive care unit
IL	Interleukin
LPS	Lipopolysaccharide
LV	Left ventricular
MAP	Mean arterial pressure
MRI	Magnetic resonance imaging
MRSA	Methicillin-resistant *Staphylococcus aureus*
NF-κB	Nuclear factor-kappa B
NO	Nitric oxide
NOS	Nitric oxide synthase
PAC	Pulmonary artery catheter
PAOP	Pulmonary artery occlusion pressure
PEEP	Positive end-expiratory pressure
RBC	Red blood cell
ROC	Receiver operating characteristic
ROS	Reactive oxygen species
$ScvO_2$	Central venous oxygen saturation
SIRS	Systemic inflammatory response syndrome
SOFA	Sequential organ failure assessment
SvO_2	Mixed venous oxygen saturation
TLR	Toll-like receptor
TNF	Tumor necrosis factor
VAP	Ventilator-associated pneumonia

I Mechanisms of Sepsis and Multiple Organ Failure

The Role of Receptor for Advanced Glycation Endproducts (RAGE) in Infection

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Introduction

During evolution, multicellular organisms have developed an impressive arsenal of defense and repair mechanisms to counteract threats such as infection and trauma. Such an inflammatory response begins with the detection of the potential life-threatening event by recognizing so-called danger signals. These signal molecules have been classically divided into: i) Exogenous, pathogen-associated molecular patterns (PAMPs) [1], which are conserved motifs on pathogens that are not found in higher eukaryocytes; and ii) endogenous innate danger molecules, also named damage-associated molecular patterns (DAMPs) or alarmins, which are structurally diverse proteins rapidly released by the host itself during infection or (sterile) tissue damage [2].

Known PAMPs include lipopolysaccharide (LPS) from the outer membrane of Gram-negative bacteria, peptidoglycan (present in most bacteria), lipoteichoic acid (in many Gram-positive bacteria), bacterial DNA, viral DNA/RNA and mannans in the yeast cell wall. PAMPs are recognized by pattern recognition receptors (PRRs), in particular Toll-like receptors (TLRs) and Nod-like receptors (NLRs), leading to an inflammatory response via several signaling pathways, including nuclear factor-kappa B (NF-κB) activation and subsequent tumor necrosis factor (TNF)-α production.

Examples of putative DAMPs, the endogenous equivalents of PAMPs, are high-mobility group box 1 (HMGB1), some S100 proteins (S100A8/A9, S100A12), interleukins such as IL-1α, heat-shock proteins (HSPs), and nucleosomes [3]. DAMPs can be secreted either actively or passively following necrosis but are not released by apoptotic cells [4] and have activating effects on receptor-expressing cells engaged in host defense. DAMPs can also be detected by TLRs and NLRs and their engagement induces NF-κB activation as well, suggesting that DAMPs and PAMPs use, at least partially, the same receptors and signaling pathways. Liu et al. [5] however, propose that the immune system treats DAMPs and PAMPs differently; they suggest that DAMPs – but not PAMPs – bring CD24-Siglec G/10 into the proximity of TLRs/NLRs, resulting in repressed DAMP-induced TLR/NLR signaling.

When invaded by pathogens, host defense systems encounter PAMPs from microorganisms and DAMPs that are released from tissues, which are recognized by TLRs and NLRs to warn the host of imminent danger. In addition, the multiligand receptor for advanced glycation endproducts (RAGE) is regarded as a prototypic DAMP receptor that can bind several DAMPs, including HMGB1 and S100A12 [6]. Other known RAGE ligands include amyloid, β-sheet fibrils, S100B

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and S100P [7]; furthermore, β2 integrins can interact with RAGE [8]. RAGE is expressed at high levels in the lungs and at low levels in normal adult tissues, including on cells involved in the innate immune system, e.g., neutrophils, T and B lymphocytes, monocytes, macrophages, dendritic cells, and endothelial cells [7]. Engagement of RAGE by its ligands leads to receptor-dependent signaling and activation of NF-κB and mitogen-activated protein kinase (MAPK) pathways [7]. Activation of RAGE plays a role in diverse experimentally-induced sterile inflammatory and infectious diseases, including cecal ligation and puncture (CLP)-induced abdominal sepsis [9], diabetic nephropathy, delayed type hypersensitivity, type II collagen induced arthritis, hepatic injury, and diabetic atherosclerosis [7, 10–12]. This review focuses on new insights into the pathogenesis of infectious diseases, including sepsis, peritonitis and pneumonia, offered by studies conducted in the RAGE research field.

RAGE: A Multiligand Receptor

RAGE consists of three immunoglobulin-like regions, a transmembrane domain, and a highly charged short cytosolic tail that is essential for intracellular signaling [13]. The V domain in the extracellular part of RAGE is essential for binding of its ligands. Because of its ability to recognize three-dimensional structures rather than specific amino acid sequences, RAGE can interact with a wide range of ligands. RAGE was first identified as a receptor for advanced glycation end-products (AGEs), explaining its name. AGEs are products of the non-enzymatic glycation and oxidation of lipids, proteins and other macromolecules that appear, in particular, under conditions of increased availability of reducing sugars and/or enhanced oxidative stress, especially when molecules turn over slowly and aldose levels are elevated. Further investigations showed that RAGE can recognize a diverse array of endogenous molecules that warn the immune system and induce a defensive immune response; the alarmins or DAMPs.

Putative RAGE Ligands in Infectious Diseases

HMGB1

HMGB1 is a non-histone DNA-binding protein that serves as a structural component to facilitate the assembly of nucleoprotein complexes in the nucleus [14]. Extracellularly, HMGB1 functions as a cytokine. In response to inflammatory stimuli, including PAMPs, HMGB1 can be actively released into the extracellular environment from a variety of cells including monocytes, macrophages, endothelial cells, enterocytes, pituicytes, dendritic cells, and natural killer cells [14]. HMGB1 can also be passively secreted into the extracellular milieu when cells die in a non-programmed way (necrosis), whereas apoptotic cells modify their chromatin so that HMGB1 binds irreversibly and consequently is not released [4]. During infectious diseases, increased HMGB1 concentrations may be due to active as well as passive release. Detection methods of HMGB1 that are currently used (and published) do not distinguish between these (and possible other) different forms of HMGB1. More studies are necessary to: 1) Report the biological activity of (different forms of) HMGB1; and 2) develop HMGB1 ELISA assays that can distinguish between these (possibly also functionally) different forms of

HMGB1. Most investigations on HMGB1 and infection involve sepsis, the second leading cause of death in non-coronary intensive care units (ICUs) and the 10th leading cause of death overall. Patients with severe sepsis display elevated circulating HMGB1 levels [15–17] and HMGB1 is predominantly released at the site of infection; patients with pneumonia and those with peritonitis showed increased concentrations in fluid obtained from the bronchoalveolar space and abdomen, respectively [17]. In an animal model of CLP-induced sepsis, the kinetics of HMGB1 secretion *in vivo* was delayed and more sustained when compared with the release of pro-inflammatory cytokines, like TNF-α, IL-1β and IL-6 [18, 19]. Similarly, various interventions that inhibit HMGB1 activity or production, such as anti-HMGB1 antibodies, the A-box segment of HMGB1, ethyl pyruvate, and nicotine, reduced CLP-induced sepsis and/or LPS lethality even if treatment was delayed for many hours, up to one day after the challenge [20, 21]. An implicated crucial event in sepsis pathophysiology is apoptosis of immune cells, playing a major role in immunosuppression and lethality [22]. HMGB1 seems to be a downstream factor of apoptosis in the final common pathway to organ damage in severe sepsis as indicated by observations that prevention of lymphocyte apoptosis improved survival after CLP [23], whereas anti-HMGB1 treatment reduced lethality in the same model without influencing apoptosis [19]. This indicates that HMGB1 secretion is a relatively late event in sepsis that contributes significantly to a worsened outcome. In addition, it has been reported that very pure HMGB1 does not have cytokine-inducing capacity itself, but activates cells indirectly by first acquiring immune stimulating CpG DNA [24], which is released in the bloodstream during bacterial sepsis. However, a recent study reported that HMGB1-mediated induction of macrophage cytokine production requires binding to TLR4, and that binding and signaling are dependent on a molecular mechanism that requires cysteine in position 106 within the B box [25]. Together these data indicate that HMGB1 may exert pro-inflammatory effects in a direct TLR4-dependent way and an indirect way via binding of DAMPs and other agonistic molecules.

S100A12

S100A12 is a calcium binding protein expressed in the cytoplasm of neutrophils, where it comprises 5 % of the total protein content. Furthermore, S100A12 – also known as EN-RAGE (extracellular newly identified ligand of RAGE) or myeloid-related protein (MRP)-6 – is found in monocytes and lymphocytes and provokes pro-inflammatory responses in endothelial cells [26]. Although many RAGE ligands are promiscuous with regard to receptor use, S100A12 has only been shown to bind to RAGE. S100A12 expression is high in inflammatory diseases such as atherosclerosis, rheumatoid arthritis, Crohn's disease, Kawaski disease, and cystic fibrosis. Within the lungs, S100A12 and RAGE are increased during acute lung injury (ALI) [26]. S100A12 expression may reflect activation of neutrophils during pulmonary inflammation and may contribute to endothelial activation via binding to RAGE [26].

β2 integrins

Recruitment of leukocytes to the site of infection is an essential step in host defense during infectious diseases against invading pathogens. RAGE plays a role

in the regulation of cell migration in several ways. First of all, RAGE is a counter-receptor for integrins on leukocytes; in particular, RAGE has been identified as a binding partner for the β2 integrins, Mac-1 and p150, 95 [8]. Second, by the interaction of RAGE with β2 integrin-mediated leukocyte recruitment *in vivo*: RAGE$^{-/-}$ mice displayed a diminished number of adherent inflammatory cells on the peritoneum after CLP [9] and a reduction in neutrophil influx in the peritoneal cavity after thioglycollate peritonitis [8]. Interestingly, HMGB1 can activate lateral (*in cis*) RAGE-Mac-1 interactions on the leukocyte cell surface, enhancing Mac-1-intercellular adhesion molecule (ICAM)-1-dependent adhesion and migration [27] (**Fig. 1**, indicated by the blue line and blue "+"). Furthermore, a recent report

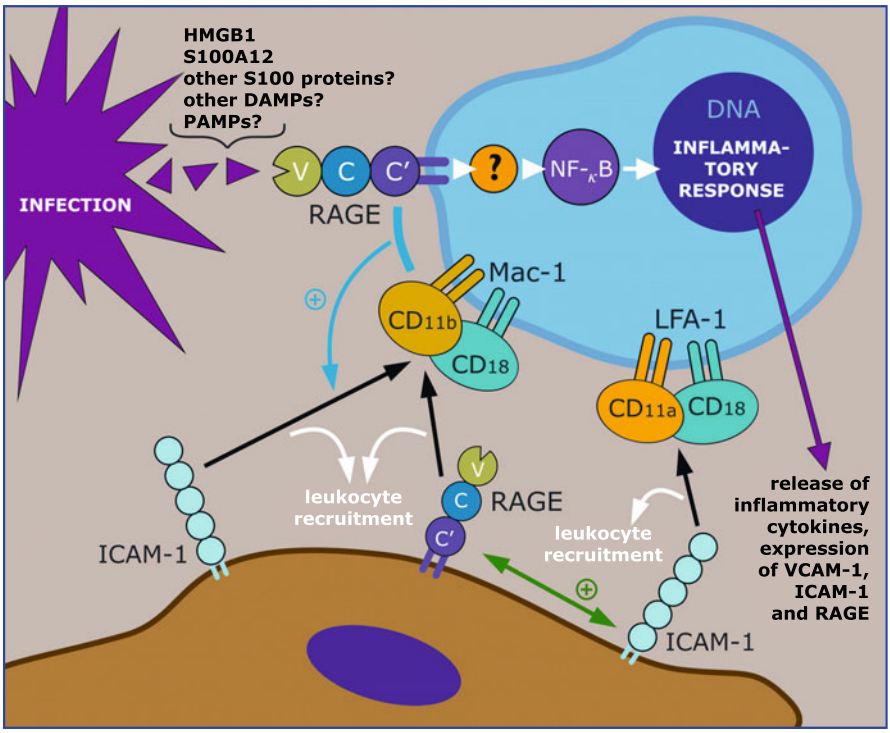

Fig. 1. Putative involvement of the receptor for advanced glycation endproducts (RAGE) during infection. The damage-associated molecular patterns (DAMPs), high-mobility group box 1 (HMGB1) and S100A12, are released during infection [15, 17, and unpublished data] and bind to and activate RAGE. It has to be determined whether other S100 proteins and other DAMPs are RAGE ligands (indicated as purple shapes) released during infection. It would be interesting to investigate whether RAGE can directly bind to, become activated and mount a first immune reaction after ligation with specific PAMPs as well. Engagement of RAGE by its ligands results in receptor-dependent signaling and activation of NF-κB leading to a pro-inflammatory response; the signaling pathway is largely unknown. In addition, RAGE interacts as an endothelial (and epithelial) adhesion receptor with the leukocyte integrin, CD11b/CD18 (Mac-1) (lower section) [8]. Furthermore, lateral (*in cis*) RAGE-Mac-1 interaction on the leukocyte surface is mediated by HMGB1 and activates Mac-1-intercellular adhesion molecule (ICAM)-1 dependent adhesion and migration and augments leukocyte recruitment [27] (indicated by the blue line and blue "+"). Moreover, a recent report shows that endothelially expressed RAGE acts in concert with ICAM-1 in mediating β_2 integrin–dependent leukocyte adhesion during acute trauma–induced inflammation [28] (indicated by the green line and green "+").

shows that endothelial expressed RAGE acts in concert with ICAM-1 in mediating β_2 integrin-dependent leukocyte adhesion during acute trauma-induced inflammation [28] (**Fig. 1**, indicated by the green line and green "+").

RAGE: A Signal Transducing Receptor

The signaling cascade(s) of RAGE – induced by engagement of its various ligands – that ultimately activates NF-κB is largely unknown. The predicted cytosolic portion of RAGE, consisting of 43 amino acids, is short compared to other PRRs, the TLRs and IL-1 receptors, and does not include a known signaling domain or motif. A RAGE mutant lacking this intracellular tail does not activate NF-κB and behaves like a dominant negative, preventing pro-inflammatory cytokine release from macrophages. These data indicate a critical role of this cytosolic portion in transducing the signal from the cell surface to the nucleus. One possibility is that RAGE uses as yet unknown adaptors framing a whole 'new' signaling cascade to NF-κB. Another possibility is that the RAGE tail interacts with a Toll/IL-1 receptor (TIR)-containing protein which then recruits the downstream TIR-containing proteins in a way analogous to TLR-mediated signaling pathways. Finally, RAGE could transduce signals from the cell surface to the nucleus by bypassing the TIR-containing adaptor, directly interacting with member(s) of the signaling cascade.

In addition to triggering NF-κB activation, RAGE engagement by its myriad ligands is linked to an array of signaling pathways, including MAPK family members, such as Jun-N-terminal kinase (JNK), p38 and extracellular signal-regulated kinase (ERK), PI3K/Akt, Rho GTPases, Jak/STAT and Src family kinases [7].

This rather extraordinary variety of observed signals may be due to the broad expression of RAGE, its diversity of ligands, and possible contaminating elements in the preparations used in experiments.

Soluble RAGE (sRAGE)

The truncated form of full-length RAGE, soluble RAGE (sRAGE), consists of only the extracellular ligand-binding domain (V-C-C') lacking the cytosolic and transmembrane domains (i.e., the parts that transfer a signal into the cell) and circulates in the bloodstream. sRAGE has been indicated to be involved in inflammatory processes in several ways. First, sRAGE blood concentrations are associated with various inflammatory diseases in patients and in rats with experimentally induced ALI [29]. Furthermore, it is suggested that sRAGE can compete with full length cell-surface RAGE for ligand engagement, preventing these ligands from binding to RAGE or other receptors and/or exerting effects otherwise. Exogenous sRAGE treatment indeed attenuated inflammatory responses in several animal models, including models of type II collagen-induced arthritis, hepatic injury, diabetic atherosclerosis, delayed type hypersensitivity, and experimental autoimmune encephalomyelitis [7]. The involvement of sRAGE during infection is not known. Based on experimental studies in rats and in patients with ALI, sRAGE has been described as a marker of lung injury [29].

I

RAGE During Infection

An increasing amount of research suggests a role for RAGE in the pathogenesis of pneumonia, peritonitis and sepsis, indicating that RAGE (ligand)-directed therapies might offer new treatment opportunities for human disease in the future.

RAGE During Pneumonia

Localization and role of RAGE in the lungs

Recent studies point to an important role of RAGE in the pulmonary compartment in physiological as well as in pathological circumstances. Physiologically, RAGE is expressed at high basal levels in the lungs relative to other tissues [26, 29–34], suggesting that RAGE may have lung-specific functions distinct from the role of RAGE in other adult tissues. In particular, although the kidney is dramatically affected by microangiopathy and fibrosis – which is substantially attributed to RAGE – in patients with diabetes, the lungs, with a significantly higher baseline RAGE expression than the kidney, remain unaffected. In addition, RAGE has been found to be specifically localized near the basal cell membrane within alveolar pneumocytes [32, 35, 36]. These two observations raise the question as to whether RAGE has a function in normal healthy lungs. Indeed, Englert et al. documented that aged $RAGE^{-/-}$ mice develop pulmonary fibrosis-like alterations spontaneously; lungs from 19 to 24 month-old $RAGE^{-/-}$ mice showed increased collagen staining and displayed increased levels of hydroxyproline relative to wild type mice [31]. RAGE knockdown in pulmonary fibroblasts increased their proliferation and migration *in vitro*, suggesting an important protective function of RAGE in the lungs and that loss of RAGE may be related to functional changes of pulmonary cell types resulting in fibrotic disease [34]. Another study demonstrated that RAGE on epithelial cells promoted their adherence to human collagen (a major component of the alveolar basal lamina) and a spreading morphology, which may facilitate gas exchange and alveolar stability *in vivo* [34, 35]. Together, these data suggest that RAGE plays a role in maintaining lung homeostasis in normal, healthy lungs. Further studies are needed to unravel the function(s) of pulmonary RAGE in physiology in more detail.

This putative functional role of RAGE in healthy lungs may be the explanation for the finding that the inhibition of RAGE signaling attenuates pathological sterile inflammatory responses in diverse non-pulmonary experimental studies [9–12], whereas in pulmonary non-infectious pathological inflammatory conditions, somewhat conflicting results emerge. Lung injury induced by either bleomycin or hyperoxia is diminished in $RAGE^{-/-}$ mice [37, 38], suggesting a deteriorating attribution of RAGE. In contrast, Englert et al. showed that $RAGE^{-/-}$ mice developed more severe lung fibrosis after asbestos administration as measured by histological scoring and total lung hydroxyproline quantification [31]. Of note, in all these studies, the mice were much younger at the time of sacrifice than the aged (19–24 month-old) $RAGE^{-/-}$ mice that developed pulmonary fibrosis spontaneously in the experiment by Englert et al. [31]. Interestingly, lung homogenates and bronchoalveolar lavage (BAL) fluid from patients suffering from idiopathic pulmonary fibrosis reveal reduced membrane bound (and soluble) RAGE protein levels compared to healthy donor samples [31, 34].

RAGE expression during pneumonia

Community-acquired pneumonia (CAP) is distinguished from hospital-acquired pneumonia (HAP) according to the time of acquisition of pneumonia and the pathogens involved. The Gram-positive bacterium, *Streptococcus pneumoniae*, is the single most frequent pathogen causing CAP, responsible for up to 60 % of cases; *Klebsiella pneumoniae*, *Haemophilus influenzae, Staphylococcus aureus*, and viruses are isolated in about 10 % of cases each and *Mycobacterium tuberculosis* is more prevalent in developing countries. Knowledge of the expression and role of RAGE in host defense during pneumonia is limited. Morbini et al. observed increased RAGE expression in patients with interstitial and postobstructive pneumonia [32]; this report left unanswered whether patients with bacterial pneumonia were included in the analysis. Notably, two other studies showed that constitutively present RAGE was not upregulated during pulmonary inflammation associated with ALI or acute respiratory distress syndrome (ARDS): First, rats with ALI induced by intratracheally administered LPS displayed no change in the distribution of RAGE-expressing cells [29]; and second, patients with ARDS did not have increased pulmonary expression of RAGE [26].

sRAGE has been suggested to be a lung injury marker based on studies in patients with ALI and on experimental studies in rats [29]. sRAGE was increased in pulmonary edema fluid and serum from patients with either ALI or ARDS and with hydrostatic pulmonary edema, and in BAL fluid from rats with either LPS- or hydrochloric acid-induced ALI [29].

Considering the ubiquitous expression of RAGE in the lungs, its putative involvement in the regulation of lung inflammation and the somewhat inconsistent findings which currently exist in the literature, we investigated its role during pneumonia, a major cause of morbidity and mortality world-wide. Recently, we reported that murine pneumonia induced by *S. pneumoniae* and by influenza A virus was associated with an upregulation of intra-alveolar (membrane bound) RAGE expression [39, 40]. Furthermore, lung tissue of mice intranasally infected with the *K. pneumoniae* or with *M. tuberculosis* also showed increased RAGE expression (unpublished data). These clinically very different types of pulmonary infection and the involvement of RAGE therein will be discussed below.

Role of RAGE in pneumonia caused by different pathogens

Levels of the high-affinity RAGE ligand, HMGB1, were higher in BAL fluid from patients with pneumonia compared to BAL fluid from healthy controls [17]. In experimentally induced pneumococcal pneumonia, the presence of RAGE was detrimental: Mice lacking RAGE had a better survival rate together with a lower pulmonary bacterial load and decreased dissemination of *S. pneumoniae* to blood and spleen compared to wild-type mice [39]. The difference was possibly partially due to an increased killing capacity of $RAGE^{-/-}$ alveolar macrophages. Additionally, lung injury and neutrophil recruitment were reduced in the $RAGE^{-/-}$ mice, which parallels findings on RAGE as an endothelial counter receptor for the β2 integrin, Mac-1, [8] and the interplay between RAGE and Mac-1 on leukocytes, required for HMGB1-mediated inflammatory cell recruitment [27]. In addition, blockade of the RAGE-HMGB1 interaction and prevention of the subsequent pro-inflammatory stimulus might be an explanation for the less severe pulmonary damage in the $RAGE^{-/-}$ mice during *S. pneumoniae* pneumonia.

Interestingly, in contrast to Gram-positive pneumonia, preliminary data from our laboratory reveal that RAGE plays a beneficial role in mice during the host

response to Gram-negative pneumonia (unpublished data). Indeed, RAGE deficiency was associated with increased mortality and increased bacterial outgrowth and dissemination after *K. pneumoniae* inoculation (unpublished data). Relative to wild type mice, lung inflammation was similar and cytokine and chemokine levels were slightly – if at all – elevated. Moreover, $RAGE^{-/-}$ mice showed an unaltered response to intranasally instilled *Klebsiella* LPS with respect to pulmonary cell recruitment and local release of cytokines and chemokines. Together, these findings indicate that RAGE contributes to an effective antibacterial host response during *K. pneumoniae* pneumonia, whereas RAGE plays an insignificant part in the lung inflammatory response to either intact *Klebsiella* or *Klebsiella* LPS.

It is unclear whether RAGE can also interact with ligands from pathogens. If so, this could be part of the explanation for our observation that RAGE involvement during Gram-positive and –negative pneumonia had such opposite effects on mortality. In addition, RAGE-mediated effects on other first-line defense mechanisms, such as chemotaxis, phagocytosis, killing (including respiratory burst), may depend on the pathogen and may contribute to the observed effects in Gram-positive and -negative pneumonia models. However, this remains speculative until investigations have been performed to analyze this interesting issue.

In addition to its potential to cause pandemics, seasonal influenza A virus infection causes over 200,000 hospitalizations and approximately 41,000 deaths in the United States annually, being the 7^{th} leading cause of mortality. We demonstrated that RAGE deficiency resulted in a better outcome from pulmonary influenza A virus infection as indicated by a relative protection from influenza A virus-induced lethality in mice [40]. This was accompanied by improved viral clearance and enhanced cellular T cell response and activation of neutrophils, suggesting that endogenous RAGE impairs the cellular immunity against respiratory tract infection with influenza A virus. RAGE ligand, HMGB1, as well as sRAGE were upregulated in BAL fluid during influenza A virus pneumonia. Hence, similar to pneumonia induced by the Gram-positive bacterium *S. pneumoniae*, RAGE is detrimental during pneumonia caused by influenza A virus. This is of particular interest, since it has been suggested that the greatest proportion of the mortality associated with influenza A virus infection is due to secondary bacterial pneumonia, with *S. pneumoniae* as the most frequent pathogen of the superinfection. Therefore, RAGE is a potential treatment target in postinfluenza pneumococcal pneumonia and further research is warranted to investigate this.

RAGE during Abdominal Sepsis

The role of RAGE in abdominal sepsis has been investigated in a limited number of studies so far. RAGE-deficient mice showed decreased mortality after induction of polymicrobial sepsis induced by CLP in two reports [9, 41]. Moreover, anti-RAGE antibody yielded a better survival even when the anti-RAGE therapy was delayed up to 24 hours after CLP in mice receiving antibiotics [41]. The protective effect provided by the absence of RAGE was related to a firm inhibition of NF-κB activation, suggesting that the lack of excessive NF-κB activation in $RAGE^{-/-}$ mice might have contributed to their reduced mortality [9]. In addition, RAGE deficiency resulted in fewer inflammatory cells in the peritoneum [9], which parallels the results of an earlier investigation by the same group of authors identifying RAGE as a counter-receptor for the β2 integrin, Mac-1 (CD11b/CD18), and thereby as a mediator of leukocyte recruitment and adhesion [8]. Furthermore,

the protective effect of RAGE inhibition in this CLP model could at least in part be the consequence of the inhibition of one of its ligands, HMGB1. Indeed, HMGB1 is secreted into the circulation after CLP and anti-HMGB1 antibody led to increased survival after CLP-induced peritonitis [18].

In the same surgically (CLP)-induced model of sepsis, RAGE deficiency and anti-RAGE therapy were reported not to affect bacterial outgrowth in the peritoneum, liver, or spleen [41]. Notwithstanding, a possible role of RAGE in antibacterial defense cannot be easily evaluated from this study because host defense against CLP depends, at least in part, on the extent of intestinal necrosis and the formation of a local abscess. Also, all mice in this experiment received broad spectrum antibiotics and bacterial outgrowth was only determined in mice that survived (i.e., not at predefined time points after CLP). For this reason, we used our model of abdominal sepsis induced by injection of the Gram-negative bacterium *Escherichia coli* into the peritoneum [42, 43] to study whether RAGE affects antibacterial defense. This model is a relevant tool to investigate the role of receptors/mediators in limiting the growth and dissemination of bacteria after a primary intra-abdominal infection and to assess the contribution of these proteins to specific immune responses. RAGE expression was upregulated during *E. coli* induced sepsis [42]. RAGE deficiency (either pharmacologically using anti-RAGE IgG antibodies or genetically using RAGE knock out mice) was related to a higher bacterial load and dissemination [42]. These data indicate that RAGE signaling contributes to an effective antibacterial response during abdominal sepsis. RAGE exerted this effect probably indirectly and not via direct interaction with *E. coli*, considering the observation that leukocytes from $RAGE^{-/-}$ mice had an unaltered capacity to phagocytose and kill *E. coli in vitro*. Furthermore, the finding that deficiency of RAGE in general was associated with an exaggerated host response during *E. coli* sepsis [42] on the one hand, and with an attenuated inflammatory response and better survival in (other) sterile models of intraperitoneal injection of LPS derived from *E. coli* [42, 44] on the other hand, suggests that although RAGE is involved in the immune reaction to *E. coli*, this function can be compensated for by other receptors in the presence of a growing bacterial load. The high-affinity RAGE ligand, HMGB1, is secreted into the circulation systemically during clinical sepsis [16–18] as well as in our experimental sepsis model of *E. coli* [43]. Importantly, HMGB1 has been shown to transduce cellular signals *in vitro* and *in vivo* by interacting with at least three other receptors, i.e., TLR2, TLR4 and TLR9 when HMGB1 is complexed with CPG DNA [24, 44, 45]. One possible explanation for the increased response in the RAGE lacking mice during *E. coli* sepsis is, therefore, that the absence of RAGE could facilitate the interaction between HMGB1 and TLR2, TLR4 and/or TLR9.

Evidence of involvement of ligands of RAGE and HMGB1 in host defense in *E. coli* abdominal sepsis was recently published by our laboratory [43]. Inhibition of multiple RAGE ligands (by the administration of sRAGE) and inhibition of HMGB1 (by the administration of anti-HMGB1 antibodies) led to an enhanced bacterial dissemination of *E. coli*, denoting an advantageous role of RAGE ligands, including HMGB1, in the antibacterial response during Gram-negative sepsis.

Interestingly, we recently found that S100A12, another high-affinity ligand of RAGE, is released systemically in patients during (abdominal) sepsis and also locally during peritonitis (unpublished data). Additionally, intravenous injection of LPS in healthy humans raised circulating S100A12 levels, implying that LPS

might partially contribute to this upregulation during Gram-negative infection. Payen et al. reported that, in patients with septic shock, mRNA S100A12 expression by circulating leukocytes was decreased during the recovery phase [46]. One possible function of S100A12 in host defense during infection and sepsis is its role as a DAMP. NF-κB mediated expression of pro-inflammatory cytokines and upregulation of ICAM-1 and vascular cell adhesion molecule (VCAM)-1 on endothelium has been documented *in vitro* after S100A12 stimulation [47]. Furthermore, S100A12 could be of benefit for the host during infection and sepsis due to its (more direct) antibacterial activity. Cole et al. determined that S100A12 has activity primarily against Gram-negative bacteria, including *E. coli* [48]. Because of the absence of S100A12 in rodents, a potential functional role of S100A12 during sepsis cannot be easily investigated by inhibiting/deleting S100A12 in animals. Altogether, the role of S100A12 during sepsis has yet to be evaluated using non-rodent models.

Bopp et al. documented that septic patients have elevated circulating sRAGE levels and that non-survivors show higher plasma sRAGE concentrations than survivors, suggesting that sRAGE is related to severity and clinical outcome in sepsis [49]. Knowledge on the role of endogenous sRAGE in sepsis is scarce. Hudson et al. demonstrated that sRAGE levels might represent an early marker of microvascular dysfunction, a phenomenon also present in sepsis [50]. Furthermore, increased sRAGE concentrations in sepsis might represent the acute inflammatory status as splice variants of RAGE or as split off variants of the cell surface RAGE, the latter analogous to ICAM-1, another member of the immunoglobulin superfamily, which is a marker of cellular damage during sepsis. Another possibility is that systemic sRAGE levels might be elevated in parallel with HMGB1/S100A12 levels as a counter-system against HMGB1/S100A12 elicited tissue effects. More research is needed to clarify the functional role of sRAGE in sepsis and its putative role as a new sepsis marker.

Conclusion

The innate immune response is the first line of defense against pathogens. The experimental studies described herein provide further insight into the role of RAGE and its ligands in host defense during clinically important infections, which eventually may contribute to better therapies against specific pathogens. While interpreting the results from preclinical investigations, one has to keep in mind that a careful balance between the inflammatory and anti-inflammatory response is vital in order to survive or recover from a severe infection.

The observation that lack of RAGE is of benefit in one pneumonia model and detrimental in another, clearly adds to the notion that the way in which RAGE mediates host defense against different pathogens relies on distinct mechanisms. It would be highly interesting to evaluate whether RAGE can directly bind to, become activated, and mount a first immune reaction after ligation with specific PAMPs. Furthermore, RAGE-mediated effects on other first-line defense mechanisms, such as chemotaxis, killing, phagocytosis and respiratory burst could depend on the pathogen. As such, targeting RAGE may be ineffective or even harmful in some infectious conditions. Therefore, more studies are necessary to justify clinical trials targeting RAGE in patients with severe infections. In this respect one could think of research on RAGE inhibition in pneumococcal and

influenza A viral pneumonia. Additionally, experiments in which RAGE targeting is delayed until after bacterial/viral infection and combined with antibiotic/antiviral therapy should be considered. Moreover, more studies need to be conducted on the role of RAGE in critical organ derangements involved in the pathogenesis of severe infection, including activation of the coagulation system and the complement system. RAGE remains a potential yet promising therapeutic target that awaits further research.

References

1. Janeway CA Jr, Medzhitov R (2002) Innate immune recognition. Annu Rev Immunol 20: 197 – 216
2. Bianchi ME (2007) DAMPs, PAMPs and alarmins: All we need to know about danger. J Leukoc Biol 81: 1 – 5
3. Harris HE, Raucci A (2006) Alarmin(g) News about danger: Workshop on innate danger signals and HMGB1. EMBO Rep 7: 774 – 778
4. Scaffidi P, Misteli T, Bianchi ME (2002) Release of chromatin protein HMGB1 by necrotic cells triggers inflammation. Nature 418: 191 – 5
5. Liu Y, Chen GY, Zheng P (2009) CD24-Siglec G/10 discriminates danger- from pathogen-associated molecular patterns. Trends Immunol 30: 557 – 561
6. Liu R, Mori S, Wake H, et al (2009) Establishment of in vitro binding assay of high mobility group box-1 and S100A12 to receptor for advanced glycation endproducts: heparin's effect on binding. Acta Med Okayama 63: 203 – 211
7. Bierhaus A, Stern DM, Nawroth PP (2006) RAGE in inflammation: a new therapeutic Target? Curr Opin Investig Drugs 7: 985 – 991
8. Chavakis T, Bierhaus A, Al Fakhri N, et al (2003) The pattern recognition receptor (RAGE) is a counterreceptor for leukocyte integrins: a novel pathway for inflammatory cell recruitment. J Exp Med 198: 1507 – 1515
9. Liliensiek B, Weigand MA, Bierhaus A, et al (2004) Receptor for advanced glycation end products (RAGE) regulates sepsis but not the adaptive immune response. J Clin Invest 113: 1641 – 1650
10. Goova MT, Li J, Kislinger T, et al (2001) Blockade of receptor for advanced glycation endproducts restores effective wound healing in diabetic mice. Am J Pathol 159: 513 – 525
11. Cataldegirmen G, Zeng S, Feirt N, et al (2005) RAGE limits regeneration after massive liver injury by coordinated suppression of TNF-alpha and NF-kappaB. J Exp Med 201: 473 – 484
12. Park L, Raman KG, Lee KJ, et al (1998) Suppression of accelerated diabetic atherosclerosis by the soluble receptor for advanced glycation endproducts. Nat Med 4: 1025 – 1031
13. Schmidt AM, Yan SD, Yan SF, Stern DM (2001) The multiligand receptor RAGE as a progression factor amplifying immune and inflammatory responses. J Clin Invest 108: 949 – 955
14. Lotze MT, Tracey KJ (2005) High-mobility group box 1 protein (HMGB1): Nuclear weapon in the immune arsenal. Nat Rev Immunol 5: 331 – 342
15. Ueno H, Matsuda T, Hashimoto S, et al (2004) Contributions of high mobility group box protein in experimental and clinical acute lung injury. Am J Respir Crit Care Med 170: 1310 – 1316
16. Wang H, Bloom O, Zhang M, et al (1999) HMG-1 as a late mediator of endotoxin lethality in mice. Science 285: 248 – 51
17. van Zoelen MA, Laterre PF, van Veen SQ, et al (2007) Systemic and local high mobility group box 1 concentrations during severe infection. Crit Care Med 35: 2799 – 2804
18. Yang H, Ochani M, Li J, et al (2004) Reversing established sepsis with antagonists of endogenous high-mobility group box 1. Proc Natl Acad Sci USA 101: 296 – 301
19. Qin S, Wang H, Yuan R, et al (2006) Role of HMGB1 in apoptosis-mediated sepsis lethality. J Exp Med 203: 1637 – 1642
20. Suda K, Kitagawa Y, Ozawa S, et al (2006) Anti-high-mobility group box chromosomal protein 1 antibodies improve survival of rats with sepsis. World J Surg 30: 1755 – 1762

21. Wang H, Liao H, Ochani M, et al (2004) Cholinergic agonists inhibit HMGB1 release and improve survival in experimental sepsis. Nat Med 10: 1216 – 1221
22. Hotchkiss RS, Nicholson DW (2006) Apoptosis and caspases regulate death and inflammation in sepsis. Nat Rev Immunol 6: 813 – 822
23. Hotchkiss RS, Chang KC, Swanson PE, et al (2000) Caspase inhibitors improve survival in sepsis: a critical role of the lymphocyte. Nat Immunol 1: 496 – 501
24. Tian J, Avalos AM, Mao SY, et al (2007) Toll-like receptor 9-dependent activation by DNA-containing immune complexes is mediated by HMGB1 and RAGE. Nat Immunol 8: 487 – 496
25. Yang H, Hreggvidsdottir HS, Palmblad K, et al (2010) A critical cysteine is required for HMGB1 binding to toll-like receptor 4 and activation of macrophage cytokine release. Proc Natl Acad Sci USA 107: 11942 – 11947
26. Wittkowski H, Sturrock A, van Zoelen MA, et al (2007) Neutrophil-derived S100A12 in acute lung injury and respiratory distress syndrome. Crit Care Med 35: 1369 – 1375
27. Orlova VV, Choi EY, Xie C, et al (2007) A novel pathway of HMGB1-mediated inflammatory cell recruitment that requires Mac-1-integrin. EMBO J 26: 1129 – 1139
28. Frommhold D, Kamphues A, Hepper I, et al (2010) RAGE and ICAM-1 Cooperate in mediating leukocyte recruitment during acute inflammation in vivo. Blood 116: 841 – 849
29. Uchida T, Shirasawa M, Ware LB, et al (2006) Receptor for advanced glycation end-products is a marker of type i cell injury in acute lung injury. Am J Respir Crit Care Med 173: 1008 – 1015
30. Cheng C, Tsuneyama K, Kominami R, et al (2005) Expression profiling of endogenous secretory receptor for advanced glycation end products in human organs. Mod Pathol 18: 1385 – 1396
31. Englert JM, Hanford LE, Kaminski N, et al (2008) A role for the receptor for advanced glycation end products in idiopathic pulmonary fibrosis. Am J Pathol 172: 583 – 591
32. Morbini P, Villa C, Campo I, Zorzetto M, Inghilleri S, Luisetti M (2006) The receptor for advanced glycation end products and its ligands: a new inflammatory pathway in lung disease? Mod Pathol 19: 1437 – 1445
33. Buckley ST and Ehrhardt C (2010) The receptor for advanced glycation end products (RAGE) and the lung. J Biomed Biotechnol 2010:917108
34. Queisser MA, Kouri FM, Konigshoff M, et al (2008) Loss of RAGE in pulmonary fibrosis: molecular relations to functional changes in pulmonary cell types. Am J Respir Cell Mol Biol 39: 337 – 345
35. Demling N, Ehrhardt C, Kasper M, Laue M, Knels L, Rieber EP (2006) Promotion of cell adherence and spreading: a novel function of RAGE, the highly selective differentiation marker of human alveolar epithelial type I cells. Cell Tissue Res 323: 475 – 488
36. Fehrenbach H, Kasper M, Tschernig T, Shearman MS, Schuh D, Muller M (1998) Receptor for advanced glycation endproducts (RAGE) exhibits highly differential cellular and subcellular localisation in rat and human lung. Cell Mol Biol (Noisy -le-grand) 44: 1147 – 1157
37. He M, Kubo H, Ishizawa K, et al (2007) The role of the receptor for advanced glycation end-products in lung fibrosis. Am J Physiol Lung Cell Mol Physiol 293:L1427-L1436
38. Reynolds PR, Schmitt RE, Kasteler SD, et al (2010) Receptors for advanced glycation end-products targeting protect against hyperoxia-induced lung injury in mice. Am J Respir Cell Mol Biol 42: 545 – 551
39. van Zoelen MA, Schouten M, de Vos AF, et al (2009) The receptor for advanced glycation end products impairs host defense in pneumococcal pneumonia. J Immunol 182: 4349 – 4356
40. van Zoelen MA, van der Sluijs KF, Achouiti A, et al (2009) Receptor for advanced glycation end products is detrimental during influenza A virus pneumonia. Virology 391: 265 – 273
41. Lutterloh EC, Opal SM, Pittman DD, et al (2007) Inhibition of the RAGE products increases survival in experimental models of severe sepsis and systemic infection. Crit Care 11:R122
42. van Zoelen MA, Schmidt AM, Florquin S, et al (2009) Receptor for advanced glycation end products facilitates host defense during Escherichia coli-induced abdominal sepsis in mice. J Infect Dis 200: 765 – 773

43. van Zoelen MA, Achouiti A, Schmidt AM, et al (2010) Ligands of the receptor for advanced glycation end products, including high-mobility group box 1, limit bacterial dissemination during escherichia coli peritonitis. Crit Care Med 38: 1414 – 1422
44. van Zoelen MA, Yang H, Florquin S, et al (2009) Role of Toll-Like receptors 2 and 4, and the receptor for advanced glycation end products in high-mobility group box 1-induced inflammation in vivo. Shock 31: 280 – 284
45. Park JS, Svetkauskaite D, He Q, et al (2004) Involvement of Toll-Like receptors 2 and 4 in cellular activation by high mobility group box 1 protein. J Biol Chem 279: 7370 – 7377
46. Payen D, Lukaszewicz AC, Belikova I, et al (2008) Gene profiling in human blood leucocytes during recovery from septic shock. Intensive Care Med 34: 1371 – 1376
47. Foell D, Wittkowski H, Vogl T, Roth J (2007) S100 Proteins expressed in phagocytes: a novel group of damage-associated molecular pattern molecules. J Leukoc Biol 81: 28 – 37
48. Cole AM, Kim YH, Tahk S, et al (2001) Calcitermin, a novel antimicrobial peptide isolated from human airway secretions. FEBS Lett 504: 5 – 10
49. Bopp C, Hofer S, Weitz J, et al (2008) SRAGE is elevated in septic patients and associated with patients outcome. J Surg Res 147: 79 – 83
50. Hudson BI, Harja E, Moser B, Schmidt AM (2005) Soluble levels of receptor for advanced glycation endproducts (SRAGE) and coronary artery disease: the next C-reactive protein? Arterioscler Thromb Vasc Biol 25: 879 – 882

I

The Endocannabinoid System: A Janus-faced Modulator of Inflammation in the Intestinal Microcirculation

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Introduction

The endocannabinoid system is a signaling system consisting of the cannabinoid receptors, their endogenous lipid ligands (endocannabinoids), and associated proteins (transporters, biosynthetic and degradative enzymes). This important biological system is now known to regulate a plethora of physiological functions crucial to homeostatic regulation within the body [1].

The Endocannabinoid System

The plant, *Cannabis sativa*, which contains more than 60 active phytocannabinoids, has been widely used for over a millennium as an anticonvulsant, analgesic, anti-emetic, anti-inflammatory, and immunosuppressant drug. However, although the therapeutic applications and psychoactive actions of the *Cannabis* plant are well documented, knowledge of the pharmacology of this ancient plant and its active constituents (cannabinoids) has only recently emerged. This understanding of the mechanisms of action of cannabinoids has resulted from several key advances, notably the isolation and characterization of the active phytocannabinoids in the *Cannabis* plant, including that of the primary psychoactive phytocannabinoid in *Cannabis*, Δ9-tetrahydrocannabinol (THC) [2, 3] and evidence for, and identification of, specific cannabinoid receptors and the endogenous ligands that activate these receptors [4, 5].

Two cannabinoid receptors, members of the superfamily of G protein coupled receptors (GPCRs), have now been cloned. CB1 receptors (CB1R), the primary target for the psychotropic actions of the phytocannabinoid, THC, are the most abundant receptors in the mammalian brain and presynaptic CB1R activation inhibits neurotransmitter release in the brain and peripheral nerves. Postsynaptic CB1R are also present in a variety of non-neural peripheral tissues and cells, including the vasculature and gut, and activation of these receptors can produce hypotension and regulate emesis and feeding. CB2 receptors (CB2R) are expressed primarily in cells of the immune and hematopoietic systems [6], but have also been indentified in selected areas of the central nervous system (CNS) [7], in nonparenchymal cells of the cirrhotic liver [8], in the endocrine pancreas [9], and in bone [10]. Both cannabinoid receptors regulate a variety of central and peripheral physiological functions, including neuronal development, neuromodulatory processes, energy metabolism, and respiratory and cardiovascular functions including the microcirculation [11]. More recently, additional evidence

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has emerged suggesting that, in addition to the transient receptor potential vanilloid 1 (TRPV1) ion channel, there are additional non-CB1R/CB2R that may mediate some of the modulatory effects of cannabinoids and their endogenous ligands [12]. Notable among these are the orphan receptors, GPR55 and GPR18, both of which have been suggested as candidates for the endothelial cannabinoid receptor that mediates anandamide (AEA) and abnormal cannabidiol (abn-CBD)-dependent vasorelaxation in microvasculature and peroxisome proliferator-activated receptors (PPARs). PPAR receptors, which include isotypes (α, δ and γ), are expressed by distinct cell types and are associated with the regulation of lipid metabolism and inflammation [13]. Several recent experimental lines of evidence identify cannabinoid receptors as potential novel therapeutic targets for many fields in medicine [14, 15].

CB1R and CB2R are activated by phytocannabinoids, synthetic cannabinoids, and endocannabinoids. Synthetic cannabinoids that bind to either CB1R or CB2R include not only compounds structurally similar to phytocannabinoids, but also analogs with different chemical structures including classic and non-classic cannabinoids and aminoalkylindoles [2, 3]. The most frequently used cannabinoid ligands are agonists (including endogenous agonists) and inverse agonists (**Table 1**). Inverse agonists exert opposite pharmacological effects to those of a receptor agonist [4–6].

Endocannabinoids are endogenous arachidonate derivatives. The two most well characterized endocannabinoids are AEA and 2-arachidonoyl glycerol (2-AG), both of which are fatty acid amides (FAAs). In addition, N-arachidonoyldopamine (NADA) has also been shown to behave as a cannabimimetic compound [8], although its pharmacology is as yet poorly understood. Other endogenous FAAs are called endocannabinoid-like compounds because they do not activate CBRs but seem to have an entourage effect, i.e., they may potentiate the activity of AEA or 2-AG at their receptors by inhibiting their degradation [9]. The actions

Table 1. Cannabinoid ligands

Agonists	
CB1R/CB2R 'Classical' cannabinoids • Δ^9 – THC – partial agonist – efficacy CB1>CB2 • HU 2010 – high CB1R/CB2R affinity – full CB1R/CB2R agonist	*CB2R selective* 'Classical' cannabinoid • JWH-133 Aminoalkylindoles • WIN55212–2
Inverse agonists	
CB1R selective Diarylpyrazoles • SR 141716A • AM251	*CB2R selective* Diarylpyrazoles • SR 144528 • AM 630
Endogenous agonists	
• Anandamide (AEA) – moderate CB1R>CB2R affinity – partial agonist, efficacy CB1R> CB2R	• 2-Arachidonoylglycerol (2AG) – moderate CB1R/CB2R affinity – high CB1R/CB2R efficacy

of AEA and 2-AG at CB1R and CB2R, account for many of the actions of the endocannabinoid system. AEA and 2-AG are produced 'on demand' through multiple biosynthetic pathways, which include key agents such as the N-acylphosphatidylethanolamines (NAPE)-hydrolyzing phospholipase D (NAPE-PLD) for AEA, palmitylethanolamide (PEA), and oleoylethanolamide (OEA), and the sn-1-specific diacylglycerol lipase for 2-AG [16]. Other enzymes are also important, especially in the formation of AEA [17]. The transport of AEA is highly cholesterol-dependent and cholesterol could be an important component of the AEA transport machinery; the possible link between the endocannabinoid system and cholesterol metabolism may be of great importance for critically ill patients [18]. Degradation of endogenous cannabinoids also occurs through multiple routes, which include fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase as major hydrolytic enzymes that have an important role in the inactivation of endocannabinoids, especially AEA [19].

CB1 and CB2 receptors are G protein coupled receptors, and are recognized by a variety of ligands with preferential coupling to $G_{i/o}$ proteins to activate multiple downstream signaling pathways, although CB1R coupling to other G proteins has also been reported. As a consequence of $G_{i/o}$ coupling, activation of CBR leads to inhibition of adenyl cyclase and reduction in cAMP accumulation in many tissues. Additionally, CB1 and CB2 receptors regulate the phosphorylation and activation of different members of the family of mitogen activated protein kinases (MAPKs) [20]. Adding to the complexity of cannabinoid receptor signaling, recent studies have indicated that, at least with respect to CB1R, different ligands can induce the receptor to couple to specific signaling pathways more strongly than others. This phenomenon is referred to as stimulus trafficking or functional selectivity [20].

Control of CBR-mediated signaling is affected by several factors, both extra- and intra-cellular, that appear to promote the specificity of cannabinoid signaling and confine cannabinoid responses in a spatial and temporal fashion [20]. Moreover, several studies have show that CB1R-mediated signaling shares a common pool of G proteins with adrenergic, somatostatin, insulin-like growth factor (IGF)-1, and opioid receptors [21]. The specific insertion of GPCRs within different membrane compartments also shapes signaling selectivity. Another characteristic of cannabinoid signaling adaptation is the variation in the magnitude and kinetics of CB1R desensitization and downregulation documented in the brain [22], all of which support the concept that prolonged exposure to cannabinoids may result in different adaptation profiles *in vivo*. The density of receptors also plays an important role in the amplitude of response to partial and full cannabinoid agonists [20].

Evidence has accumulated lately for a variety of mechanisms that influence CBR signaling, which allow for diversification and for specificity in cannabinoid-mediated responses. However, the physiological (and even clinical) implications of such complexity is difficult to determine due to several extracellular (e.g., ligand profile, timing and location of ligand release, co-activation of other GPCR ligands, extracellular environment) and intracellular (e.g., expression of different signaling partners, post-transcriptional and post-translational modifications) factors. Obviously, the ligand profile is crucial in dictating the cellular response and subsequently the response to manipulation of the endocannabinoid system.

Cannabinoid Receptors and Sepsis

The endocannabinoid system is upregulated during local and systemic inflammation, e.g., sepsis [23], and endocannabinoids released from macrophages, dendritic cells, platelets and parenchymal cells in response to inflammatory stimuli and oxidative stress are present in elevated levels in the sera of patients and animals in septic shock [24]. CB2Rs are present on macrophages, neutrophils and lymphocytes and activation of these receptors has been generally associated with anti-inflammatory and immunsuppressive effects. In particular, 2-AG has been shown to inhibit cytokine production, including tumor necrosis factor (TNF)-α released from lipopolysaccharide (LPS)-treated rat microglial cells [25] and murine macrophages [26] and IL-2 secretion in activated murine splenocytes [27]. However, in contrast to these studies, others have reported pro-inflammatory effects of endocannabinoid CB2R activation, which was abolished by treatment with a selective CB2R antagonist [28]. In 2009, two papers were published in the *Journal of Immunology* [29] and *PLoS ONE* [30], studying the impact of CB2R modulation on survival and other parameters in experimental sepsis (cecal ligation and puncture model). Although both groups used CB2R knockout mice, the studies yielded opposite results. Tschöp et al. found that following sepsis, CB2R knockout mice had a higher mortality and the administration of the selective CB2R agonist, GP1a, improved survival of wild-type mice [29]. In contrast, Csoka et al. showed that CB2R knockout mice had a better survival from sepsis than wild-type mice [30].

With respect to the contribution of CB1R to inflammation and sepsis, the data are also unclear although several studies have suggested that activation of CB1R located on the presynaptic terminals of autonomic nerves or the vascular walls may contribute to the hypotension associated with septic shock. However, the contribution of CB1R in this action was also called into question, when LPS still produced an acute hypotension response in CB1R or CB1R/CB2R knock-out mice.

Inflammation and the Intestinal Microcirculation

Impairment of the microcirculation represents a key event in the pathophysiology of sepsis [31–34]. Effects on all components of the microcirculation, including smooth muscle cells, endothelial cells, leukocytes and red blood cells (RBCs) have been identified and lead to a severely dysfunctional microvasculature with subsequent organ dysfunction and organ failure. The intestinal microcirculation is involved early in the course of sepsis [35]. Intestinal hypoperfusion occurs frequently during the disease development and reperfusion may result in an additional release of pro-inflammatory mediators into the systemic circulation. This enhances the systemic inflammatory response syndrome and contributes to early multiple organ failure and death [35]. Intestinal mucosal hypoperfusion may also cause a breakdown of gut epithelial barrier function thus releasing bacteria and their toxins into the systemic circulation (bacterial translocation) creating a 'gut-derived' septic state [35]. In the late phase of sepsis with predominant immunosuppression, a new infectious challenge may cause late multiple organ failure and death. Therefore, the intestinal microcirculation has been suggested as acting as the "motor" of multiple organ failure in systemic inflammation. Consequently, the

study of the intestinal microcirculation is relevant in two aspects: As a pathophysiological origin and as a therapeutic target in severe systemic inflammation. Identification of therapies that can target the different cellular and inflammatory components of the compromised intestinal microcirculation in sepsis to reduce microcirculatory dysfunction is essential in order to preserve barrier function, ensure adequate tissue oxygenation, maintain immune function, and provide a conduit for the delivery of drug therapies to cell targets. However, improvement of the intestinal microcirculation is difficult to achieve in the acute phase of severe systemic inflammation and sepsis. While vasoconstriction is the physiological response in this microvascular area (centralization of the circulation, redistribution of the cardiac output to the vital organs), therapeutic vasodilation may deteriorate the macrocirculation. Given that therapeutic escalation of cardiac output to improve organ perfusion is also limited (physiological high cardiac output during systemic inflammation and early sepsis), several approaches are employed at different stages of sepsis progression (**Fig. 1**). These strategies include: Pathogen removal (strategy A), modulation of receptors and mediator release (strategy B), and adjuvant therapy (strategy C). However, while pathogen removal (strategy A) is necessary in every case, it does not guarantee a positive outcome. Strategy C (adjuvant therapy) is necessary in many cases, but does not directly influence the pathomechanisms of sepsis. Therefore, modulation of receptors and mediator release (strategy B), represents the best option for the development of novel approaches to improve the intestinal microcirculation in sepsis. As the endocannabinoid system contributes to the regulation of vascular function via a CB1R-mediated response, as well as having immune modulatory roles via CB2R, modulation of the endocannabinoid system may be useful to improve the intestinal microcirculation in sepsis.

The limitation to the therapeutic utility of cannabinoids is the occurrence of psychoactive effects due to the activation of brain cannabinoid CB1R [36]. However, the *Cannabis* plant contains a number of non-psychotropic cannabinoids of

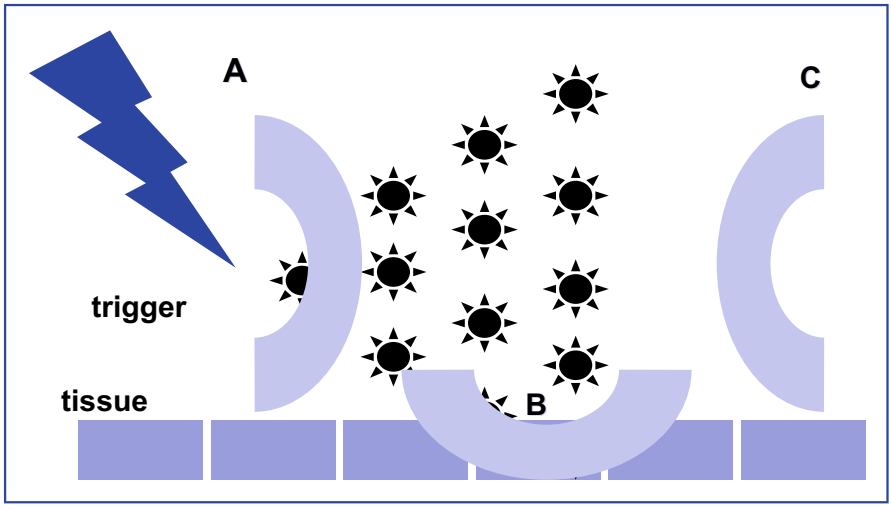

Fig. 1. General approaches in sepsis therapy. A: Inhibition of inflammatory trigger; B: Modulation of receptors and mediators; C: substitution/adjuvant therapy

pharmacological interest, which retain some pharmacological, and potentially therapeutic actions; these include cannabigerol, cannabichromene, tetrahydrocannabivarin, and cannabidiol [1]. Among these compounds, the most extensively studied is cannabidiol, which has antioxidant, anti-inflammatory, and immunomodulatory effects [37]. Furthermore, a considerable number of synthetic cannabinoids are now available that lack psychotropic effects [38, 39]. Additionally, an increasing number of new cannabinoid ligands continue to be developed that do not cross the blood brain barrier, thus avoiding the possibility of behavioral effects. In addition to these ligands, increasing evidence suggests that use of allosteric modulators that bind to receptor sites on cannabinoid receptors that are distinct from those of endocannabinoids holds considerable promise for modulating endocannabinoid system activity.

Massa et al. showed that CB1Rs mediate intrinsic protective signals that counteract pro-inflammatory responses in the large intestine [40]. Intrarectal infusion of 2,4-dinitrobenzene sulfonic acid (DNBS) and oral administration of dextran sulfate sodium induced stronger inflammation (tissue myeloperoxidase activity) in CB1R-deficient mice (CB1R–/–) than in wild-type littermates (CB1R+/+). Treatment of wild-type mice with the specific CB1R antagonist, N-(piperidino-1-yl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-pyrazole-3-carboxamide (SR141716A), mimicked the phenotype of CB1R–/– mice, showing an acute requirement of CB1R for protection from inflammation. Consistently, treatment with the cannabinoid receptor agonist, R(-)-7-hydroxy-Δ6-tetra-hydrocannabinol-dimethylheptyl (HU210), or genetic ablation of the endocannabinoid-degrading enzyme fatty acid amide hydrolase (FAAH) resulted in protection against DNBS-induced colitis.

In the small intestine, involvement of CB1Rs in the control of intestinal motility during croton oil–induced inflammation was recently evidenced. Izzo et al. showed that pharmacological administration of cannabinoids was able to delay gastrointestinal transit in croton oil–treated mice [41]. Increased levels of CB1R expression in inflamed jejuna may contribute to this protective effect. However, this work was not able to reveal a physiologically protective action of the endogenous cannabinoid system against enteritis, since administration of the CB1R antagonist, SR141716A, alone failed to specifically worsen inflammation-induced gut hypermotility.

In contrast to the findings of beneficial effects of CB1R activation on intestinal inflammation, rimonabant – a CB1R antagonist – also showed potentially beneficial anti-inflammatory effects which were similar to those evoked by cannabinoid receptor agonists. These paradoxical effects do not seem to be mediated by cannabinoid receptors. Rimonabant reduced indomethacin-induced intestinal ulcers to a similar extent in wild-type, and in CB1R knock-out mice [42]. These effects appear to be mediated by down-regulation of inducible nitric oxide synthase (iNOS) and cyclooxygenase (COX)-2 [43]. It is important to highlight that the effect of rimonabant seems to be specific to that compound, and is not shared by other CB1R antagonists, such as AM215 [44]. Of note, rimonabant, which was being marketed for weight loss but being tested for improving cardiovascular outcomes, induced a level of serious neuropsychiatric effects that was deemed unacceptable by regulatory authorities, and both the drug and the trial were abruptly terminated [45].

Recent evidence also highlights the role of CB2Rs in intestinal inflammation. In the LPS model of intestinal hypermotility in the rat, the control of intestinal

motility was mediated almost completely by CB2R-mechanisms; hypermotility was normalized by a CB2R, but not by a CB1R agonist [46]. The CB2R agonist, JHW015, reduced motility in the inflamed gut (crotonoil-induced ileitis), but not in control mice [47].

Protection against inflammatory stimuli may be provided through direct activation of cannabinoid receptors, or indirectly through the use of FAAH or endocannabinoid membrane transporter (EMT) inhibitors, which prevent anandamide inactivation. D'Argenio et al. reported significant elevation of anandamide levels in the colon of DNBS-treated mice [48]. The EMT inhibitor, VDM-11, further increased anandamide levels and concomitantly abolished inflammation, whereas the FAAH inhibitor, N-arachidonoyl-serotonin (AA-5-HT), did not affect endocannabinoid levels and was less efficacious at attenuating colitis [48]. More recently, this protective effect of the inhibitors of endocannabinoid inactivation was confirmed by experiments in CB1R- and CB2R-deficient mice. Thus blocking FAAH and EMT with URB597 and VDM11, respectively, protected against trinitrobenzene sulphonic acid (TNBS)-induced colitis in wild type but not in CB1R- or CB2R-deficient mice. Interestingly, the combination of VDM11 and URB597 was not superior to either given alone, suggesting a lack of additive effect [49].

Direct observations of the intestinal microcirculation under the influence of therapeutic modulation of the endocannabinoid system in experimental sepsis, e.g., by intravital microscopy, have not yet been published. Using intravital microscopy, Ni et al. studied how cannabinoid receptor agonists interfered with leukocyte rolling and adhesion in an experimental autoimmune encephalomyelitis (EAE) model using six to eight week old C57BL/6 mice [50]. The results demonstrated that EAE increased leukocyte rolling and firm adhesion in the brain, and that this increased leukocyte/endothelial interaction could be attenuated by administration of WIN 55212–2 (CB1R and CB2R agonist). Furthermore, use of selective antagonists for the CB1R (SR 141716A) and the CB2R (SR144528) in this study demonstrated that the cannabinoid's inhibitory effects on leukocyte/endothelial interactions can be mediated by activating the CB2R.

We carried out a series of experiments to study the impact of CB1R and CB2R modulation on leukocyte activation and capillary perfusion within the intestinal microcirculation during experimental endotoxemia. Our findings suggest that CB1R stimulation during endotoxemia may decrease leukocyte activation whereas CB2R inhibition is able to reduce leukocyte activation (Kianian et al.: Effects of CB2 receptor modulation on the intestinal microcirculation in experimental sepsis. Proceedings of the 19th Symposium on the Cannabinoids. ICRS, Lund, Sweden. 2010). Reduced leukocyte activation within the intestinal microcirculation correlated with improved functional capillary density, a marker of microvascular perfusion. Similar results were obtained in a model of polymicrobial sepsis – the colon ascendens stent peritonitis (CASP)-induced sepsis model. The results regarding the CB2R were surprising as the literature suggests an anti-inflammatory effect of CB2R activation (see above). Based on these results we hypothesize that reciprocal modulation of the endocannabinoid system – CB1R stimulation and CB2R inhibition – has an anti-inflammatory effect (attenuation of leukocyte activation and improvement of capillary perfusion) in sepsis.

Conclusion

Taken together, the evidence suggests that release of endocannabinoids and activation of cannabinoid receptors occurs during intestinal inflammation and sepsis and that manipulation of the endocannabinoid system may represent an important therapeutic target in managing sepsis and microcirculatory disturbances. However, it remains essential to resolve whether activation of cannabinoid receptors is pro- or anti-inflammatory in sepsis and which receptor subtypes (CB2R and/or CB1R or non-CB1R/CB2R) are individually or collectively involved in mediating these actions.

References

1. Hanus LO (2008) Pharmacological and therapeutic secrets of plant and brain (endo) cannabinoids. Med Res Rev 29: 213 – 271
2. Gaoni Y, Mechoulam R (1964) Isolation, structure and partial synthesis of an active constituent of hashish. J Am Chem Soc 86: 1646 – 1647
3. Mechoulam R, Gaoni Y (1967) The absolute configuration of delta-1-tetrahydrocannabinol, the major active constituent of hashish. Tetrahedron Lett 12: 1109 – 1111
4. Jones G, Pertwee RG, Gill EW, et al (1974) Relative pharmacological potency in mice of optical isomers of delta 1-tetrahydrocannabinol. Biochem Pharmacol 23: 439 – 446
5. Matsuda LA, Lolait SJ, Brownstein MJ, Young AC, Bonner TI (1990) Structure of a cannabinoid receptor and functional expression of the cloned cDNA. Nature 346: 561 – 564
6. Munro S, Thomas KL, Abu-Shaar M (1993) Molecular characterization of a peripheral receptor for cannabinoids. Nature 365: 61 – 65
7. Van Sickle MD, Duncan M, Kingsley PJ, et al (2005) Identification and functional characterization of brainstem cannabinoid CB2 receptors. Science 310: 329 – 332
8. Julien B, Grenard P, Teixeira-Clerc F, et al (2005) Antifibrogenic role of the cannabinoid receptor CB2 in the liver. Gastroenterology 128: 742 – 755
9. Juan-Pico P, Fuentes E, Bermudez-Silva FJ, et al (2006) Cannabinoid receptors regulate Ca(2+) signals and insulin secretion in pancreatic beta-cell. Cell Calcium 39: 155 – 162
10. Ofek O, Karsak M, Leclerc N, et al (2006) Peripheral cannabinoid receptor, CB2, regulates bone mass. Proc Natl Acad Sci USA 103: 696 – 701
11. Di Marzo V (2009) The endocannabinoid system: its general strategy of action, tools for its pharmacological manipulation and potential therapeutic exploitation. Pharmacol Res 60: 77 – 84
12. Stella N (2010) Cannabinoid and cannabinoid-like receptors in microglia, astrocytes, and astrocytomas. Glia 58: 1017 – 1030
13. O'Sullivan SE (2007) Cannabinoids go nuclear: evidence for activation of peroxisome proliferator-activated receptors. Br J Pharmacol 152: 576 – 582
14. Maccarrone M, Gasperi V, Catani MV, et al (2010) The endocannabinoid system and its relevance for nutrition. Ann Rev Nutr 30: 423 – 440
15. Kinsey SG, Long JZ, O'Neal ST, et al (2009) Blockade of endocannabinoid-degrading enzymes attenuates neuropathic pain. J Pharmacol Exp Ther 330: 902 – 910
16. Bisogno T, Howell F, Williams G, et al (2003) Cloning of the first sn1-DAG lipases points to the spatial and temporal regulation of endocannabinoid signaling in the brain. J Cell Biol 163: 463 – 468
17. De Petrocellis L, Di Marzo V (2009) An introduction to the endocannabinoid system: from the early to the latest concepts. Best Pract Res Clin Endocrinol Metab 23: 1 – 15
18. Di Pasquale E, Chahinian H, Sanchez P, Fantini J (2009) The insertion and transport of anandamide in synthetic lipid membranes are both cholesterol-dependent. PloS ONE 4:e4989
19. Massi P, Valenti M, Vaccani A, et al (2008) 5-Lipoxygenase and anandamide hydrolase (FAAH) mediate the antitumor activity of cannabidiol, a non-psychoactive cannabinoid. J Neurochem 104: 1091 – 100

20. Bosier B, Muccioli GG, Hermans E, Lambert DM (2010) Functionally selective cannabinoid receptor signalling: therapeutic implications and opportunities. Biochem Pharmacol 80: 1 – 12
21. Shapira M, Vogel Z, Sarne Y (2000) Opioid and cannabinoid receptors share a common pool of GTP-binding proteins in cotransfected cells, but not in cells which endogenously coexpress the receptors. Cell Mol Neurobiol 20: 291 – 304
22. McKinney DL, Cassidy MP, Collier LM, et al (2008) Dose-related differences in the regional pattern of cannabinoid receptor adaptation and in vivo tolerance development to delta9-tetrahydrocannabinol. J Pharmacol Exp Ther 324: 664 – 673
23. Varga K, Wagner JA, Bridgen DT, Kunos G (1998) Platelet- and macrophage-derived endogenous cannabinoids are involved in endotoxin-induced hypotension. Faseb J 12: 1035 – 1044
24. Orliac ML, Peroni R, Celuch SM, Adler-Graschinsky E (2003) Potentiation of anandamide effects in mesenteric beds isolated from endotoxemic rats. J Pharmacol Exp Ther 304: 179 – 184
25. Facchinetti F, Del Giudice E, Furegato S, Passarotto M, Leon A (2003) Cannabinoids ablate release of TNFalpha in rat microglial cells stimulated with lypopolysaccharide. Glia 41: 161 – 168
26. Gallily R, Breuer A, Mechoulam R (2000) 2-Arachidonylglycerol, an endogenous cannabinoid, inhibits tumor necrosis factor-alpha production in murine macrophages, and in mice. Eur J Pharmacol 406:R5 – 7
27. Ouyang Y, Hwang SG, Han SH, Kaminski NE (1998) Suppression of interleukin-2 by the putative endogenous cannabinoid 2-arachidonyl-glycerol is mediated through down-regulation of the nuclear factor of activated T cells. Mol Pharmacol 53: 676 – 683
28. Oka S, Wakui J, Gokoh M, Kishimoto S, Sugiura T (2006) Suppression by WIN55212 – 2, a cannabinoid receptor agonist, of inflammatory reactions in mouse ear: Interference with the actions of an endogenous ligand, 2-arachidonoylglycerol. Eur J Pharmacol 538: 154 – 162
29. Tschöp J, Kasten KR, Nogueiras R, et al (2009) The cannabinoid receptor 2 is critical for the host response to sepsis. J Immunol 183: 499 – 505
30. Csoka B, Nemeth ZH, Mukhopadhyay P, et al (2009) CB2 cannabinoid receptors contribute to bacterial invasion and mortality in polymicrobial sepsis. PLoS ONE 4: e6409
31. Spanos A, Jhanji S, Vivian-Smith A, Harris T, Pearse RM (2010) Early microvascular changes in sepsis and severe sepsis. Shock 33: 387 – 391
32. Ince C (2005) The microcirculation is the motor of sepsis. Crit Care 9 Suppl 4: S13 – 19
33. Li Y, Li Y, Ni J, et al (2010) Involvement of cannabinoid-1 and cannabinoid-2 receptors in septic ileus. Neurogastroenterol Motil 22: 350-e88
34. Salgado DR, Ortiz JA, Favory R, Creteur J, Vincent J, De Backer D (2010) Microcirculatory abnormalities in patients with severe influenza A (H1N1) infection. Can J Anaesth 57: 940 – 946
35. Moore FA (1999) The role of the gastrointestinal tract in postinjury multiple organ failure. Am J Surg 178: 449 – 453
36. Mechoulam R, Fride E, Di Marzo V (1998) Endocannabinoids. Eur J Pharmacol 359: 1 – 18
37. de Filippis D, Iuvone T, D'amico A, et al (2008) Effect of cannabidiol on sepsis-induced motility disturbances in mice: involvement of CB receptors and fatty acid amide hydrolase. Neurogastroenterol Motil 20: 919 – 927
38. Felder CC, Dickason-Chesterfield AK, Moore SA (2006) Cannabinoids biology: the search for new therapeutic targets. Mol Interv 6: 149 – 161
39. Vemuri VK, Janero DR, Makriyannis A (2008) Pharmacotherapeutic targeting of the endocannabinoid signaling system: drugs for obesity and the metabolic syndrome. Physiol Behav 93: 671 – 686
40. Massa F, Marsicano G, Hermann H, et al (2004) The endogenous cannabinoid system protects against colonic inflammation. J Clin Invest 113: 1202 – 1209
41. Izzo AA, Fezza F, Capasso R, et al (2001) Cannabinoid CB1-receptor mediated regulation of gastrointestinal motility in mice in a model of intestinal inflammation. Br J Pharmacol 134: 563 – 570
42. Croci T, Landi M, Galzin A, Marini P (2003) Role of cannabinoid CB1 receptors and tumor

necrosis factor-alpha in the gut and systemic anti-inflammatory activity of SR 141716 (rimonabant) in rodents. Br J Pharmacol 140: 115 – 122
43. Malfitano AM, Laezza C, Pisanti S, Gazzerro P, Bifulco M (2008) Rimonabant (SR141716) exerts anti-proliferative and immunomodulatory effects in human peripheral blood mononuclear cells. Br J Pharmacol 153: 1003 – 1010
44. Greenhough A, Patsos HA, Williams AC, Paraskeva C (2007) The cannabinoid delta(9)-tetrahydrocannabinol inhibits RAS-MAPK and PI3K-AKT survival signalling and induces BAD-mediated apoptosis in colorectal cancer cells. Int J Cancer 121: 2172 – 2180
45. Topol EJ, Bousser M, Fox KA, et al (2010) Articles Rimonabant for prevention of cardiovascular events (CRESCENDO): a randomised, multicentre, placebo-controlled trial. Lancet 376: 517 – 523
46. Mathison R, Ho W, Pittman QJ, Davison JS, Sharkey KA (2004) Effects of cannabinoid receptor-2 activation on accelerated gastrointestinal transit in lipopolysaccharide-treated rats. Br J Pharmacol 142: 1247 – 1254
47. Capasso R, Borrelli F, Aviello G, et al Cannabidiol, extracted from Cannabis sativa, selectively inhibits inflammatory hypermotility in mice. Br J Pharmacol 154: 1001 – 1008
48. D'Argenio G, Valenti M, Scaglione G, Cosenza V, Sorrentini I, Di Marzo V (2006) Up-regulation of anandamide levels as an endogenous mechanism and a pharmacological strategy to limit colon inflammation. FASEB J 20: 568 – 570
49. Storr MA, Keenan CM, Emmerdinger D, et al (2008) Targeting endocannabinoid degradation protects against experimental colitis in mice: involvement of CB1 and CB2 receptors. J Mol Med 86: 925 – 936
50. Ni X, Geller EB, Eppihimer MJ, Eisenstein TK, Adler MW, Tuma RF (2004) Win 55212 – 2, a cannabinoid receptor agonist, attenuates leukocyte/endothelial interactions in an experimental autoimmune encephalomyelitis model. Multiple Sclerosis 10: 158 – 164

I Remote Ischemic Conditioning against Ischemia/reperfusion Injury

P. Meybohm and B. Bein

Introduction

Ischemia/reperfusion injury triggers a burst of reactive oxygen species (ROS) that in turn lead to the expression of a number of pro-inflammatory genes. The subsequent serious inflammatory response maintains a vicious cycle of cell death finally causing organ damage [1]. Acute myocardial ischemia and ischemic stroke are the leading causes of morbidity and mortality worldwide. In the perioperative setting, patients with multiple comorbidities still have a high risk of morbidity and mortality, although multiple therapeutic strategies have been investigated to reduce the incidence of major cardiovascular events [2, 3]. Because most major adverse events show an unpredictable onset in an individual patient, the number needed to treat – or to prevent an event – is very high. Specifically, a considerable proportion of ischemic episodes may occur postoperatively on the intensive care unit (ICU) because of hemodynamic instability or oxygenation problems. Therefore, evaluating the effectiveness of any pre-treatment with a potent organ protective intervention is extremely difficult in most patients. In contrast, cardiac surgery with cross-clamping of the ascending aorta results in predictable ischemia/reperfusion injury. Similarly, predictable ischemia/reperfusion injury happens following organ transplantation and trauma leading to postoperative organ insufficiency. Many experimental techniques have been shown to profoundly modify the extent of ischemia/reperfusion injury. However, very few of these techniques have reached clinical practice because of lack of effectiveness when applied to patients with comorbidities and co-medications [4]. Therefore, the development of new strategies to prevent and to attenuate ischemia/reperfusion injury continues to be the focus of extensive research.

An interesting approach to this problem is ischemic preconditioning. The most promising clinical candidates for ischemic preconditioning are angina preceding myocardial infarction or transient ischemic attacks preceding a full stroke; these sub-lethal stressors are thought to enhance the tolerance of the organ to cope with the subsequent ischemic event. However, the clinical applicability of local ischemic preconditioning is limited by the need to induce ischemia in the vulnerable target organ, a process that itself may aggravate organ injury and dysfunction. A more clinically relevant stimulus is exerted by remote ischemic preconditioning as a powerful, innate protection where ischemia of non-vital tissue protects remote organs against ischemia/reperfusion injury. Most recently, a newly conceived idea of applying a remote conditioning stimulus after the onset of ischemia but prior to reperfusion – remote ischemic *post*conditioning – may further emerge as a strategy to ameliorate the deleterious sequelae of an unpredict-

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able ischemia/reperfusion injury, such as acute myocardial infarction or ischemic stroke.

Remote Ischemic Preconditioning

Proposed Mechanisms (Fig. 1)

The initial study suggesting that one vascular bed could confer protection on another vascular bed came from Przyklenk et al. in 1993 [5]. Using anesthetized dogs, they showed that a brief period of myocardial ischemia achieved by four 5 min cycles of coronary artery occlusion protected local and remote myocardium from 60 min sustained myocardial ischemia/reperfusion injury. Subsequent studies have demonstrated that brief ischemia of non-vital organs and tissues, e.g., kidney, small intestine, and skeletal musculature, reduces ischemia/reperfusion injury of remote organs, e.g., heart, kidney, liver, and brain. The actual mechanisms of signal transduction from the remote tissue to the target organ, however, remain to be fully elucidated.

Humoral mediators and neural pathways

The hypothesis that remote ischemic preconditioning is accomplished by humoral factors that are washed out into circulating blood during reperfusion was fuelled by a study reporting that cardiac protection was transferred from rabbits that had undergone remote ischemic preconditioning to non-preconditioned rabbits undergoing sustained myocardial ischemia/reperfusion injury simply by whole blood transfusion [6]. Thus, remote ischemic preconditioning generates one or more humoral mediators that are released into the circulation and subsequently travel to the remote target organs [7]. Convincing evidence in support of a humoral mechanism for remote ischemic preconditioning was provided by Konstantinov et al. who found that remote ischemic preconditioning of a recipient animal led to protection against ischemia/reperfusion injury in the denervated donor heart taken from a brain-dead donor pig [8].

Endogenous substances such as opioids [9], endocannabinoids [10, 11], adenosine [12], bradykinin [13], and calcitonin-gene related protein [14] are supposed to be released from the remote organ during remote ischemic preconditioning and to be transferred to target organs with the blood stream. In addition to the hypothesis of humoral factors, an earlier study by Gho et al. showed that ganglion blockade with hexamethonium abolished cardioprotection by mesenteric artery occlusion suggesting that neural pathways were involved in transferring the preconditioning stimulus [15]. This finding developed into the hypothesis that there is kind of a neuronal reflex arc with an afferent signal from the remote organ during ischemia that stimulates the efferent signal to the target organ. Again, adenosine, bradykinin, and calcitonin gene-related peptide have been reported as important mediators within this neural pathway, especially in the afferent loop.

It should be emphasized that adenosine and bradykinin play an important role in this suggested neural pathway [13]. Liem et al. suggested that adenosine is initially released in the preconditioned remote tissue which subsequently triggers a neural pathway leading to adenosine release in the remote organ (heart) [12]. A recent experimental study has provided confirmatory evidence that an intact neural pathway is required for the sensory afferent neural signaling from the precon-

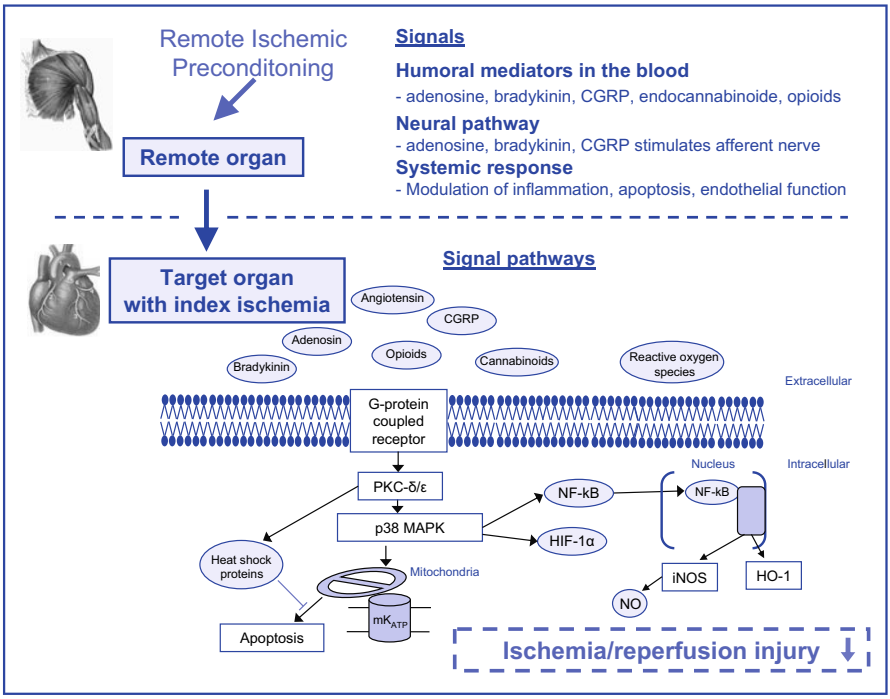

Fig. 1. Pathways of remote ischemic preconditioning. The humoral hypothesis states that endogenous mediators (e.g., adenosine, bradykinin, opioids, calcitonin gene-related peptide (CGRP), endocannabinoids, angiotensin) produced in the remote organ, e.g., skeletal musculature, enter the blood stream and activate their respective receptors in the distant organ, e.g., heart. The neural hypothesis proposes that ischemic preconditioning at the remote organ generates endogenous substances (e.g., adenosine, bradykinin or CGRP), which then activate a neural circuit in which the efferent nerve terminates at the distant target organ and mediates protection. The third hypothesis is based on a systemic response which modulates inflammation, apoptosis, and endothelial function. The following mechanism for remote ischemic preconditioning at the distant organ has been suggested: Remote ischemic preconditioning triggers intracellular signal pathways converging on the mitogen activated protein kinase (MAPK) stress signal pathway including protein kinase C (PKC)-δ/ε. This in turn activates heat shock proteins and p38 MAPK which results in immediate protection through activation of mitochondrial K_{ATP}-channels and inhibition of apoptosis. Activation of p38 MAPK also results in delayed protection via activation of the transcription factor hypoxia-inducible factor-1α pathway and translocation of nuclear factor-kappa B (NF-κB) to the nucleus and synthesis of the proteins inducible nitric oxide synthase (iNOS) and hemoxygenase (HO)-1. Reactive oxygen species have also been suggested to be involved in the protection achieved by remote ischemic preconditioning.

ditioned limb, as the cardioprotective effects by remote ischemic preconditioning were abolished by dissecting the femoral and sciatic nerves [16].

Signal transduction pathways involved in conferring protection on the target organ undergoing sustained ischemia

Once the cardioprotective signal has been conveyed from the remote preconditioned organ (e.g., upper limb) to the target organ (e.g., heart), intracellular signal pathways are triggered via G-protein-coupled receptors for adenosine, bradykinin, opioids, angiotensin, and endocannabinoids converging on the mitogen-

activated protein kinase (MAPK) stress signal pathway [17, 18]. This in turn activates p38 MAPK, which results in immediate protection through activation of mitochondrial K_{ATP} channels [19] and heat shock proteins [20]. Activation of p38 MAPK also results in delayed protection after translocation of nuclear factor-kappa B (NF-κB) to the nucleus and expression of inducible nitric oxide synthase (iNOS) and hemoxygenase-1 [21]. Whether remote ischemic preconditioning is also involved in activation of pro-survival kinases of the reperfusion injury salvage kinase pathway and inhibition of the mitochondrial permeability transition pore remains to be determined.

Other studies have revealed further potential underlying mechanisms of remote ischemic preconditioning. A study by Weinbrenner and colleagues suggested a possible beneficial signaling role for ROS in the setting of remote ischemic preconditioning. These authors discovered that a free radical scavenger was able to abolish the protection elicited by remote ischemic preconditioning [22]. Recent experimental studies have further implicated the transcription factor, hypoxia-inducible factor (HIF)-1α [23], and erythropoietin [24] as potential mediators of remote ischemic preconditioning-induced cardioprotection. A further mechanism could be the ability of remote ischemic preconditioning to mediate the release of fibrinolytic substances, e.g., tissue-type plasminogen activator, which is known to be released from the endothelium during mechanical compression of a vessel [25].

Remote Ischemic Preconditioning in Healthy Volunteers

MacAllister's group [26–28] studied the effect of remote ischemic preconditioning on endothelial ischemia/reperfusion injury in human volunteers. *In vivo* endothelial ischemia/reperfusion injury was induced by 20 min of upper limb ischemia caused by inflating a blood pressure cuff to 200 mmHg followed by deflation (reperfusion). Venous occlusion plethysmography was used to assess forearm blood flow in response to acetylcholine. The vasodilating response to acetylcholine was attenuated by endothelial injury in control volunteers. Remote ischemic preconditioning applied to the contralateral arm was able to prevent the attenuation of the vasodilating effect of acetylcholine, thus reducing the endothelial dysfunction in the target limb with ischemia/reperfusion injury. The same experimental model has been used to evaluate the concept of delayed protection by remote ischemic preconditioning, in which preconditioning conferred an improvement in endothelial dysfunction in the opposite upper limb 24 h and 48 h later [27].

In addition to release of humoral circulating factors and neural pathways, Konstantinov et al. demonstrated that remote ischemic preconditioning also has anti-inflammatory effects that might be relevant to its effectiveness [29]. In healthy volunteers, remote ischemic preconditioning suppressed pro-inflammatory gene expression in circulating leukocytes. Genes encoding key proteins involved in cytokine synthesis, leukocyte chemotaxis, adhesion and migration, innate immunity signaling pathways, and apoptosis were all suppressed within 15 min (early phase) and still further after 24 h (late phase – second window). Very recently, the same group reported that the observed changes in gene expression lead to functional changes in neutrophils, including reduced adhesion and apoptosis [30]. This effect may contribute to the protective effect of remote ischemic preconditioning against ischemia/reperfusion injury and may have further implications in

other inflammatory settings. Transient limb ischemia with remote ischemic preconditioning administered before a prolonged ischemic insult has systemic protective effects against ischemia/reperfusion injury in human volunteers.

Remote Ischemic Preconditioning in Patients

With many experimental data and studies in human volunteers demonstrating the effectiveness of transient limb ischemia to induce distant organ protection, the potential of this procedure as a clinical intervention was suggested. Evolving evidence from clinical studies currently points to the effectiveness of remote ischemic preconditioning in different settings of ischemia/reperfusion injury (**Table 1**).

Cardiac surgery

Cardiac surgery with cardiopulmonary bypass (CPB) is generally associated with a predictable incidence of myocardial, neurological, and renal ischemia/reperfusion injury leading to an increased risk of postoperative myocardial stunning, neurological deficits, and acute renal failure. Cardiac surgery is further associated with a substantial systemic inflammatory response and oxidative stress, which contribute to multiple organ dysfunction syndrome [31].

Table 1. Human studies on remote ischemic conditioning in healthy volunteers and patients

Study	Ischemia/reperfusion	Stimulus	Endpoints	n
Kharbanda (2002) [26]	UL-I – endothelial dysfunction	UL-I (3 x 5 min)	Endothelial dysfunction ↓	14
Shimizu (2010) [30]	UL-I systemic inflammation	UL-I (3 x 5 min)	Neutrophil adhesion ↓ exocytosis ↓, phagocytosis ↓	5
Zhou (2010) [20]	Congenital heart surgery	UL-I (3 x 5 min)	Troponin I ↓, Inotropic support ↓, Lung function ↑, Inflammatory cytokines ↓, Heat shock protein-70 ↑	60
Hausenloy (2007) [32]	Coronary artery bypass surgery	UL-I (3 x 5 min)	Troponin T ↓	57
Ali (2007) [35]	Abdominal aortic aneurysm surgery	LL-I (2 x 10 min)	Troponin I ↓, Myocardial infarction ↓, Renal dysfunction ↓	82
Walsh (2010) [39]	Carotid endarterectomy	LL-I (2 x 10 min)	Neurological impairment ↓	70
Hoole (2009) [40]	Elective percutaneous coronary intervention	UL-I (3 x 5 min)	Troponin I ↓, Major adverse cardiac & cerebral events ↓	242
Botker (2010) [44]	ST-elevation myocardial infarction	UL-I (3 x 5 min)	Myocardial salvage ↑, Infarct size at 1 month ↓ Remote postconditioning	333

UL-I = upper-limb ischemia; LL-I = lower-limb ischemia

These adverse effects are amplified in children undergoing congenital cardiac surgery, in which aortic cross-clamping and CPB are usually sustained, and complete circulatory arrest may be used during complex procedures. The first clinical study of remote ischemic preconditioning by transient limb ischemia showed reduced myocardial injury, reduced inotropic support, and improved lung function using a randomized study design involving 37 children (20 control, 17 remote ischemic preconditioning) undergoing congenital cardiac surgery. A subsequent study in 60 infants undergoing repair of ventricular septal defects (30 control, 30 remote ischemic preconditioning) confirmed the beneficial effects of limb remote ischemic preconditioning in terms of increased tolerance against myocardial and pulmonary ischemia/reperfusion injury and attenuation of systemic inflammatory response syndrome (SIRS) [20].

In a similar proof-of-principle study enrolling 57 adults undergoing elective coronary artery bypass graft (CABG) surgery and receiving predominantly cross-clamp fibrillation for myocardial protection, Hausenloy et al. showed the protective effect of remote ischemic preconditioning by limb ischemia [32]. The endpoint was troponin release, which was significantly lower in the remote ischemic preconditioning group (n = 27) than in the control group (n = 30). Recently, the effectiveness of remote ischemic preconditioning has been further suggested in adult patients undergoing CABG, when cold-blood [33] or crystalloid cardioplegia [34] was used instead of cross-clamp fibrillation for myocardial protection.

Thus, remote ischemic preconditioning reduces myocardial injury in children and adults undergoing cardiac surgery. However, the clinical relevance of these findings has yet to be defined, and large studies are underway to address this issue. A review of ClinicalTrials.gov in September 2010 yielded 18 registered studies that are using limb ischemia in cardiac surgery to assess the effects of remote ischemic preconditioning on myocardial, cerebral, and renal protection.

Non-cardiac surgery

In major vascular surgery, the surgical procedure results in ischemia/reperfusion injury to vital organs directly, but many patients also suffer from acute myocardial infarction perioperatively. The ability of remote ischemic preconditioning to protect the heart and kidneys was investigated in a clinical trial of patients undergoing elective aortic aneurysm repair [35]. Remote ischemic preconditioning was induced by intermittent femoral artery occlusion and reperfusion in 82 patients (41 controls, 41 remote ischemic preconditioning). The results were remarkable. Remote ischemic preconditioning reduced the incidence of myocardial injury by 27 %, the incidence of myocardial infarction by 22 %, and decreased renal impairment by 23 %. Two further studies by Walsh et al., however, showed controversial results in terms of renal injury in this kind of surgery [36, 37].

In patients undergoing decompression spine surgery for cervical spondylotic myelopathy, remote ischemic preconditioning has been found to improve neurological outcome and to reduce release of serum protein S-100B and neurone specific enolase indicating less spinal cord ischemia/reperfusion injury [38]. Carotid endarterectomy is the preferred treatment modality for symptomatic carotid stenosis, but is also associated with major cerebral complications. In a small pilot study (30 control, 25 remote ischemic preconditioning), Walsh et al. recently found less neurological impairment if patients were preconditioned using 10 min of lower limb ischemia/reperfusion [39]. Again, large-scale trials are required to

determine whether remote ischemic preconditioning confers clinical benefits in these high-risk non-cardiac surgical patients.

In visceral organ transplantation, the donor organ is subjected to substantial ischemia before reperfusion in the recipient. Reduction of ischemia/reperfusion injury might, therefore, improve graft function and survival. This idea has been translated into clinical trials, and studies are underway in renal and liver transplantation to test the potential of remote ischemic preconditioning to reduce graft injury and to improve outcome.

Percutaneous coronary intervention

Hoole et al. extended the concept of remote conditioning to show, in a prospective, randomized controlled trial including 242 patients, that remote ischemic preconditioning before elective percutaneous coronary intervention was associated with reduced troponin release, less procedure-related ischemic chest discomfort, and fewer electrocardiographic (EKG) findings of coronary ischemia [40]. Perhaps the most intriguing finding was a reduction in major adverse cardiac and cerebral events at 6 months (4 versus 13 patients; hazard ratio 0.28). These data suggest that the systemic effects of remote ischemic preconditioning by even a short intervention might have secondary beneficial effects. In contrast to local coronary ischemic preconditioning by repetitive balloon inflation and deflation, which may be effective, but also contributes to repetitive endothelial trauma and emboli of thrombotic debris, transient limb ischemia by remote ischemic preconditioning is non-invasive and has been shown to have no adverse effects.

Remote Ischemic Postconditioning

The clinical application of ischemic preconditioning is hampered by the requirement to intervene before the onset of acute ischemia, which in most instances, such as acute myocardial infarction or stroke, is clearly not possible. In order to circumvent this problem, the concept of ischemic postconditioning has evolved. Postconditioning is defined as a short and repeated interruption of blood flow during reperfusion and has been successfully applied to attenuate ischemia/reperfusion injury in the heart, brain, spinal cord, kidney, liver, muscle, lung and intestines in experimental settings [41]. Clinical trials have also revealed the beneficial effect of direct ischemic postconditioning on myocardial infarction in patients undergoing percutaneous coronary intervention [42]. But again, direct coronary ischemic conditioning by repetitive balloon inflation and deflation leads to repetitive endothelial trauma. In this respect, remote ischemic postconditioning by transient limb ischemia has emerged as an alternative to attenuate cardiac reperfusion injury. Andreka et al. demonstrated that applying intermittent limb ischemia at the end of a sustained period of myocardial ischemia reduced myocardial infarct size assessed by cardiac magnetic resonance imaging (MRI) [43]. Using the *in vivo* model of endothelial dysfunction, Loukogeorgakis et al. showed that remote ischemic postconditioning is also feasible and effective in humans [28], suggesting a huge clinical potential in patients with unpredictable ischemia/reperfusion injury, such as acute myocardial infarction or stroke. More importantly, a randomized trial enrolled 333 patients with an acute ST-elevation myocardial infarction who received remote ischemic postconditioning or control intervention in the ambulance during transfer for revascularization by primary

percutaneous intervention [44]. The primary endpoint of myocardial salvage assessed by nuclear scintigraphy was significantly increased in the intervention group. Remote ischemic postconditioning may even have the potential to ameliorate adverse left ventricular remodeling, heart failure, and mortality. However, large-scale trials are necessary to establish the effects of remote ischemic postconditioning on relevant clinical endpoints and future research that addresses other organ systems to identify beneficial effects of remote ischemic pre- and post-conditioning, particularly in critically ill patients with microcirculatory failure, impaired tissue oxygenation or regional ischemia, is urgently needed. In addition, patients suffering from global ischemia/reperfusion following successful resuscitation from cardiac arrest, cardiogenic or hemorrhagic shock may benefit from remote conditioning. But again, convincing evidence from experimental and clinical studies is still lacking.

Overview of Potential Clinical Settings for Remote Ischemic Conditioning

Considering the current literature, remote organ protection may be feasible in the following clinical settings:

- Remote ischemic preconditioning
  - Protecting vital organs during cardiac surgery requiring CPB
  - Protecting the brain during neurosurgical procedures and carotid endarterectomy
  - Protecting heart, kidney and intestine during major vascular surgery
  - Protecting donor organs before excision and transport
  - Reducing myocardial injury during elective percutaneous coronary intervention
- Remote ischemic postconditioning
  - Patients with acute myocardial infarction and ischemic stroke
  - ICU patients with impaired tissue oxygenation, microcirculatory failure or regional ischemia (kidney, liver, small intestine)
  - ICU patients after global ischemia/hypoperfusion following cardiac arrest, cardiogenic shock or hemorrhagic shock

Conclusion

Remote ischemic preconditioning has been rapidly translated from experimental discovery ('bench-side') into encouraging proof-of-principle human studies using surrogate endpoints ('bedside'). Further studies are underway to define the potential clinical use of remote ischemic preconditioning in other organs, e.g., brain, kidney, and liver. However, large-scale, multicenter, prospective randomized phase III studies that are adequately powered to show effects on relevant clinical endpoints will be needed to change practice. Since remote conditioning can also be applied effectively during the ischemic phase and early into reperfusion, limb ischemia may also be beneficial when performed after the onset of index ischemia, while patients are being transferred to reperfusion therapy remote ischemic postconditioning. Although the outlook for this clinical method seems promising, current enthusiasm generated by these studies should be used

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to encourage studies that deal with the exact dose of ischemia needed, and the influence of age, co-medications, or comorbidities on the effectiveness of remote ischemic pre- and post-conditioning.

References

1. Yellon DM, Hausenloy DJ (2007) Myocardial reperfusion injury. N Engl J Med 357: 1121 – 1135
2. Devereaux PJ, Yang H, Yusuf S, et al (2008) Effects of extended-release metoprolol succinate in patients undergoing non-cardiac surgery (POISE trial): a randomised controlled trial. Lancet 371: 1839 – 1847
3. De Hert SG, Preckel B, Hollmann MW, Schlack WS (2009) Drugs mediating myocardial protection. Eur J Anaesthesiol 26: 985 – 995
4. Hausenloy DJ, Yellon DM (2008) Clinical translation of cardioprotective strategies: report and recommendations of the Hatter Institute 5th International Workshop on Cardioprotection. Basic Res Cardiol 103: 493 – 500
5. Przyklenk K, Bauer B, Ovize M, Kloner RA, Whittaker P (1993) Regional ischemic 'preconditioning' protects remote virgin myocardium from subsequent sustained coronary occlusion. Circulation 87: 893 – 899
6. Dickson EW, Reinhardt CP, Renzi FP, Becker RC, Porcaro WA, Heard SO (1999) Ischemic preconditioning may be transferable via whole blood transfusion: preliminary evidence. J Thromb Thrombolysis 8: 123 – 129
7. Wang L, Oka N, Tropak M, et al (2008) Remote ischemic preconditioning elaborates a transferable blood-borne effector that protects mitochondrial structure and function and preserves myocardial performance after neonatal cardioplegic arrest. J Thorac Cardiovasc Surg 136: 335 – 342
8. Konstantinov IE, Li J, Cheung MM, et al (2005) Remote ischemic preconditioning of the recipient reduces myocardial ischemia-reperfusion injury of the denervated donor heart via a Katp channel-dependent mechanism. Transplantation 79: 1691 – 1695
9. Patel HH, Moore J, Hsu AK, Gross GJ (2002) Cardioprotection at a distance: mesenteric artery occlusion protects the myocardium via an opioid sensitive mechanism. J Mol Cell Cardiol 34: 1317 – 1323
10. Hajrasouliha AR, Tavakoli S, Ghasemi M, et al (2008) Endogenous cannabinoids contribute to remote ischemic preconditioning via cannabinoid CB2 receptors in the rat heart. Eur J Pharmacol 579: 246 – 252
11. Su B, Dong H, Ma R, Zhang X, Ding Q, Xiong L (2009) Cannabinoid 1 receptor mediation of spinal cord ischemic tolerance induced by limb remote ischemia preconditioning in rats. J Thorac Cardiovasc Surg 138: 1409 – 1416
12. Liem DA, Verdouw PD, Ploeg H, Kazim S, Duncker DJ (2002) Sites of action of adenosine in interorgan preconditioning of the heart. Am J Physiol Heart Circ Physiol 283: H29 – 37
13. Schoemaker RG, van Heijningen CL (2000) Bradykinin mediates cardiac preconditioning at a distance. Am J Physiol Heart Circ Physiol 278: H1571 – 1576
14. Wolfrum S, Nienstedt J, Heidbreder M, Schneider K, Dominiak P, Dendorfer A (2005) Calcitonin gene related peptide mediates cardioprotection by remote preconditioning. Regul Pept 127: 217 – 224
15. Gho BC, Schoemaker RG, van den Doel MA, Duncker DJ, Verdouw PD (1996) Myocardial protection by brief ischemia in noncardiac tissue. Circulation 94: 2193 – 2200
16. Lim SY, Yellon DM, Hausenloy DJ (2010) The neural and humoral pathways in remote limb ischemic preconditioning. Basic Res Cardiol 105: 651 – 655
17. Jones WK, Fan GC, Liao S, et al (2009) Peripheral nociception associated with surgical incision elicits remote nonischemic cardioprotection via neurogenic activation of protein kinase C signaling. Circulation 120:S1 – 9
18. Kanoria S, Jalan R, Seifalian AM, Williams R, Davidson BR (2007) Protocols and mechanisms for remote ischemic preconditioning: a novel method for reducing ischemia reperfusion injury. Transplantation 84: 445 – 458
19. Heidbreder M, Naumann A, Tempel K, Dominiak P, Dendorfer A (2008) Remote vs. ischa-

emic preconditioning: the differential role of mitogen-activated protein kinase pathways. Cardiovasc Res 78: 108 – 115
20. Zhou W, Zeng D, Chen R, et al (2010) Limb ischemic preconditioning reduces heart and lung injury after an open heart operation in infants. Pediatr Cardiol 31: 22 – 29
21. Tapuria N, Junnarkar SP, Dutt N, et al (2009) Effect of remote ischemic preconditioning on hepatic microcirculation and function in a rat model of hepatic ischemia reperfusion injury. HPB (Oxford) 11: 108 – 117
22. Weinbrenner C, Schulze F, Sarvary L, Strasser RH (2004) Remote preconditioning by infrarenal aortic occlusion is operative via delta1-opioid receptors and free radicals in vivo in the rat heart. Cardiovasc Res 61: 591 – 599
23. Kant R, Diwan V, Jaggi AS, Singh N, Singh D (2008) Remote renal preconditioning-induced cardioprotection: a key role of hypoxia inducible factor-prolyl 4-hydroxylases. Mol Cell Biochem 312: 25 – 31
24. Diwan V, Jaggi AS, Singh M, Singh N, Singh D (2008) Possible involvement of erynhropointin in remote renal preconditioning-induced cardioprotection in rats. J Cardiovasc Pharmacol 51: 126 – 130
25. Lund SS (2010) Ischaemic conditioning for myocardial salvage after AMI. Lancet 375: 1691 – 1692
26. Kharbanda RK, Mortensen UM, White PA, et al (2002) Transient limb ischemia induces remote ischemic preconditioning in vivo. Circulation 106: 2881 – 2883
27. Loukogeorgakis SP, Panagiotidou AT, Broadhead MW, Donald A, Deanfield JE, MacAllister RJ (2005) Remote ischemic preconditioning provides early and late protection against endothelial ischemia-reperfusion injury in humans: role of the autonomic nervous system. J Am Coll Cardiol 46: 450 – 456
28. Loukogeorgakis SP, Williams R, Panagiotidou AT, et al (2007) Transient limb ischemia induces remote preconditioning and remote postconditioning in humans by a K(ATP)-channel dependent mechanism. Circulation 116: 1386 – 1395
29. Konstantinov IE, Arab S, Kharbanda RK, et al (2004) The remote ischemic preconditioning stimulus modifies inflammatory gene expression in humans. Physiol Genomics 19: 143 – 150
30. Shimizu M, Saxena P, Konstantinov IE, et al (2010) Remote ischemic preconditioning decreases adhesion and selectively modifies functional responses of human neutrophils. J Surg Res 158: 155 – 161
31. De Hert SG (2008) Outcome after cardiovascular surgery: where do we stand? Curr Opin Anaesthesiol 21: 47 – 49
32. Hausenloy DJ, Mwamure PK, Venugopal V, et al (2007) Effect of remote ischaemic preconditioning on myocardial injury in patients undergoing coronary artery bypass graft surgery: a randomised controlled trial. Lancet 370: 575 – 579
33. Venugopal V, Hausenloy DJ, Ludman A, et al (2009) Remote ischaemic preconditioning reduces myocardial injury in patients undergoing cardiac surgery with cold-blood cardioplegia: a randomised controlled trial. Heart 95: 1567 – 1571
34. Thielmann M, Kottenberg E, Boengler K, et al (2010) Remote ischemic preconditioning reduces myocardial injury after coronary artery bypass surgery with crystalloid cardioplegic arrest. Basic Res Cardiol 105: 657 – 664
35. Ali ZA, Callaghan CJ, Lim E, et al (2007) Remote ischemic preconditioning reduces myocardial and renal injury after elective abdominal aortic aneurysm repair: a randomized controlled trial. Circulation 116: I98 – 105
36. Walsh SR, Boyle JR, Tang TY, et al (2009) Remote ischemic preconditioning for renal and cardiac protection during endovascular aneurysm repair: a randomized controlled trial. J Endovasc Ther 16: 680 – 689
37. Walsh SR, Sadat U, Boyle JR, et al (2010) Remote ischemic preconditioning for renal protection during elective open infrarenal abdominal aortic aneurysm repair: randomized controlled trial. Vasc Endovascular Surg 44: 334 – 340
38. Hu S, Dong HL, Li YZ, et al (2010) Effects of remote ischemic preconditioning on biochemical markers and neurologic outcomes in patients undergoing elective cervical decompression surgery: a prospective randomized controlled trial. J Neurosurg Anesthesiol 22: 46 – 52

39. Walsh S, Nouraei SR, Tang T, Sadat U, Carpenter R, Gaunt M (2010) Remote ischemic preconditioning for cerebral and cardiac protection during carotid endarterectomy: Results from a pilot randomized clinical trial. Vasc Endovascular Surg 44: 334 – 340
40. Hoole SP, Heck PM, Sharples L, et al (2009) Cardiac Remote Ischemic Preconditioning in Coronary Stenting (CRISP Stent) Study: a prospective, randomized control trial. Circulation 119: 820 – 827
41. Zhao ZQ (2010) Postconditioning in reperfusion injury: a status report. Cardiovasc Drugs Ther 24: 265 – 279
42. Xue F, Yang X, Zhang B, et al (2010) Postconditioning the human heart in percutaneous coronary intervention. Clin Cardiol 33: 439 – 444
43. Andreka G, Vertesaljai M, Szantho G, et al (2007) Remote ischaemic postconditioning protects the heart during acute myocardial infarction in pigs. Heart 93: 749 – 752
44. Botker HE, Kharbanda R, Schmidt MR, et al (2010) Remote ischaemic conditioning before hospital admission, as a complement to angioplasty, and effect on myocardial salvage in patients with acute myocardial infarction: a randomised trial. Lancet 375: 727 – 734

Hypoxia-inducible Factors and the Prevention of Acute Organ Injury

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Introduction

Hypoxic preconditioning has long been considered as organ-protective, and its clinical usage has been suggested in elective procedures, such as coronary surgery and organ transplantation. Although the mechanisms have not been clearly elucidated, it has been postulated that changes in cell-membrane composition and upregulation of various cellular protective mechanisms are responsible for a better tolerance of acute injury. Remote preconditioning (i.e., hypoxic stress in one organ conferring resistance to acute hypoxia in other organs) suggests organ cross-talk, perhaps mediated by cytokines and the immune system.

Increased expression of heme-oxygenase (HO)-1, heat-shock proteins (HSP), growth factors such as vascular endothelial factor (VEGF), and erythropoietin (EPO) are among the numerous adaptive responses to sublethal injury that are believed to participate in tissue tolerance during subsequent stress. EPO, for instance, is a ubiquitous pleiotropic survival and growth factor that attenuates experimental acute injury in various organ systems, including neuronal, retinal, cardiac, renal, and hepatic tissues. Its clinical efficacy, though suggested in critically ill patients, is yet to be defined [1].

The expression of these protective mediators and many others is regulated by hypoxia-sensing mechanisms through the induction and stabilization of so called hypoxia-inducible factors (HIF) [2]. In this chapter, we will outline the control and action of HIF as key regulators of hypoxic adaptive response, and particularly examine HIF expression during hypoxic stress. We shall discuss recently developed measures that enable HIF signal modification and describe their potential use in conferring tissue tolerance during incipient organ injury.

HIF Regulation and Action

HIFs are heterodimers (**Fig. 1**), composed of a constitutive β-subunit (HIF-β) and one of three different oxygen-dependent and transcriptionally active α-subunits, among which HIF-1α and -2α are acknowledged as promotors of hypoxia adaptation, whereas the role of HIF-3α remains unclear. Under normoxia, HIF-α subunits are constantly produced, but not allowed to accumulate, since they are rapidly hydroxylated by oxygen-dependent HIF prolyl-4-hydroxylase domain enzymes (PHD), subsequently captured by the ubiquitin ligase Von-Hippel-Lindau protein (VHL), and degraded by the proteasome. Under oxygen deficiency, PHD activity is reduced, HIF-α accumulates within the cytosol,

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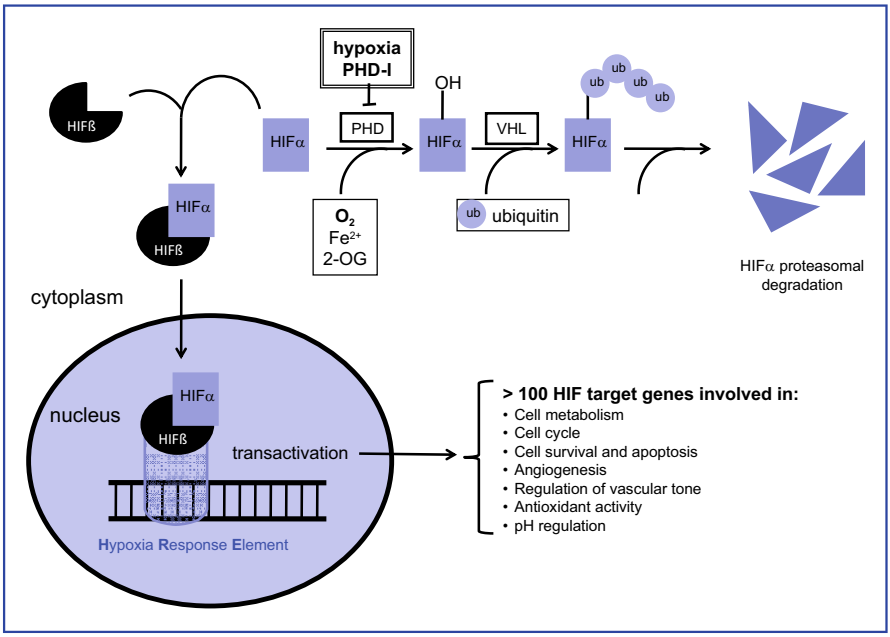

Fig. 1. A schematic display of hypoxia-inducible factor (HIF) regulation and biological action. Prolyl-4 hydroxylases (PHDs) serve as oxygen sensors and under normoxic conditions promote degradation of HIF-α isoforms in the proteasome following binding with the ubiquitin ligase, Von-Hippel-Lindau protein (VHL). Hypoxia inhibits PHDs and leads to HIF-α accumulation with HIF-β, and the αβ heterodimer translocates into the nucleus, binds with hypoxia-response elements (HRE) and activates numerous genes important in cell metabolism, proliferation and survival. Many of these genes play a central role in injury tolerance and promotion of tissue oxygenation, such as erythropoietin (EPO), vascular endothelial growth factor (VEGF), inducible NO synthase (iNOS), heme oxygenase (HO)-1, glucose transporter-1, or carbonic anhydrase (CA)-9. Underscored is the inactivation of the HIF-HRE axis by hypoxia, which can be mimicked by carbon monoxide (functional anemia) or by transition metals like cobaltous chloride. Hypoxia-mimetic PHD inhibitors (PHD-I) are potent newly developed measures in the induction of the HIF-HRE axis. For simplicity, numerous additional factors involved in HIF regulation and action are not included in this cartoon and the reader is referred to comprehensive reviews such as references [3, 12].

αβ-dimers are formed, translocate into the nucleus, and bind to hypoxia response elements (HREs) in the promoter enhancer region of genes, which are subsequently transactivated [2–4].

The biological effects of the more than 100 acknowledged HIF target genes are multiple, and include key steps in cell metabolism and survival. Many of the HIF-target genes constitute a reasonable adaptation to hypoxia, such as erythropoiesis (EPO), increased glucose uptake (glucose transporter-1), switch of metabolism to glycolysis (several key enzymes of glycolysis), increased lactate utilization (lactate dehydrogenase), angiogenesis (VEGF), vasodilation (inducible nitric oxide synthase [iNOS]), removal of protons (carbonic anhydrase 9), and scavenging of free radicals (HO-1) [2–4].

Biological and Therapeutic Modes of HIF Activation

Every cell type has the potential to upregulate HIF, principally by the inhibition of PHD, under conditions when cellular oxygen demand exceeds oxygen supply, namely under cellular hypoxia. However, the threshold and extent of HIF activation may depend on the hypoxic stimulus and cell type involved. To some extent, these cellular variations may reflect different expression of various PHD isoforms in different tissues [5–7].

As HIF stimulation may potentiate hypoxia tolerance, studies were conducted to explore its clinical application. Widespread experimental hypoxic stimuli are listed in **Table 1**, all acting principally by the control of HIF-α degradation, initiated by PHDs. Except for carbon monoxide exposure, which is currently being tested in patients, none of these stimuli seems suitable for preconditional HIF activation in humans.

Apart from hypoxic stabilization, widely proven *in vivo*, HIF activation has also been demonstrated to occur under normal ambient oxygen tensions, mostly in cell cultures challenged with cytokines and growth factors. However, under stress, oxygen demand likely is increased, thus possibly leading to intracellular hypoxia even in cells kept under room air. For technical reasons, it is probably impossible to rule out such local cellular hypoxia that may exist predominantly within the mitochondria. Beyond this academic distinction between true cellular hypoxia and normoxia, it is important to recognize that clinical conditions, like inflammation, infection and sepsis, may lead to HIF activation. Thus, theoretically, cytokines or growth factors could be used for preconditional HIF activation in humans.

Table 1. Modes of HIF signal enhancement

Stimulus/Agent	Remarks	Potential Clinical Applications
Inhibition of PHDs by the induction of cellular physiologic hypoxia		
Hypoxic chamber (e.g., 8 % O_2 in ambient air)	depressed systemic PO_2	
Carbon monoxide admixture to ambient air	functional anemia normal systemic PO_2	✓
Anemia	normal systemic PO_2	
Arterial clamping	normal systemic PO_2	
Chemical inhibition of PHDs by hypoxia-mimetics		
$CoCl_2$ (interferes with Fe^{2+})	non-specific	
Mimosine (2-oxoglutarate analogue)	non-specific	
Other patented PHD inhibitors	specific	✓
Molecular biology techniques		
Von-Hippel-Lindau knockout	non-specific	
PHD siRNA transfection	PHD-specific	
Constitutively active HIF-α transgenes	organ-specific	✓

PHD: prolyl hydroxylase domain enzyme

Although not a reasonable therapeutic intervention, strong and stable normoxic HIF activation can be achieved by deletion of the VHL gene, which is a constant phenomenon in Von Hippel Lindau Disease and in renal clear cell carcinoma, and is also encountered in other tumors. Transgenic animals with VHL knockout serve to test the potential of HIF activation in ischemic/hypoxic diseases (C Rosenberger, unpublished data) [8]. Additional experimental probes for enhancing HIF signal are by transfection with PHD siRNA [9] or with the generation of constitutively active HIF-α transgenes [10].

So-called hypoxia mimetics block PHD activity, thus upregulating HIF under normoxia. PHDs require 2-oxoglutarate and ferrous iron as co-substrates. Non-specific PHD inhibitors are either 2-oxoglutarate analogues or interfere with Fe^{2+}. Recently, more specific PHD inhibitors (PHD) have been synthesized [11], and are currently being tested in animal and human studies.

Figure 1 represents a simplistic scheme of the canonical HIF regulation and action. Recent discoveries underscore a host of additional compound biological pathways, associated with the regulation of the HIF signal, including the control of HIF synthesis, HIF controlling PHD synthesis, putative competing/intervening impacts of HIF-3α and PHD-3, cross-talk of HIF and other key regulators of gene expression (STAT, p-300 and others), further modification of HIF-α activity at the level of DNA hypoxia-responsive elements by small ubiquitin-like modifiers (SUMO) and factor inhibiting HIF (FIH), and the effect of reactive oxygen species (ROS), NO and Krebs cycle metabolites on HIF degradation. These complex pathways are beyond the scope of this review, and the interested reader is referred to additional references [3, 5, 12–18].

HIF Expression under Hypoxic Stress and Tissue Injury

The kidney serves as an excellent example for understanding HIF expression under hypoxic stress. Renal oxygenation is very heterogeneous, with PO_2 falling to levels as low as 25 mmHg in the outer medulla under normal physiologic conditions and to even lower values in the papilla [3, 4, 19]. Changes in renal parenchymal microcirculation and oxygenation have been thoroughly investigated in acute and chronic renal disorders [19, 20]. Finally, the complex renal anatomy in which different cell types are in close proximity to regions with comparable ambient oxygenation, enables comparisons of cellular HIF response.

Interestingly, HIF expression is below detection threshold by immunostaining in the renal medulla, despite low physiologic ambient oxygenation.[1] Conceivably, this reflects the plasticity of HIF control to adjust for 'physiologically normal' oxygenation (i.e., adjusted rates of HIF-α generation and degradation under normal conditions.

Enhanced renal HIF-α is noted in rodents subjected to hypoxia or to inhaled carbon monoxide (chemical hypoxia) [21], and in hypoxic isolated perfused kidneys [22]. Different cells express diverse HIF isoforms: Whereas tubular segments

1 It should be emphasized that this statement regarding negative HIF immunostaining in the normally hypoxic medulla relates to kidneys perfusion-fixed *in vivo* without an interruption of renal oxygenation before fixation. Other modes of tissue harvesting for HIF determination, either by immunostaining or by molecular biology techniques may be falsely positive, as hypoxia-induced inhibition of PHD activity is instantaneous, and may lead to HIF-α stabilization even over short periods of hypoxia

express HIF-1α, HIF-2α is principally produced by vascular endothelial and interstitial cells [21–23]. Interestingly, HIF-dependent genes are also selectively expressed in different cell types. For instance HIF-2-triggered EPO generation is specifically found in interstitial cells in the deep cortex [24]. In hypoxic isolated perfused kidneys, attenuation of severe medullary hypoxia by the inhibition of tubular transport markedly enhanced HIF expression, probably underscoring a window of opportunity to generate HIF and HIF-mediated adaptive responses only under moderate and sublethal hypoxic stress [22]. This pattern is consistent with HIF expression at the border of renal infarct zones only, indicating that dying cells within the critically ischemic region are incapable of mounting a hypoxia adaptive response [25].

We also found that HIF-α isoforms are stabilized in acute hypoxic stress, predominantly in the cortex in rhabdomyolysis-induced kidney injury [26], in the outer stripe of the outer medulla following ischemia and reperfusion [27, 28], or in the inner stripe and inner medulla following the induction of distal tubular hypoxic injury by radiocontrast agent, or after the inhibition of prostaglandin or NO synthesis or with their combinations [23]. Outer medullary HIF stabilization is also noted in chronic tubulointerstitial disease [29] and in experimental diabetes [30], again spatially distributed in areas with proven hypoxia. HIF was also detected in biopsies from transplanted kidneys [31]. Thus, HIF immunostaining is chronologically and spatially distributed in renal regions with abnormally low PO_2.

Normal mice subjected to warm ischemia and reperfusion display limited injury only, as compared with extensive damage in HIF (+/-) mice [32]. Thus, the importance of mounting an HIF response during hypoxic stress is undeniable.

Hypoxia-driven HIF stabilization during hypoxic stress has been encountered in other organs as well. HIF-1α and PHD-2 expression increased in the neonatal rat brain following hypoxia [33] and HIF was detected in the hypoxic subendocardium [34] and in the ischemic liver [27]. HIF is also found within hypoxic regions in tumors, and may play an important role in tumor progression via upregulation of growth promoting and angiogenic factors [35].

Potential Usage of HIF Modulation in Clinical Practice

The impact of HIF stimulation on the expression of HIF-dependent tissue-protective genes led to the expectation that timely upstream HIF stimulation may have great potential in the protection of endangered organs by downstream induction of protective genes [12]. Indeed, repeated systemic hypoxia, for instance, results in enhanced expression of renal HIF and HIF-dependent genes and attenuates warm-ischemic injury [36].

The use of hypoxia-mimetic PHD inhibitors is a promising potential new treatment option in diseases such as myocardial infarction, stroke, renal or liver injury, peripheral vascular disease, or severe anemia. Studies with PHD inhibitors and other manipulations of HIF upregulation favor this hypothesis [11].

Anemia

Specific PHD inhibitors induce HIF-2α expression in interstitial fibroblasts in the deep cortex [24], enhance erythropoietin generation, and were found to provoke

erythrocytosis in primates [37]. Phase 2 clinical trials in patients with chronic kidney disease are currently under way, studying the effect of oral PHD inhibitors as potential substitutes to EPO injection.

Acute Kidney Injury

The potential protective impact of HIF upregulation by PHD inhibitors has been extensively studied in acute kidney injury. In isolated kidneys perfused with low-oxygen containing medium, pre-treatment with a PHD inhibitor improved renal blood flow and attenuated medullary hypoxic damage [38]. Conditional inactivation of VHL in mice (hence HIF stabilization) resulted in tolerance to renal ischemia and reperfusion [8] and to rhabdomyolysis-induced acute kidney injury (Rosenberger C, unpublished data). Whereas gene transfer of negative-dominant HIF led to severe damage in the normally hypoxic renal medulla in intact rats, transfer of constitutively active HIF (HIF/VP16) induced expression of various HIF-regulated genes and protected the medulla against acute ischemic insults [39]. Furthermore, in rats and mice subjected to warm ischemia and reflow, PHD inhibitors and carbon monoxide pre-treatment (i.e., functional anemia) markedly attenuated kidney damage and dysfunction [32, 40]. Donor pre-treatment with a PHD inhibitor also prevented graft injury and prolonged survival in an allogenic kidney transplant model in rats [41]. Finally, rats preconditioned by carbon monoxide, displayed reduced cisplatin renal toxicity, with attenuation of renal dysfunction and the extent of tubular apoptosis and necrosis [42]. Taken together, all these observations indicate that HIF stabilization seemingly is a promising novel interventional strategy in acute kidney injuries [12].

Myocardial Injury

Activation of the HIF system has also been found to be cardioprotective. In a model of myocardial ischemia in rabbits, pre-treatment with a PHD inhibitor induced robust expression of HO-1 and markedly attenuated infarct size and myocardial inflammation [43]. In another report, PHD inhibitors did not reduce infarct size, but improved left ventricular function and prevented remodeling [44]. In the same fashion, selective silencing of PHD-2 with siRNA 24 h before global myocardial ischemia/reperfusion in mice reduced the infarct size by 70 % and markedly improved left ventricular systolic function [9]. Remote preconditioning by intermittent renal artery occlusion also resulted in cardiac protection, conceivably through PHD inhibition [45].

Enhanced levels of PHD-3 were traced in the hibernating myocardium [34] and in end-stage heart failure in humans, associated also with elevated HIF-3α [46] (which may act as a competitive inhibitor of active HIF-α isoforms [14]). Thus, PHD inhibitors may conceivably also be beneficial in these disorders. Finally, cardioprotection during heat acclimation is also mediated in part by HIF upregulation [47], providing another potential situation for the administration of PHD inhibitors.

Neuronal Injuries

The effect of PHD inhibitors has also been assessed in disorders of the central nervous system. *In vitro*, rotenone-induced neuronal apoptosis was attenuated

and autophagy increased, as the result of enhanced HIF following deferoxamine administration [48]. *In vivo*, PHD inhibitors have shown promising results in the attenuation of ischemic stroke [49], and might be neuroprotective in metabolic chronic neurodegenerative conditions [50]. However, studies showing inhibition of PHD-1 by ROS suggest non-HIF-mediated neuronal protection under normoxic conditions [51].

Lung Injury

Preterm lambs developing respiratory distress syndrome display upregulation of PHDs with a reciprocal fall in HIF-α isoforms and HIF-dependent VEGF [53]. This observation implies that PHD inhibitors might have therapeutic potential in this clinical setup.

Liver Disease

Hepatic HIF-1α is upregulated following warm ischemia [27], and is required for restoration of gluconeogenesis in the regenerating liver [52], implying yet another potential use for PHD inhibitors in acute liver disease.

Peripheral Vascular Disease

In a model of limb ischemia in mice, PHD inhibitors enhanced HIF expression and downstream VEGF and VEGF-receptor Flk-1, leading to improved capillary density, indicating a potential therapeutic use of PHD inhibitors in promoting angiogenesis in ischemic diseases, such as severe peripheral vascular disease [54]. Transfection with HIF-1α, combined with PHD inhibitor-treated bone marrow-derived angiogenic cells increased perfusion, motor function, and limb salvage in old mice with ischemic hind limbs [55]. Results of a phase-1 study in patients with critical limb ischemia indicate that transfection with a constitutively active form of HIF-1α might also promote limb salvage [10]. Further clinical trials with PHD inhibitors are currently under way in burn wound healing and salvage of critically ischemic limbs.

Oxidative Stress

Enhanced cellular ROS concentrations, as happens with shock and tissue hypoxia, result in increased PHD activity, and this effect is antagonized by ROS scavengers [15]. This situation may lead to HIF de-stabilization and inadequate HIF response to hypoxia. For example, hypoxia-mediated HIF expression in the diabetic renal medulla is substantially improved by the administration of the membrane-permeable superoxide dismutase mimetic tempol [30]. It is, therefore, tempting to assume that ROS scavengers, as well as PHD inhibitors may improve tissue adaptive responses to hypoxia, coupled with oxidative stress. However, contradicting evidence exists, indicating that ROS might trigger HIF in the absence of hypoxia. This has been suggested by studying liver tissue in acetaminophen-induced liver injury, before the development of overt liver injury and hypoxia [56], and in aged well-fed animals [57]. The role of HIF stimulation during oxidative stress therefore needs further assessment.

Important Considerations

HIF stimulation is not all-protective. The wide range of HIF-dependent genes, and its tight cross-communication with other key regulators of gene expression [13, 58, 59] raise concern regarding concomitant non-selective activation of protective as well as harmful systems. Among potential unwanted outcomes is the enhancement of tumor growth [60], promotion of fibrosis [61] or the induction of pre-eclampsia in pregnant women [62]. Indeed, whereas HIF activation is considered renoprotective in acute kidney injury, it may play a role in the progression of chronic kidney disease and certainly is an important factor in the promotion of renal malignancy [3, 20].

Diverse characteristics and distribution patterns of different PHDs [5–7] and particular actions of various PHD inhibitors [11, 37] might enable selective manipulation of the HIF system in a more desired way, selectively favoring advantageous HIF-dependent responses in preferred tissues. Furthermore, it is believed that activation of adverse responses requires protracted HIF stimulation, whereas short-term and transient HIF activation might suffice to activate tissue-protective systems without continuing induction of harmful systems. However, this concept needs confirmation in clinical trials.

Conclusion

Elucidating the mechanisms involved in HIF-mediated cellular responses to acute hypoxic stress has led to the discovery of novel potential therapeutic options for the prevention or attenuation of tissue injury. The non-selective enhancement of gene expression by current modes of HIF augmentation warrants caution, since undesired enhancement of certain genes may be hazardous.

We anticipate that in the coming years the use of PHD inhibitors and other stimulants of the HIF system will be tested in many clinical scenarios associated with critical care and emergency medicine, while HIF silencing strategies may be tested in chronic diseases, such as malignancies and disorders with enhanced tissue scarring.

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References

1. Bernhardt WM, Eckardt KU (2008) Physiological basis for the use of erythropoietin in critically ill patients at risk for acute kidney injury. Curr Opin Crit Care 14: 621–626
2. Semenza G (2002) Signal transduction to hypoxia-inducible factor 1. Biochem Pharmacol 64: 993–998
3. Gunaratnam L, Bonventre JV (2009) HIF in kidney disease and development. J Am Soc Nephrol 20: 1877–1887
4. Rosenberger C, Rosen S, Heyman S (2005) Current understanding of HIF in renal disease. Kidney Blood Press Res 28: 325–340
5. Willam C, Maxwell PH, Nichols L, et al (2006) HIF prolyl hydroxylases in the rat; organ distribution and changes in expression following hypoxia and coronary artery ligation. J Mol Cell Cardiol 41: 68–77

6. Li N, Yi F, Sundy CM, et al (2007) Expression and actions of HIF prolyl-4-hydroxylase in the rat kidneys. Am J Physiol Renal Physiol 292: F207-F216
7. Schodel J, Klanke B, Weidemann A, et al (2009) HIF-prolyl hydroxylases in the rat kidney: physiologic expression patterns and regulation in acute kidney injury. Am J Pathol 174: 1663 – 1674
8. Iguchi M, Kakinuma Y, Kurabayashi A, et al (2008) Acute inactivation of the VHL gene contributes to protective effects of ischemic preconditioning in the mouse kidney. Nephron Exp Nephrol 110: e82-e90
9. Natarajan R, Salloum FN, Fisher BJ, Kukreja RC, Fowler III AA (2006) HIF-1 activation by prolyl 4-hyroxylase-2 gene silencing attenuates myocardial ischemia-reperfusion injury. Circ Res 98: 133 – 140
10. Rajagopalan S, Olin J, Deitcher S, et al (2007) Use of a constitutively active hypoxia-inducible factor-1alpha transgene as a therapeutic strategy in no-option critical limb ischemia patients: phase I dose-escalation experience. Circulation 115: 1234 – 1243
11. Myllyharju J (2009) HIF prolyl 4-hydroxylases and their potential as drug targets. Curr Pharm Des 15: 3878 – 3885
12. Nangaku M (2009) Novel therapeutic approach targeting the HIF-HRE system in the kidney. Adv Exp Med Biol 645: 81 – 86
13. Webb JD, Coleman ML, Pugh CW (2009) Hypoxia, hypoxia-inducible factors (HIF), HIF hydroxylases and oxygen sensing. Cell Mol Life Sci 66: 3539 – 3554
14. Tanaka T, Wiesener M, Bernhardt W, Eckardt KU, Warnecke C (2009) The human HIF (hypoxia-inducible factor)-3alpha gene is a HIF-1 target gene and may modulate hypoxic gene induction. Biochem J 424: 143 – 151
15. Callapina M, Zhou J, Schmid T, Kohl R, Brune B (2005) NO restores HIF-1alpha hydroxylation during hypoxia: role of reactive oxygen species. Free Radic Biol Med 39: 925 – 936
16. Haase VH (2006) The VHL/HIF oxygen-sensing pathway and its relevance to kidney disease. Kidney Int 69: 1302 – 1307
17. Koivunen P, Hirsila M, Remes AM, Hassinen IE, Kivirikko KI, Myllyharju J (2007) Inhibition of hypoxia-inducible factor (HIF) hydroxylases by citric acid cycle intermediates: possible links between cell metabolism and stabilization of HIF. J Biol Chem 282: 4524 – 4532
18. Serra-Perez A, Planas AM, Nunez-O'Mara A, et al (2010) Extended ischemia prevents HIF1alpha degradation at reoxygenation by impairing prolyl-hydroxylation: role of Krebs cycle metabolites. J Biol Chem 285: 18217 – 1824
19. Rosenberger C, Rosen S, Heyman SN (2006) Renal Parenchymal Oxygenation and Hypoxia Adaptation in Acute Kidney Injury. Clin Exp Pharmacol Physiol 33: 980 – 988
20. Heyman SN, Khamaisi M, Rosen S, Rosenberger C (2008) Renal parenchymal hypoxia, hypoxia response and the progression of chronic kidney disease. Am J Nephrol 28: 998 – 1006
21. Rosenberger C, Mandriota S, Jurgensen JS, et al (2002) Expression of hypoxia-inducible factor-1alpha and -2alpha in hypoxic and ischemic rat kidneys. J Am Soc Nephrol 13: 1721 – 1732
22. Rosenberger C, Shina A, Rosen S, Goldfarb M, Eckardt K, Heyman SN (2006) Hypoxia inducible factors and tubular cell survival in isolated perfused kidneys. Kidney Int 70: 60 – 70
23. Rosenberger C, Heyman SN, Rosen S, et al (2005) Upregulation of HIF in acute renal failure – evidence for a protective transcriptional response to hypoxia. Kidney Int 67: 531 – 542
24. Paliege A, Rosenberger C, Bondke A, et al (2010) Hypoxia-inducible factor-2α-expressing interstitial fibroblasts are the only renal cells that express erythropoietin under hypoxia-inducible factor stabilization. Kidney Int 77: 312 – 318
25. Rosenberger C, Griethe W, Gruber G, et al (2003) Cellular responses to hypoxia after renal segmental infarction. Kidney Int 64: 874 – 886
26. Rosenberger C, Goldfarb M, Shina A, et al (2008) Evidence for sustained renal hypoxia and transient hypoxia adaptation in experimental rhabdomyolysis-induced acute kidney injury. Nephrol Dial Transpl 23: 1135 – 1143
27. Cursio R, Miele C, Filippa N, Van Obberghen E, Gugenheim J (2008) Liver HIF-1 alpha

induction precedes apoptosis following normothermic ischemia-reperfusion in rats. Transplant Proc 40: 2042 – 2045
28. Heyman SN, Rosenberger C, Rosen S (2010) Experimental ischemia-reperfusion – biases and myths: the proximal vs. distal hypoxic tubular injury debate revisited. Kidney Int 77: 9 – 16
29. Goldfarb M, Rosenberger C, Abassi Z, et al (2006) Acute-on-chronic renal failure in the rat: Functional compensation and hypoxia tolerance. Am J Nephrol 26: 22 – 33
30. Rosenberger C, Khamaisi M, Abassi Z, et al (2008) Adaptation to hypoxia in the diabetic rat kidney. Kidney Int 73: 34 – 42
31. Rosenberger C, Pratschke J, Rudolph B, et al (2007) Immunohistochemical Detection of Hypoxia-Inducible Factor-1alpha in Human Renal Allograft Biopsies. J Am Soc Nephrol 18: 343 – 351
32. Hill P, Shukla D, Tran MG, et al (2008) Inhibition of hypoxia inducible factor hydroxylases protects against renal ischemia-reperfusion injury. J Am Soc Nephrol 19: 39 – 46
33. Jones NM, Lee EM, Brown TG, Jarrott B, Beart PM (2006) Hypoxic preconditioning produces differential expression of hypoxia-inducible factor-1alpha (HIF-1alpha) and its regulatory enzyme HIF prolyl hydroxylase 2 in neonatal rat brain. Neurosci Lett 404: 72 – 77
34. May D, Gilon D, Djonov V, et al (2008) Transgenic system for conditional induction and rescue of chronic myocardial hibernation provides insights into genomic programs of hibernation. Proc Natl Acad Sci USA 105: 282 – 287
35. Pugh CW, Ratcliffe PJ (2003) Regulation of angiogenesis by hypoxia: role of the HIF system. Nat Med 9: 677 – 684
36. Yang CC, Lin LC, Wu MS, Chien CT, Lai MK (2009) Repetitive hypoxic preconditioning attenuates renal ischemia/reperfusion induced oxidative injury via upregulating HIF-1 alpha-dependent bcl-2 signaling. Transplantation 88: 1251 – 1260
37. Hsieh MM, Linde NS, Wynter A, et al (2007) HIF prolyl hydroxylase inhibition results in endogenous erythropoietin induction, erythrocytosis, and modest fetal hemoglobin expression in rhesus macaques. Blood 110: 2140 – 2147
38. Rosenberger C, Rosen S, Shina A, et al (2008) Activation of hypoxia inducible factors (HIF) ameliorates hypoxic distal tubular injury in the isolated perfused rat kidney. Nephrol Dial transplant 23: 3472 – 3478
39. Manotham K, Tanaka T, Ohse T, et al (2005) A biologic role of HIF-1 in the renal medulla. Kidney Int 67: 1428 – 1439
40. Bernhardt WM, Campean V, Kany S, et al (2006) Preconditional activation of hypoxia-inducible factors ameliorates ischemic acute renal failure. J Am Soc Nephrol 17: 1970 – 1978
41. Bernhardt WM, Gottmann U, Doyon F, et al (2009) Donor treatment with a PHD-inhibitor activating HIFs prevents graft injury and prolongs survival in an allogenic kidney transplant model. Proc Natl Acad Sci USA 106: 21276 – 21281
42. Weidemann A, Bernhardt WM, Klanke B, et al (2008) HIF activation protects from acute kidney injury. J Am Soc Nephrol 19: 486 – 494
43. Ockaili R, Natarajan R, Salloum F, et al (2005) HIF-1 activation attenuates postischemic myocardial injury: role for heme oxygenase-1 in modulating microvascular chemokine generation. Am J Physiol Heart Circ Physiol 289: H542-H548
44. Philipp S, Jurgensen JS, Fielitz J, et al (2006) Stabilization of hypoxia inducible factor rather than modulation of collagen metabolism improves cardiac function after acute myocardial infarction in rats. Eur J Heart Fail 8: 347 – 354
45. Kant R, Diwan V, Jaggi AS, Singh N, Singh D (2008) Remote renal preconditioning-induced cardioprotection: a key role of hypoxia inducible factor-prolyl 4-hydroxylases. Mol Cell Biochem 312: 25 – 31
46. Zolk O, Solbach TF, Eschenhagen T, Weidemann A, Fromm MF (2008) Activation of negative regulators of the hypoxia-inducible factor (HIF) pathway in human end-stage heart failure. Biochem Biophys Res Commun 376: 315 – 320
47. Horowitz M, Assadi H (2010) Heat acclimation-mediated cross-tolerance in cardioprotection: do HSP70 and HIF-1alpha play a role? Ann N Y Acad Sci 1188: 199 – 206
48. Wu Y, Li X, Xie W, Jankovic J, Le W, Pan T (2010) Neuroprotection of deferoxamine on

rotenone-induced injury via accumulation of HIF-1 alpha and induction of autophagy in SH-SY5Y cells. Neurochem Int 57: 198 – 205
49. Harten SK, Ashcroft M, Maxwell PH (2010) Prolyl hydroxylase domain inhibitors: a route to HIF activation and neuroprotection. Antioxid Redox Signal 12: 459 – 480
50. Niatsetskaya Z, Basso M, Speer RE, et al (2010) HIF prolyl hydroxylase inhibitors prevent neuronal death induced by mitochondrial toxins: therapeutic implications for Huntington's disease and Alzheimer's disease. Antioxid Redox Signal 12: 435 – 443
51. Siddiq A, Aminova LR, Troy CM, et al (2009) Selective inhibition of hypoxia-inducible factor (HIF) prolyl-hydroxylase 1 mediates neuroprotection against normoxic oxidative death via HIF- and CREB-independent pathways. J Neurosci 29: 8828 – 8838
52. Grover TR, Asikainen TM, Kinsella JP, Abman SH, White CW (2007) Hypoxia-inducible factors HIF-1alpha and HIF-2alpha are decreased in an experimental model of severe respiratory distress syndrome in preterm lambs. Am J Physiol Lung Cell Mol Physiol 292: L1345-L1351
53. Tajima T, Goda N, Fujiki N, et al (2009) HIF-1alpha is necessary to support gluconeogenesis during liver regeneration. Biochem Biophys Res Commun 387: 789 – 94
54. Milkiewicz M, Pugh CW, Egginton S (2004) Inhibition of endogenous HIF inactivation induces angiogenesis in ischaemic skeletal muscles of mice. J Physiol 2004 560: 21 – 26
55. Rey S, Lee K, Wang CJ, et al (2009) Synergistic effect of HIF-1alpha gene therapy and HIF-1-activated bone marrow-derived angiogenic cells in a mouse model of limb ischemia. Proc Natl Acad Sci USA 106: 20399 – 20404
56. James LP, Donahower B, Burke AS, McCullough S, Hinson JA (2006) Induction of the nuclear factor HIF-1alpha in acetaminophen toxicity: evidence for oxidative stress. Biochem Biophys Res Commun 343: 171 – 176
57. Kang MJ, Kim HJ, Kim HK, et al (2005) The effect of age and calorie restriction on HIF-1-responsive genes in aged liver. Biogerontology 6: 27 – 37
58. Serchov T, Dubois-Pot-Schneider H, Charlot C, Rosl F, Wasylyk B (2010) Involvement of net and HIF-1alpha in distinct yet intricately linked hypoxia-induced signaling pathways. J Biol Chem 285: 21223 – 21232
59. Nechemia-Arbely Y, Rosenberger C, Khamaisi M, Koesters R, Shina A, Klaus S, Shriki A, Rosen S, Axelrod JH, Heyman SN (2009) Renal hypoxia inducible factors (HIF) and STAT3 cross-talk in vivo. J Am Soc Nephrol 20: F-FC184 (abst)
60. Jokilehto T, Jaakkola PM (2010) The role of HIF prolyl hydroxylases in tumour growth. J Cell Mol Med 14: 758 – 770
61. Higgins DF, Kimura K, Bernhardt WM, et al. (2007) Hypoxia promotes fibrogenesis in vivo via HIF-1 stimulation of epithelial-to-mesenchymal transition. J Clin Invest 117: 3810 – 3820
62. Nevo O, Soleymanlou N, Wu Y, et al. (2006) Increased expression of sFlt-1 in in vivo and in vitro models of human placental hypoxia is mediated by HIF-1. Am J Physiol Regul Integr Comp Physiol 291: R1085-R1093

II Coagulation System

Are Microparticles Reliable Deleterious Effectors in Septic Coagulopathy?

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Introduction

Hemostasis has evolved from an archaic innate defense system that maintains vascular integrity by a tightly regulated equilibrium between procoagulant and anticoagulant as well as profibrinolytic and antifibrinolytic systems. This defense system acts by preventing intravascular coagulation (thrombosis), repairing vascular lesion (hemostasis and fibrinolysis), and limiting pathogen invasion.

Systemic activation of blood coagulation during sepsis has been described for a long time in its most explosive clinical expression, purpura fulminans, with distal purpura and necrosis, diffuse bleeding, and death. It is now established that blood coagulation is one part of a systemic inflammatory response during sepsis, and that blood coagulation occurs with dual consequences: (1) limitation of pathogen diffusion; and (2) deposition of platelet-rich clots and fibrin in microvessels resulting in the thrombotic microangiopathy involved in the multiple organ failure syndrome. Thus, the host response is deregulated and excessive with increased thrombin generation and increased fibrinolysis, resulting in a major disorder termed 'coagulopathy'.

In this chapter, we will describe this deregulation-induced-coagulopathy and discuss the emerging role of microparticles that display pro- and anticoagulant patterns and offer new insights into host-pathogen interactions.

How is Coagulopathy Initiated during Sepsis?

This question includes both 'how does the host initiate hemostasis?' and 'how does the pathogen activate blood coagulation?'.

Hemostasis

Clot formation is determined by flow conditions and cellular interactions (endothelial cells, platelets, erythrocytes, monocytes and neutrophils) with matrix (collagen) and proteins (blood coagulation factors and cofactors, and inhibitors).

Platelet and endothelial cell activation and microparticle release

Normal hemostasis is triggered by two major events: Subendothelial collagen exposure and endothelial cell activation. Collagen is the most potent platelet agonist, enabling rolling and adhesion, cytoskeleton contraction, membrane remodeling, secretion of α- and dense-granules and (auto-)activation. Cellular activa-

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tion allows calcium influx, and the activation of various calcium-dependent proteases, such as calpains or caspases, which in turn cleave the cytoskeleton [1]. Membrane remodeling occurs with reorganization of asymmetric phospholipid distribution, protein-lipid raft domain formation and blebbing [2]. In addition to membrane remodeling, with phosphatidylserine exposure at the outer leaflet, endothelial cell activation results in encrypted tissue factor (TF) expression and secretion of ultra-large von Willebrand factor multimers (UL-vWF) from Weibel-Palade bodies. Microparticles are ultimately released and constitute a reservoir of bioactive mediators involved in inflammation and thrombosis [3]. Microparticles were first described in the 1960s as platelet fragments with procoagulant activity. Specific to their cellular origin, microparticles can transfer receptors, organelles, mRNA and other proteins to target cells. They also constitute a secretion pathway for several cytokines, such as mature interleukin (IL)-1β. As mediators of cellular communication, microparticles are actors and possible mediators in the interplay between thrombosis and inflammation, a process previously described for vascular injury during inflammatory diseases [4]. The multiple properties of microparticles and the variety of their possible cellular targets suggest they have a key-role in cell reprogramming and tissue remodeling with physiological or pathological consequences. Microparticles could, therefore, play a major role in propagating procoagulant activity in sepsis. In the vascular compartment, including the arterial wall, the particular settings of sepsis and the tuning abilities of microparticles point to the endothelium as a pivotal target [5].

Initiation of thrombin generation: Role of tissue factor

Initiation of thrombin generation supervenes after binding of negatively-charged factor (F)VII to TF and phosphatidylserine, leading to auto-activation of FVIIa. Small amounts of FVIIa activate FX, and FXa promotes the generation of traces of thrombin (FIIa) by cleavage of prothrombin (FII). UL-vWF enables platelet adhesion under high shear-stress and fibrinogen allows aggregation after $GP_{IIbIIIa}$ activation. Thrombin is a multipotent molecule with different targets according to its molecular environment. Linked to phosphatidylserine, FIIa activates cofactors FV and FVIII, whereas when linked to platelet $GP_{Ib\alpha}$, it promotes activation of platelet FXI [6]. Plasma Fxa (not bound to phosphatidylserine) is captured by TF pathway inhibitor (TFPI) and protein S as a TFPI cofactor. This complex inactivates cellular TF and stops FVIIa generation. It is now well established that microparticles are a source of active TF [7], and that these TF-bearing microparticles are able to transfer functional TF to various vascular cells such as neutrophils and platelets [8, 9]. TF-bearing microparticles have been identified in human meningococcal disease [10] and may originate from cells with inducible TF expression (endothelial cells, monocytes).

Amplification of thrombin generation: The Josso' loop

While initiation of thrombin generation by TF is partly inhibited by TFPI, the Josso' loop becomes the main thrombin generation pathway. Explosive thrombin generation during the propagation phase is not TF-dependent, but occurs on the membrane of activated platelets, with activation of platelet-exposed FXI (of megacaryocytic origin) by $GP_{Ib\alpha}$-bound FIIa. FXIa activates FIX, and the assembly of the tenase complex (FIXa-FVIIIa) generates FXa from FX allowing the formation of the prothrombinase complex able to cleave FII into thrombin. $GP_{Ib\alpha}$-FXI(a)-bearing microparticles released after platelet activation constitute an addi-

tional catalytic surface for tenase assembly and propagation of procoagulant effectors. Thrombin generates soluble fibrin monomers from fibrinogen, which are transformed into an insoluble fibrin network by FXIIIa, a transaminase generated by FIIa cleavage at the fibrin surface. The resulting fibrin network retains erythrocytes and activated platelets [6] in a wide-mesh net with persistent low flow resupply of 'fresh' factors enabling thrombus growth [11].

A renewed role for the 'contact' pathway

Inorganic phosphates can form linear polymers linked by energy-rich phosphoanhydride bonds of more than 100 residues. Polyphosphates are a major source of energy for prokaryotes and lower eukaryotes, and are present in platelet dense-granules. In contrast to FXII activation in the 'contact-phase', it is now well established that the TF (extrinsic) pathway is the relevant process in physiological thrombin generation [12]. Physiological FXI activation is under thrombin dependence at the platelet surface through the Josso' loop. The 'intrinsic pathway' is of importance at the laboratory level to explore hemophilia using the activated partial thromboplastin time (aPTT) where the 'contact activator' is glass or kaolin. Polyphosphates are now recognized as physiological 'contact activators' implicated in the rapid generation of traces of FVa and thrombin. In addition, polyphosphates abrogate the action of TFPI as a regulator of thrombin generation and modify the clot into a strengthened structure [13].

Host-induced Hemostasis

Hemostasis is a 'primitive' line of defense against pathogens, as are innate immunity and the complement system. All three are finely tuned and are interdependent. The global response is a systemic inflammatory response syndrome (SIRS), with fever, chills, hypotension, drowsiness, oliguria. Clinical presentations range from sepsis to septic shock, and result from an equilibrium between pathogenicity and host responses. This means that septic shock, the most severe presentation with persistent hypotension despite fluid resuscitation and vasopressors and leading to organ dysfunction, is due to overwhelming host responses rather than to high bacterial virulence.

In contrast to the physiological mechanisms of hemostasis, thrombin generation is not limited to one point but is multifocal rather than disseminated. In sepsis, endothelial cell damage is also the *primum movens*, with subendothelial collagen denudation, cellular membrane remodeling with TF and phosphatidylserine exposure, and secretion of UL-vWF. Platelets are recruited at sites of multifocal lesions, thrombin is generated. Microthrombi in small vessels are responsible for ischemic lesions. Dissemination of this procoagulant activity occurs by at least two complementary mechanisms. The first is monocyte recruitment as a major source of TF [14], and the second is cellular membrane blebbing and microparticle formation (**Fig. 1**). In septic states, microparticles disseminated in the blood are from endothelial cells, monocytes, platelets, and erythrocytes [15]; the respective contributions of these microparticles are not yet known. Circulating TF-bearing microparticles are well characterized during meningococcemia in humans [10], and have been found in a cohort of patients with septic shock irrespective of the causative agent (personal data). The elevation in microparticle levels probably enables multiple fusion events that promote microparticle-mediated cellular cross-talk [4]. Neutrophilic integrin, $\alpha_M\beta_2$ (Mac-1), can activate platelet

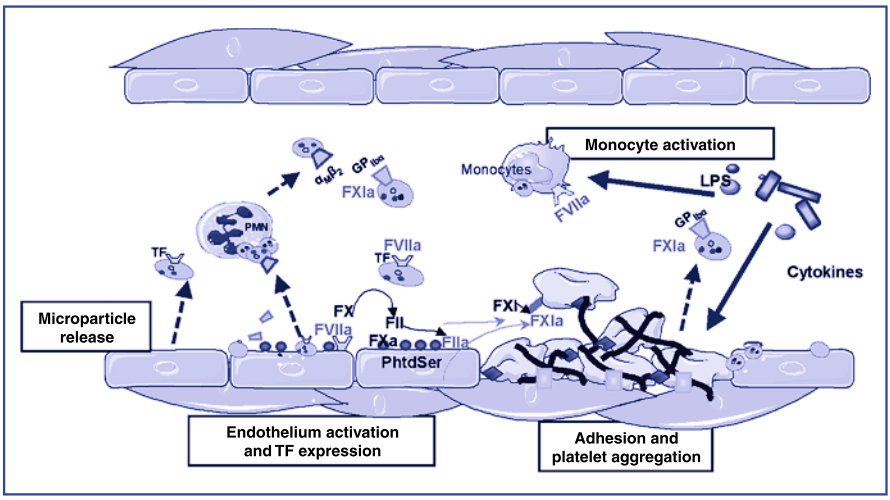

Fig. 1. Thrombin generation during sepsis. Plasma membranes of endothelial cells and monocytes are reorganized with externalization of phosphatidylserine (PhtdSer) and encrypted tissue factor (TF) expression allowing factor VII activation (FVIIa) and thrombin (FIIa) generation at the cell surface. Blebbing occurs, with release of microparticles bearing TF, resulting in an increased surface for procoagulant reactions. Platelet adhesion and aggregation also supervene with release of microparticles; platelets and microparticles bear $GP_{Ib\alpha}$, a cofactor for FXI activation by thrombin, leading to a propagation phase with high levels of thrombin generation and fibrin formation. Endothelial TF-bearing microparticles allow transfer of TF to polymorphonuclear leukocytes (PMN), increasing TF dissemination. LPS: lipopolysaccharide; PMN: polymorphonuclear leukocyte

$GP_{Ib\alpha}$ in neutrophil-platelet aggregates. In an amplification loop, Mac-1-bearing microparticles obtained after *ex vivo* stimulation of human neutrophils by lipopolysaccharide (LPS), platelet activating factor (PAF) or phorbol myristate acetate (PMA) were also demonstrated to be platelet activators [16]. Although not yet proven, the role of microparticles in disseminating procoagulant activity not only *via* TF-bearing microparticles but also *via* $GP_{Ib\alpha}$-FXIa-bearing microparticles is highly evocative.

Pathogen-induced Hemostasis

Direct activation of host hemostasis by pathogens can coexist with the host response. Whereas the latter is a defense mechanism (even if overwhelming and resulting in thrombotic disorders that contribute to organ failure), the former is aggressive. As reported above, microorganisms are rich in polyphosphates, which can allow (auto-)activation of FXII to FXIIa. FXIIa can in turn not only initiate thrombin generation *via* the 'contact phase' but also activate complement, bradykinin formation (and increased vascular permeability) and vascular matrix remodeling. Bacterial polyphosphate is about 200 residues and is more potent than platelets (75–100 residues) at activating FXII. Polyphosphates are hydrolyzed by phosphatases with a plasma half-life of about 2 hours [17].

Two bacteria highlight the direct action of pathogens on hemostasis, *Bacillus anthracis* and *Yersinia pestis*. Anthrax is due to a non-motile Gram-positive spore-forming bacterium, *B. anthracis*. The disease is now rare, but this bacte-

rium can be used as a biological weapon. Inhalation of spores results in pneumonia with pleural effusion, and thrombotic and hemorrhagic disorders. InhA1, a bacterial secreted zinc metalloprotease, is responsible for coagulopathy with direct activation of FX and FII (independently of FXIIa and TF-FVIIa), fibrin deposition [18], inhibition of ADAMTS13 (disintegrin-like metalloproteinase that limits vWF multimer size) with the consecutive formation of platelet-rich thrombi, and hemorrhage *via* the degradation of vWF by an independent proteolytic mechanism [19]. Moreover, this coagulopathy seems not to result from the total amount of circulating bacteria (referred to as 'quorum sensing') but rather from their spatial localization ('quorum acting') [18].

Y. pestis is a Gram-negative bacterium that expresses outer membrane aspartyl proteases referred to as omptins. Their enzymatic activity requires rough LPS (with short O-antigen side chains) [17]. The most studied member of the omptin family is Pla from *Y. pestis* (responsible for the plague). Pla has many effects on host hemostasis and is responsible for virulence and pathogenicity [17]. Pla activates thrombin generation by direct protealytic conversion of FVII to FVIIa and inhibition of TFPI. Hemostatic 'containment' due to protective fibrin deposits allows *Y. pestis* to escape inflammatory cells and phagocytosis. After bacterial growth, Pla activates fibrinolysis/matrix proteolysis by direct activation of plasminogen, cleavage of plasminogen activator inhibitor-1 (PAI-1) and thrombin-activatable fibrinolysis inhibitor (TAFI), and inhibition of α_2-antiplasmin, resulting in lymph node remodeling (lymphadenitis, necrosis, hemorrhage and thrombosis) and bacterial dissemination. Dysplasminogenemia ($Ala^{601}\rightarrow Thr$) is a common feature affecting nearly 2 % of the Chinese, Korean and Japanese population. Although plasminogen activity is reduced to 10 %, these populations are 'positively-selected' by lower responsiveness to *Y. pestis* infection. Knock-out mice for plasminogen and fibrinogen depict similar patterns of protection against *Y. Pestis*, confirming the clinical relevance of this bacterial-induced fibrinolysis [20]. Other Gram-negative bacteria also have omptins, with PgtE (*Salmonella enterica* serovar *typhimurium*) and Kop (*Klebsiella pneumoniae*) strictly selective for PAI-1 inactivation [21].

Why is Hemostasis not Efficiently Regulated During Sepsis?

Thrombin generation and fibrinolysis are regulated locally and temporally with complex interactions (**Fig. 2**). Under physiological conditions, platelet aggregation and adhesion, initiation of thrombin, and amplification are controlled by tuned mechanisms relying on specific inhibitors, namely TFPI, activated protein C (APC) and antithrombin. Secondary clot lysis is also regulated by plasmin/α_2-antiplasmin and TAFI. Under high shear stress, adhesion is reduced but UL-vWF multimers are present. UL-vWF multimers are cleaved into lower molecular weight fragments by a specific plasma enzyme, ADAMTS13.

Regulation of thrombin generation is controlled by APC with protein S as a cofactor. Bound to endothelial thrombomodulin, FIIa activates PC-EPCR (endothelial protein C receptor), and APC-protein S inactivates FVa thus limiting thrombin generation. Moreover, thrombin dissemination is prevented by its binding to plasma antithrombin, a serpin (serine protease inhibitor), recruited in the endothelial vicinity by glycosaminoglycans.

Reperfusion occurs by defacing the fibrin network. Circulating tissue-type plasminogen activator (t-PA) is bound to PAI-1 and is unable to cleave free plas-

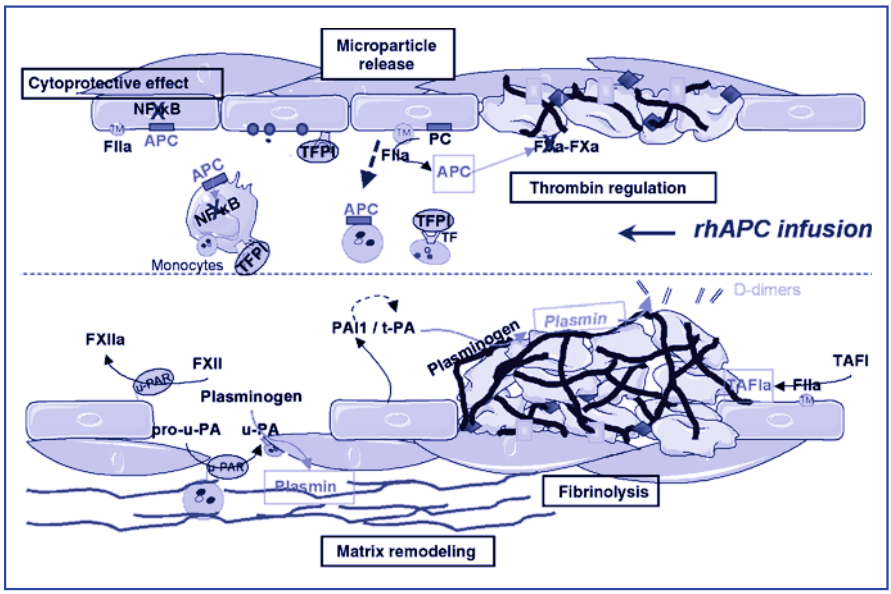

Fig. 2. Regulation and fibrinolysis/matrix remodeling. Tissue factor (TF)-initiation of blood coagulation is quickly downregulated by TF pathway inhibitor (TFPI) on endothelial and monocyte cell surfaces as on microparticles. Endothelial protein C receptor (EPCR)-bound protein C is activated by thrombin-thrombomodulin complex and activated protein C (APC) inhibits FVa limiting the propagation phase. EPCR-bound APC also regulates nuclear factor-kappa B (NF-κB), with cytoprotective effects on endothelial cells and monocytes. Infusion of recombinant APC (rhAPC) induces blebbing and release of EPCR-microparticles that allow protein C activation with anticoagulant and cytoprotective activity dissemination *in vitro*.

Fibrinolysis denotes fibrin network defacing by plasmin, resulting in fibrin degradation products (including D-dimers). Fibrin-bound plasminogen is activated by tissue-type plasminogen activator (t-PA) dissociated from its natural inhibitor, plasminogen activator inhibitor-1 (PAI-1). Clot fibrinolysis is delayed by removal of C-terminal lysine residues from fibrin by activated thrombin activatable fibrinolysis inhibitor (TAFIa). TAFI is activated by the thrombin-thrombomodulin complex. Matrix remodeling results from plasminogen activation by urokinase-type plasminogen activator (u-PA) linked to a specific receptor, u-PAR.

minogen. Plasminogen binds fibrin at lysine C-terminal moieties. t-PA has a greater affinity for fibrin-bound plasminogen than for PAI-1, allowing t-PA driven activation of plasminogen into plasmin. Fibrin-bound plasmin defaces the fibrin network into D-dimers as fibrin degradation products. Released plasmin is inactivated by α_2-antiplasmin (a serpin). Fibrinolysis is delayed after lysine-removal from fibrin by activated TAFI resulting in limited plasminogen binding sites. TAFI is activated by the thrombomodulin-thrombin (TM-FIIa) complex, and has an important role in inflammation, not only by limiting fibrinolysis but also as a carboxypeptidase involved in inhibition of bradykinin and C5a [22].

In addition to reperfusion, pericellular matrix remodeling occurs when plasminogen is activated by urokinase-type plasminogen activator (u-PA) bound to a glycosyl-phosphatidyl-inositol (GPI)-anchored receptor, u-PAR. u-PAR is also associated with FXII activation, bradykinin generation from high molecular weigh kininogen, and endothelial cellular activation. The net action of u-PAR is

plasmin-dependent matrix proteolysis, vasodilation mediated by endothelial nitric oxide (NO) and prostacyclin (PGI_2), and bradykinin-dependent capillary leakage.

Controlled hemostasis implies that a single endothelial lesion induces the hemostatic waterfall at one point of the vascular tree, regulation occurs with inhibition of the TF pathway, inactivation of FVa and reperfusion by plasmin. In contrast, sepsis promotes multifocal phenotypic changes in the endothelium. The endothelial surface becomes pro-inflammatory and prothrombotic. Cell adhesion molecules (ICAM-1, VCAM-1) and membrane TF are upregulated whereas thrombomodulin and EPCR synthesis are decreased [23]. In parallel, endothelial cells become capable of recruiting and activating platelets. Endothelial damage is no longer localized and thrombin generation and platelet activation occur at different sites and at different times in the course of the disease.

The prime mechanism for thrombin generation deregulation is consumption of inhibitors by ongoing thrombin generation, which occurs through multiple ways. Platelet adhesion to subendothelial collagen and aggregation are increased at sites of endothelial lesion because of reduced blood flow as a result of hypotension and rheologic disturbances and of high amounts of UL-vWF that occur from the inhibition of ADAMTS13 by thrombin and granulocyte elastase. During sepsis, TFPI has a key role in downregulating thrombin generation, and is quickly reduced by consumption, direct degradation by granulocyte elastase and sometimes by bacterial products (e.g., Pla), [17, 24]. Moreover, free protein S availability is decreased because of the inflammatory response that leads to the elevation in plasma C4b binding protein, a multimeric plasma protein S transporter.

Antithrombin is a 'negative-phase' protein in inflammatory responses and its synthesis is downregulated during inflammation. Loss of glycosaminoglycans due to endothelial cell damage reduces antithrombin activity. Moreover, antithrombin is degraded by granulocyte elastase. Activation of the protein C pathway requires thrombomodulin and EPCR. Thrombomodulin is widely expressed on various cell types (endothelial cells, platelets, neutrophils, monocytes, astrocytes) whereas EPCR is expressed on endothelial cells of large vessels (but not in the microvasculature), monocytes and neutrophils. During sepsis, impaired activation of protein C has been described with low levels of plasma APC [23]. Neutrophil-derived enzymes are able to cleave thrombomodulin, resulting in increased soluble thrombomodulin in plasma and lower activation of TAFI and protein C. Soluble thrombomodulin levels have been correlated with severity and prognosis of sepsis. In addition, C-reactive protein (CRP), which is able to downregulate thrombomodulin and EPCR, may contribute to the deficient APC pathway. Recently, in an experimental model, EPCR was also shown to be involved in FVIIa clearance with caveolin-dependent intracellular internalization and trafficking [25].

Two forms of circulating EPCR are present in the plasma of septic patients: Soluble EPCR (sEPCR) released by enzymatic cleavage and membrane-bound on microparticles EPCR (mpEPCR) [26]. sEPCR is able to capture protein C, thereby preventing activation by TM-FIIa, and inactivating APC. mpEPCR is released in response to treatment with recombinant APC (drotrecogin alfa [activated]). APC-EPCR-bound microparticles remain biologically active. *In vitro*, they promote inactivation of FVa with anticoagulant effects and cleave protease-activated receptor (PAR)-1, the thrombin receptor. Endothelial cytoprotection has been reported through different pathways triggered by APC-EPCR-microparticles [27]. *In vivo*,

recombinant APC's cytoprotective effects were evidenced in a baboon model of heatstroke with reduced IL-6, soluble thrombomodulin and TF-bearing microparticle release. Unfortunately, this model did not allow investigation of mortality [28]. Altogether, these observations suggest that microparticles are a key storage pool in the tuning of hemostatic balance.

The antithrombotic activities of microparticles would be overwhelmed by their procoagulant ones when microparticles are released under high thrombotic conditions with a major increase in TF induction at the cell surface, as observed during sepsis. Indeed, in purified monocyte suspensions, thrombomodulin anticoagulant activity and TF coexist at the surface of microparticles, but when released by LPS treatment, TF activity is predominant on microparticles [29]. Pharmacological treatment of septic shock by APC infusion could be of value by counterbalancing the procoagulant microparticles bearing TF and $GP_{Ib\alpha}$ through the generation and delivery of anticoagulant and anti-inflammatory EPCR-bearing microparticles.

Impairment of fibrinolysis regulation is of importance during sepsis and septic shock. PAI-1 is secreted by injured endothelial cells with inhibition of t-PA and TAFI is activated by FIIa-thrombomodulin complex allowing fibrin growth. While thrombin is overproduced and fibrin deposition occurs, the consumption of procoagulant factors limits clot formation. Thereafter, fibrinolysis is induced with massive clot lysis, reperfusion and massive and diffuse bleeding. Interestingly, several cellular models have shown that $\alpha_M\beta_2$ exposed at the endothelial and neutrophil microparticle surface can interact with u-PA, plasminogen and metalloproteases (MMP)-2 and -5, suggesting a role in fibrinolysis and in local tissue remodeling [16, 30]. u-PA/u-PAR bearing microparticles of endothelial cell origin can promote a disseminated fibrinolytic potential with activation of plasminogen on platelets, fibrin, fibronectin or extracellular matrix, suggesting their possible role in further vascular leakage [31].

Why and How to Treat Septic Coagulopathy?

Coagulopathy and Organ Dysfunction

Clinical evidence of thrombotic microangiopathy during sepsis is less frequent than the biological diagnosis of 'coagulopathy' on laboratory test, questioning the rationale for treatment. Do we have to correct laboratory values or treat thrombi and necrosis? Biological criteria for overt or non-overt disseminated intravascular coagulopathy (DIC) were defined in 2001 by the International Society on Thrombosis and Hemostasis but they are not helpful in therapeutic decision making. Trials aimed at the pharmacological control of DIC point to a more complex vascular pathology.

Overview of (Disappointing) Therapies to Modulate Thrombin Generation in Sepsis

Negative results in large clinical trials with TFPI and antithrombin substitution have been reported. In the Optimist trial (recombinant TFPI, Tifacogin), excessive bleeding was observed with no advantage in mortality [32]. Reviewing the pathophysiogical role of TFPI in regulation of the initiation of thrombin, one can suppose that TFPI substitution was applied at a late step not allowing control of the amplification phase. The Kybersept trial (antithrombin, with or without hepa-

rin) was also negative [33], but patients with overt-DIC and not treated with concomitant heparin seemed to have improved prognosis in a secondary analysis [34]. This treatment is not yet recommended by the Surviving Sepsis Campaign, and a novel recombinant antithrombin molecule is under investigation.

Recombinant APC (drotrecogin alfa [activated]) reduced 28-day mortality in a large trial (PROWESS) unrelated to DIC diagnosis, but results with this agent were disappointing in pediatrics and low-risk of mortality patients (ADDRESS). This treatment is, therefore, still controversial, and a new trial is ongoing (PROWESS-SHOCK). In line with the observation that the prognostic value of APC treatment might not be related to its anticoagulant effect, fundamental data argue for a cytoprotective effect of APC [27].

Microparticles as a Therapeutic Target in Septic Coagulopathy

Because microparticles constitute a real storage pool of vascular effectors in the vessel, one could argue that their therapeutic control might prove beneficial. Different methods could be investigated: Modulation of pro/anticoagulant microparticles *via* APC infusion [27], mechanical removal by hemofiltration, and/or enhancement of physiological clearance by reticuloendothelial cells.

Indeed, although bearing phosphatidylserine, which is a signal for phagocytosis, microparticles seem to survive longer than their parental apoptotic cell, probably because of their size, which does not allow optimal exposure of a cluster of senescence signals. Dasgupta et al. [35] recently described a major role of lactadherin in the removal of phosphatidylserine-expressing platelet microparticles from human plasma. Lactadherin is a macrophage opsonin that mediates the clearance of apoptotic lymphocytes. Knock-out lactadherin (-/-) mice show increased levels of circulating platelet microparticles and a hypercoagulable state; lactadherin supplementation restores the normal clearance of microparticles. There are currently no data on the effect that microparticle clearance has on the hemostatic balance under physiological or pathological settings.

Using the hypothesis that an efficient cut-off can be obtained, one could suggest the removal of deleterious microparticles from plasma during renal replacement therapy by continuous hemofiltration. Patients with chronic renal failure have a peak of microparticle generation at the beginning of hemodialysis (with increased risk of circuit thrombosis), followed by a decrease below their baseline at the end of the session suggesting a direct removal [36]; a similar pattern is observed during septic shock (personal data).

Conclusion

Hemostasis is a complex and finely tuned equilibrium that controls the interactions between vascular cells and proteins. Thrombin generation and clot formation are followed by restoration of vascular integrity and reperfusion. Microorganisms disturb the intricate control pathways and disrupt the balance by targeting both pro- and anticoagulation. The clinical presentation reflects this deregulation with microthrombi and organ failure on one hand, and the occurrence of diffuse bleeding in the other hand. In sepsis, microparticles released from activated cells (endothelial cells, platelets, and leukocytes) are another example of this duality. These microparticles are able to disseminate a prime procoagulant

phenotype but this might prove beneficial. Indeed, TF-bearing microparticles can support thrombin generation and transfer of functional TF to target cells, such as granulocytes and platelets. On the other hand, recombinant APC can reverse this effect, with EPCR-bearing microparticles able to disseminate a cytoprotective and anticoagulant message to target cells. The role of microparticles in fibrinolysis is the next challenging issue in our understanding of microparticles as vascular effectors in sepsis. Therapeutic interventions to control thrombin generation have been disappointing despite a good rationale for treatment. More precise comprehension of the mechanisms involved and the emerging role of microparticles as modulators of the pro/anticoagulation equilibrium could reveal novel therapeutic options.

References

1. Cohen Z, Gonzales RF, Davis-Gorman GF, Copeland JG, McDonagh PF (2005) Thrombin activity and platelet microparticle formation are increased in type 2 diabetic platelets: a potential correlation with caspase activation. Thromb Res 107: 217–221
2. Zwaal RF, Schroit AJ (1997) Pathophysiologic implications of membrane phospholipid asymmetry in blood cells. Blood 89: 1121–1132
3. Hugel B, Martinez MC, Kunzelmann C, Freyssinet JM (2005) Membrane microparticles: two sides of the coin. Physiology (Bethesda) 20: 22–27
4. Morel O, Morel N, Freyssinet JM, Toti F (2008) Platelet microparticles and vascular cells interactions: a checkpoint between the haemostatic and thrombotic responses. Platelets 19: 9–23
5. Mortaza S, Martinez MC, Baron-Menguy C, et al (2009) Detrimental hemodynamic and inflammatory effects of microparticles originating from septic rats. Crit Care Med 37: 2045–2050
6. Lane DA, Philippou H, Huntington JA (2005) Directing thrombin. Blood 106: 2605–2612
7. Key NS (2010) Analysis of tissue factor positive microparticles. Thromb Res 125: S42–45
8. Chou J, Mackman N, Merrill-Skoloff G, Pedersen B, Furie BC, Furie B (2004) Hematopoietic cell-derived microparticle tissue factor contributes to fibrin formation during thrombus propagation. Blood 104: 3190–3197
9. Egorina EM, Sovershaev MA, Olsen JO, Osterud B (2008) Granulocytes do not express but acquire monocyte-derived tissue factor in whole blood: evidence for a direct transfer. Blood 111: 1208–1216
10. Nieuwland R, Berckmans RJ, McGregor S, et al (2000) Cellular origin and procoagulant properties of microparticles in meningococcal sepsis. Blood 95: 930–935
11. Orfeo T, Brummel-Ziedins KE, Gissel M, Butenas S, Mann KG (2008) The nature of the stable blood clot procoagulant activities. J Biol Chem 283: 9776–9786
12. Smith SA, Mutch NJ, Baskar D, Rohloff P, Docampo R, Morrissey JH (2006) Polyphosphate modulates blood coagulation and fibrinolysis. Proc Natl Acad Sci USA 103: 903–908
13. Müller F, Mutch NJ, Schenk WA, et al (2009) Platelet polyphosphate are proinflammatory and procoagulant mediators in vivo. Cell 139: 1143–1156
14. Satta N, Toti F, Feugeas O, et al (1994) Monocyte vesiculation is a possible mechanism for dissemination of membrane-associated procoagulant activities and adhesion molecules after stimulation by lipopolysaccharide. J Immunol 153: 3245–3255
15. Itakura Sumi Y, Ogura H, Tanaka H, et al (2003) Paradoxical cytoskeleton and microparticle formation changes in monocytes and polymorphonuclear leukocytes in severe systemic inflammatory response syndrome patients. J Trauma 55: 1125–1132
16. Pluskota E, Woody NM, Szpak D, et al (2008) Expression, activation, and function of integrin alphaMbeta2 (Mac-1) on neutrophil-derived microparticles. Blood 112: 2327–2335
17. Yun TH, Morrissey JH (2009) Polyphosphate and omptins: novel bacterial procoagulant agents. J Cell Mol Med 13: 4146–4153
18. Kastrup CJ, Boedicker JQ, Pomerantsev AP, et al (2008) Spatial localization of bacteria controls coagulation of human blood by 'quorum sensind'. Nat Chem Biol 4: 742–750

19. Chun MC, popova TG, Jorgensen SC et al. (2008) Degradation of circulating von Willebrand factor and its regulator ADAMTS13 implicates secreted Bacillus anthracis metalloproteases in anthrax consumptive coagulopathy. J Biol Chem 283: 9531 – 9542
20. Degen JL, Bugge TH, Coguen JD (2007) Fibrin and fibrinolysis in infection and host defense. J Thromb Haemost 5(S1): 24 – 31
21. Haiko J, Laakkonen L, Juuti K, Kalkkinen K, Korhonen TK (2010) The omptins of *Yersinia pestis* and *Salmonella enterica* cleave the reactive center loop of plasminogen activator 1. J Bacteriol 192: 4553 – 4561
22. Rijken DC, Lijnen HR (2009) New insights into the molecular mechanisms of the fibrinolytic system. J Thromb Haemost 7: 4 – 13
23. Schouten M, Wiersinga WJ, Levi M, van der Poll T (2008) Inflammation, endothelium and coagulation in sepsis. J Leukoc Biol 83: 536 – 545
24. Massberg S, Grahl L, von Bruehl ML, et al (2010) Reciprocal coupling of coagulation and innate immunity via neutrophil serine proteases. Nat Med 16: 887 – 897
25. Nayak RC, Sen P, Ghosh S, et al (2009) Endothelial cell protein C receptor cellular localization and trafficking: potential functional implications. Blood 114: 1974 – 1986
26. Perez-Casal M, Downey C, Fukudome K, Marx G, Toh CH (2005) Activated protein C induces the release of microparticle-associated endothelial protein C receptor. Blood 105: 1515 – 1522
27. Perez-Casal M, Downey C, Cutillas-Moreno B, Zuzel M, Fukudome K, Toh CH (2009) Microparticle-associated endothelial protein C receptor and the induction of cytoprotective and anti-inflammatory effects. Haematologica 94: 387 – 394
28. Bouchama A, Kunzelmann C, Debbi M, et al (2008) Recombinant activated protein C attenuates endothelial injury and inhibits procoagulant microparticles release in baboon heatstroke. Arterioscler Thromb Vasc Biol 28: 1318 – 1325
29. Satta N, Freyssinet JM, Toti F (1997) The significance of human monocyte thrombomodulin during membrane vesiculation and after stimulation by lipopolysaccharide. Br J Haematol 96: 534 – 542
30. Lacroix R, Sabatier F, Mialhe A, et al (2007) Activation of plasminogen into plasmin at the surface of endothelial microparticles: a mechanism that modulates angiogenic properties of endothelial progenitor cells in vitro. Blood 110: 2432 – 2439
31. Dejouvencel T, Doeuvre L, Lacroix R et al (2010) Fibrinolytic cross-talk: a new mechanism for plasmin formation. Blood 115: 2048 – 2056
32. Abraham E, Reinhart K, Opal S, et al (2003) Efficacy and safety of Tifacogin (recombinant tissue factor pathway inhibitor) in severe sepsis. JAMA 290: 238 – 247
33. Warren BL, Eid A, Singer P, et al (2001) High-dose antithrombin III in severe sepsis: a randomized control trial (KyberSept). JAMA 286: 1869 – 1878
34. Kienast J, Juers M, Wiedermann CJ, et al (2006) Treatment effects of high-dose antithrombin without concomitant heparin in patient with and without dissaminated intravascular coagulopathy. J Thromb Haemost 4: 90 – 97
35. Dasgupta SK, Abdel-Monem H, Niravath P, et al (2009) Lactadherin and clearance of platelet-derived microvesicles. Blood 113: 1332 – 1339
36. Morel O, Chantrel F, Hugel B, et al (2001) High levels of circulating procoagulant microparticles in patients on hemodialysis. Thromb Haemost 71: 270 (abst)

The Inflammatory Potential of Fibrin(ogen) and its Degradation Products

II

C. Jennewein, N. Tran, and K. Zacharowski

Introduction

Coagulation is a constant attendant of inflammation and is fundamental to confine infection and/or the inflammatory response to a limited area. Coagulation is tightly controlled by various factors, such as tissue factor (TF), finally activating thrombin, which cleaves fibrinogen to initiate fibrin clot formation. Systemic inflammatory response syndrome (SIRS) and sepsis remain a major health concern on intensive care units (ICUs) in the western world often ending in multiple organ dysfunction and death. The pathogenesis of both systemic disorders are attributed to an uncontrolled inflammatory response and dysregulated coagulation, the latter often causing disseminated intravascular coagulation (DIC), microvascular failure and multiple organ dysfunction [1, 2]. Fibrin(ogen) degradation products, D-dimers, Bβ15-42 and soluble fibrin are increased in septic patients with organ dysfunction [3, 4], but the contribution of these fragments to the pathogenesis of sepsis remains unclear.

This chapter provides a state-of-the art review of the inflammatory potential of fibrinogen, fibrin and their degradation products. The entire cross-talk of inflammation and coagulation is extensively reviewed in [5–8].

Fibrinogen and Fibrin Structure

Fibrinogen, a 340 kDa glycoprotein synthesized in the liver, is composed of two sets of three polypeptide chains: Aα, Bβ and γ. The chains are connected by disulfide bridges at their N-termini composing the central E nodule, whereas the C-termini of Bβ and γ form the two outer D domains. During coagulation, thrombin cleaves fibrinogen releasing the N-termini of Aα (Aα1-16, fibrinopeptide A (FpA)) and of Bβ (Bβ1-15, FpB). This initiates fibrin clot formation by polymerization [9, 10].

Fibrinolysis is mainly controlled by plasmin, which cleaves fibrin resulting in D dimers, D and E fragments, Bβ15-42 and smaller mostly α chain fragments [11, 12]. **Figure 1** schematically displays the structure of fibrin(ogen) and its cleavage sites.

Inflammatory Potential of Fibrinogen and Fibrin

Fibrinogen and fibrin affect inflammation by modulating leukocyte adhesion on the one hand and by altering cytokine/chemokine expression of leukocytes and

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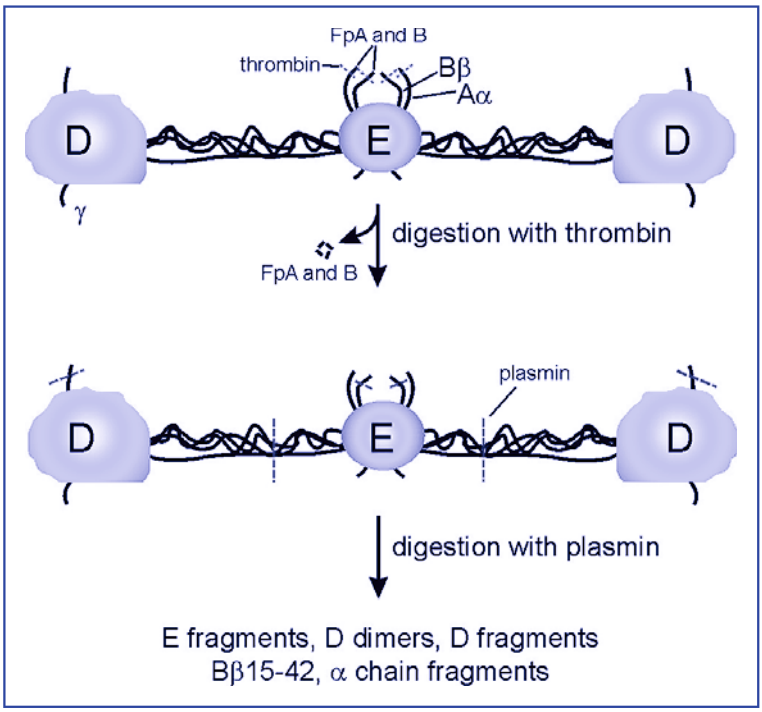

Fig. 1. Structure of fibrin(ogen) and its cleavage sites. During coagulation thrombin cleaves fibrinogen (marked by dotted lines) releasing the fibrinopeptides (Fp) A and B thereby triggering fibrin polymerization. Proteolysis of fibrin by plasmin (broken lines mark plasmin cleavage sites) generates various fibrin fragments, such as D dimer, D and E fragment, Bβ15-42 and α chain fragments.

endothelial cells on the other. Leukocyte adhesion is mostly attributed to binding of fibrin(ogen) to various integrins and adhesion molecules, such as $\alpha_V\beta_3$ or $\alpha_x\beta_2$ (CD11c/CD18) [13, 14]. The leukocyte integrin, $\alpha_M\beta_2$ integrin (also named macrophage antigen-1 (Mac-1) or CD11b/CD18), is one of the main fibrinogen receptor recognizing specific sequences within the γ chain of the D nodule that mediates leukocyte migration [15, 16]. By binding to the intercellular adhesion molecule-1 (ICAM-1) of endothelial cells, fibrinogen acts as a bridging molecule enhancing leukocyte-endothelial interaction [17], which is augmented by induction of ICAM-1 expression in response to fibrinogen and fibrin [18]. Although there is a lot of evidence for fibrin(ogen)-dependent leukocyte adhesion, *in vivo* studies have shown that leukocytes and platelets do not readily accumulate on fibrin clots either because of soluble fibrinogen [19] or plasminogen binding to the surface of fibrin clots [20].

However, in addition to affecting leukocyte adhesion to the endothelium, fibrinogen and fibrin also modulate the inflammatory response of peripheral blood mononuclear cells (PBMCs) and endothelial cells by regulating cytokine and chemokine expression. Thus, fibrin exposure to endothelial cells induced expression of the chemokine interleukin (IL)-8 in a time- and concentration-dependent manner [21]. In PBMCs, fibrin(ogen) induced production of tumor necrosis factor (TNF)-α, IL-1β, IL-6 and reactive oxygen species (ROS). Increased

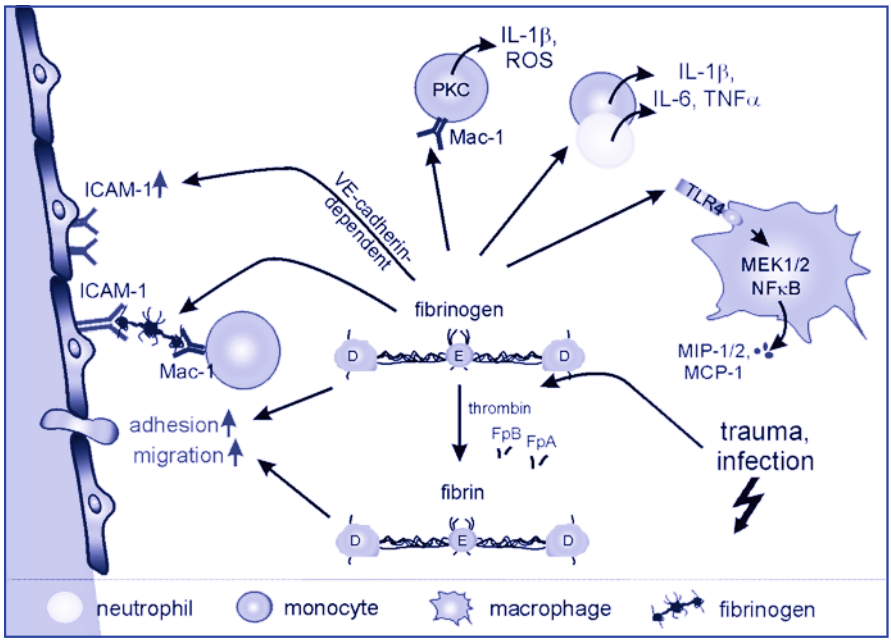

Fig. 2. Inflammatory potential of fibrinogen and fibrin. Following trauma and/or infection, thrombin is activated and coagulation is induced. Fibrinogen is converted to fibrin, which in turn is degraded by plasmin. Fibrinogen and fibrin modulate the inflammatory response by affecting leukocyte recruitment, adhesion and migration but also by inducing cytokine/chemokine expression. Fp: fibrinopeptide; ICAM: intercellular adhesion molecule; IL: interleukin; Mac-1: macrophage antigen 1; MCP: macrophage chemoattractant protein; MIP: macrophage inflammatory protein; PAI: plasminogen activator inhibitor; PKC: protein kinase C; ROS: reactive oxygen species; VE-cadherin: vascular endothelial-cadherin.

IL-1β in response to monocyte adhesion to fibrin(ogen) was mediated by Mac-1, protein kinase C (PKC), and nuclear factor-kappa B (NF-κB) [14]. Moreover, fibrinogen exposure to macrophages induced chemokine expression, i.e., macrophage inflammatory protein-1 (MIP-1), MIP-2 and macrophage chemoattractant protein-1 (MCP-1), which was abolished in macrophages derived from C3H/HeJ mice. These mice express a mutant form of Toll-like receptor 4 (TLR4) indicating that fibrinogen acts via TLR4 signaling [22] (**Fig. 2**).

The importance of fibrin(ogen) and its fragments during inflammation is supported by various knock out studies. Fibrinogen deficient mice showed abrogated macrophage adhesion to the peritoneal cavity and reduced MCP-1 and IL-6 expression in response to thioglycolate. Whereas intraperitoneally administered thrombin induced macrophage adhesion, protease activated receptor (PAR)-1 deficient mice revealed no reduction in adhesion upon thioglycolate exposure [23]. This strongly indicates the involvement of fibrin(ogen) and its fragments, while excluding direct thrombin effects or at least thrombin effects mediated via PAR-1 signaling. Moreover, the thrombin inhibitor, hirudin, gave greater protection against renal injury and inflammation in a mouse crescentic glomerulonephritis model than PAR-1 deficiency. Hirudin significantly reduced crescent formation, CD4 T cell and macrophage infiltration as well as fibrin deposition [24]. PAR-1 deficiency also reduced these parameters, but to a lower extent, suggesting

that fibrin(ogen) and/or its fragments also contribute to inflammation and injury. Taken together, this indicates the involvement of fibrin and/or its fragments in modulating an immune response independently of any direct inflammatory effects of thrombin.

Inflammatory Potential of Fibrin Fragments

As mentioned above, various fragments are generated during coagulation and fibrinolysis. Initiation of clotting comprises the release of fibrinopeptides A (FpA) and B (FpB). Furthermore, fibrin-digestion by plasmin generates D and E fragments and also smaller fragments, like the immunosuppressive peptide, Bβ15-42.

Pro-Inflammatory Effects of Fibrin Fragments

In contrast to the other described fragments, FpA and B are released during the cleavage of fibrinogen by thrombin during the first step of coagulation, namely during fibrin formation. There is only little evidence for an inflammatory potential of fibrinopeptides, although FpB and probably FpA increased MCP-1 expression and caused neutrophil chemotaxis *in vitro* and *in vivo* [25, 26]. However, further evidence is needed to assess potential inflammatory activity of FpA and B.

Fibrin fragments have been of greater interest so far, especially since fibrin degradation products such as D-dimers or Bβ15 – 42 are increased in septic patients with DIC. D-dimers are generated by plasmin digestion of fibrin and used as a marker of fibrinolysis and DIC in humans, and there is little evidence of an immunomodulatory function. Exposure to D-dimers induced IL-1β, IL-6, PAI and TF expression in a promonocytic leukemia cell line, NOMO-1 [27], and also in peripheral blood monocytes [28]. It is unknown whether D fragments further affect inflammation, e.g., by activating the endothelium.

In rat peritoneal macrophages, fibrin fragment E and fibrinogen fragment E, but not fragment D, were capable of inducing IL-6 and IL-1β production probably by a CD11c or α chain-mediated mechanism [29]. Moreover, adherent fibrin fragment E induced IL-1β production in the human monocytic cell line, THP-1 [30]. In addition to studies with physiological fibrin fragment E, the biological activity of fibrin fragment E has often been assessed by a fragment named NDSKII (N terminal disulfide knot II). NDSKII is synthetically generated via cleavage of fibrinogen by cyanogen bromide and following digestion with thrombin. The resulting complex shows nearly the same composition as physiological fibrin fragment E (fibrin fragment E: Aα17-78, Bβ15-122 and γ1-62; NDSKII: Aα17-51, Bβ15-118, γ1-78 [31, 32]), also exposing the Bβ15-42. Bach et al. studied the interaction of NDSKII with human umbilical vein endothelial cells (HUVECs). Binding assays revealed that interaction was dependent on the Bβ15-42 region, since NDSK (generated after cyanogen bromide digestion without thrombin cleavage) that did not expose Bβ15-42 showed no affinity. Moreover, NDSKII associated with vascular-endothelial cadherin (VE-cadherin) [33], triggering leukocyte migration. Analyzing the underlying mechanism revealed that lymphocyte migration depended on VE-cadherin and was inhibited by Bβ15-42, whereas monocyte and neutrophil migration was mediated by binding of the α-chain of NDSKII to CD11c [34]. Further investigation is required to elucidate the full pro-inflammatory activity of fibrin degradation products.

II

The Anti-inflammatory Peptide, Bβ15-42 (or FX06)

Bβ15-42, a fragment of the N-terminal β chain, is generated by plasmin cleavage of fibrin. In contrast to the other fragments described so far, Bβ15-42 (also named FX06) has anti-inflammatory potential and is of major interest as a promising new therapeutic agent. Administration of Bβ15-42 protects the myocardium against ischemia/reperfusion injury demonstrated by reduced infarct size and reduced leukocyte accumulation. Interestingly, the protective effect was abrogated in fibrinogen deficient mice suggesting that Bβ15-42 reduces fibrinogen dependent inflammation. Indeed, by competing with NDSKII for the VE-cadherin binding site, Bβ15-42 abrogates NDSKII-induced leukocyte recruitment [34] (**Fig. 3**). Based on this study, Bβ15-42 was tested in a multicenter phase IIa clinical trial to investigate whether it would limit infarct size in patients with ST-segment elevation myocardial infarction when given as an adjunct to percutaneous coronary intervention. FX06 significantly reduced the size of the necrotic core zone of infarcts whereas total infarct size at 5 days, assessed by late gadolinium-enhanced cardiac magnetic resonance imaging, was not significantly different between the control and FX06-treated groups [35].

In a pig model of hemorrhagic shock, FX06-treated animals showed improved pulmonary and circulatory function. FX06 further reduced neutrophils in the myocardium, liver and small intestine and also IL-6 plasma levels, protecting heart, lung, liver and small intestine from shock [36]. In addition to competing

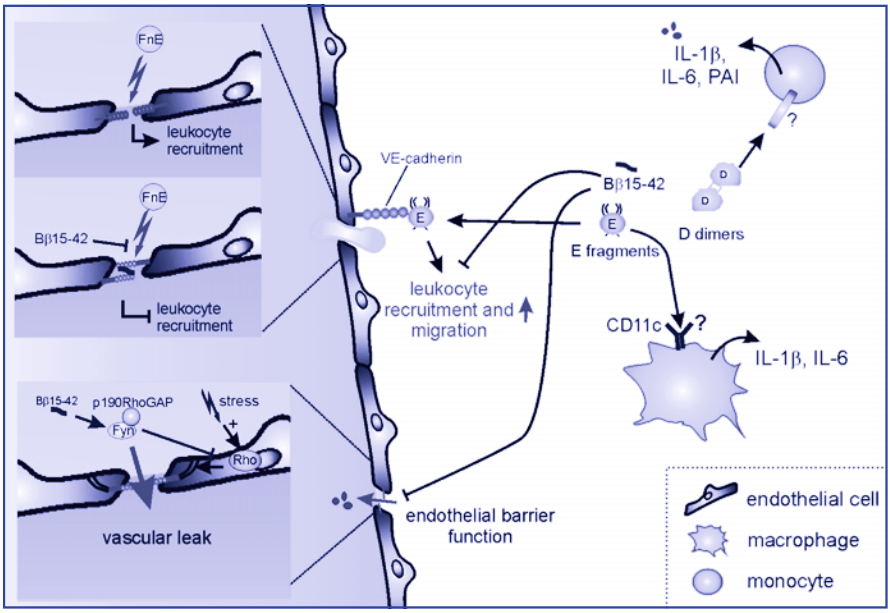

Fig. 3. Inflammatory potential of fibrin fragments. Monocytes show increased interleukin (IL)-1β, IL-6 and plasminogen inhibitor activator (PAI) expression upon D-dimer exposure via an as yet unknown receptor. Fibrin fragment E induces leukocyte recruitment and migration by binding to vascular endothelial-cadherin (VE-cadherin) as well as cytokine expression in macrophages. The immunosuppressive peptide, Bβ15-42, attenuates fibrin fragment E (FnE)-dependent leukocyte recruitment and stress-induced vascular leak by inhibiting Rho kinase activation and subsequent junction opening.

with NDSKII and thereby reducing leukocyte migration, Bβ15-42 also functions as a signaling molecule. In two different shock models – dengue shock syndrome and a lipopolysaccharide (LPS)-induced shock model – Bβ15-42 preserved endothelial barrier function by inhibiting stress-induced opening of the junctions between endothelial cells. Cell-cell contact between endothelial cells is mainly formed by VE-cadherin, which in turn is under the control of RhoGTPases regulating actin dynamics and junction stability. Rho kinase is activated in response to stress, e.g., inflammation, and causes loss of the endothelial barrier function. FX06 prevented Rho kinase activation by dissociating Fyn from VE-cadherin which in turn associates to p190RhoGAP. Therewith, Bβ15-42 preserved stress-induced junction opening [37]. This mechanism may also be responsible for reduced leukocyte migration, although further evidence is needed. However, FX06-treated animals had improved survival rates and reduced hemoconcentration and fibrinogen consumption [37]. As a result, Bβ15-42 also attenuated ischemia/reperfusion injury in a cardiac transplant model [38].

Conclusion

There is strong evidence that fibrin fragments play an important role in inflammatory conditions such as sepsis. Notably, septic patients with organ dysfunction show enhanced plasma levels of fibrin fragments. This suggests that fibrin fragments may also be a consequence as well as a further trigger of DIC within the pathophysiology of organ dysfunction. Therefore, we suggest that novel therapeutic approaches are feasible to modulate the effects of fibrin fragments either by utilizing the anti-inflammatory potential of Bβ15-42 or by inhibiting pro-inflammatory fragments, such as fibrin fragment E, with antibodies or their signaling pathways. Whether fibrin fragments are useful as biomarkers warrants further investigation.

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References

1. Taylor FB Jr, Toh CH, Hoots WK, Wada H, Levi M (2001) Towards definition, clinical and laboratory criteria, and a scoring system for disseminated intravascular coagulation. Thromb Haemost 86: 1327 – 1330
2. Levi M, Ten Cate H (1999) Disseminated intravascular coagulation. N Engl J Med 341: 586 – 592
3. Iba T, Kidokoro A, Fukunaga M, et al (2005) Association between the severity of sepsis and the changes in hemostatic molecular markers and vascular endothelial damage markers. Shock 23: 25 – 29
4. Fareed J, Hoppensteadt DA, Leya F, et al (1998) Useful laboratory tests for studying thrombogenesis in acute cardiac syndromes. Clin Chem 44: 1845 – 1853
5. Levi M, van der Poll T, Buller HR (2004) Bidirectional relation between inflammation and coagulation. Circulation 109: 2698 – 2704
6. Medcalf RL (2007) Fibrinolysis, inflammation, and regulation of the plasminogen activating system. J Thromb Haemost 5 Suppl 1: 132 – 142

7. Knoebl P (2010) Blood coagulation disorders in septic patients. Wien Med Wochenschr 160: 129–138
8. Levi M (2010) The coagulant response in sepsis and inflammation. Hamostaseologie 30: 10–12, 14–16
9. Mosesson MW (2005) Fibrinogen and fibrin structure and functions. J Thromb Haemost 3: 1894–1904
10. Lord ST (2007) Fibrinogen and fibrin: scaffold proteins in hemostasis. Curr Opin Hematol 14: 236–241
11. Smith EB, Keen GA, Grant A, Stirk C (1990) Fate of fibrinogen in human arterial intima. Arteriosclerosis 10: 263–275
12. Walker JB, Nesheim ME (1999) The molecular weights, mass distribution, chain composition, and structure of soluble fibrin degradation products released from a fibrin clot perfused with plasmin. J Biol Chem 274: 5201–5212
13. Hynes RO (1992) Integrins: versatility, modulation, and signaling in cell adhesion. Cell 69: 11–25
14. Altieri DC (1999) Regulation of leukocyte-endothelium interaction by fibrinogen. Thromb Haemost 82: 781–786
15. Ugarova TP, Yakubenko VP (2001) Recognition of fibrinogen by leukocyte integrins. Ann N Y Acad Sci 936: 368–385
16. Flick MJ, Du X, Degen JL (2004) Fibrin(ogen)-alpha M beta 2 interactions regulate leukocyte function and innate immunity in vivo. Exp Biol Med (Maywood) 229: 1105–1110
17. Languino LR, Plescia J, Duperray A, et al (1993) Fibrinogen mediates leukocyte adhesion to vascular endothelium through an ICAM-1-dependent pathway. Cell 73: 1423–1434
18. Harley SL, Sturge J, Powell JT (2000) Regulation by fibrinogen and its products of intercellular adhesion molecule-1 expression in human saphenous vein endothelial cells. Arterioscler Thromb Vasc Biol 20: 652–658
19. Lishko VK, Burke T, Ugarova T (2007) Antiadhesive effect of fibrinogen: a safeguard for thrombus stability. Blood 109: 1541–1549
20. Lishko VK, Yermolenko IS, Ugarova TP (2010) Plasminogen on the surfaces of fibrin clots prevents adhesion of leukocytes and platelets. J Thromb Haemost 8: 799–807
21. Qi J, Goralnick S, Kreutzer DL (1997) Fibrin regulation of interleukin-8 gene expression in human vascular endothelial cells. Blood 90: 3595–3602
22. Smiley ST, King JA, Hancock WW (2001) Fibrinogen stimulates macrophage chemokine secretion through toll-like receptor 4. J Immunol 167: 2887–2894
23. Szaba FM, Smiley ST (2002) Roles for thrombin and fibrin(ogen) in cytokine/chemokine production and macrophage adhesion in vivo. Blood 99: 1053–1059
24. Cunningham MA, Rondeau E, Chen X, et al (2000) Protease-activated receptor 1 mediates thrombin-dependent, cell-mediated renal inflammation in crescentic glomerulonephritis. J Exp Med 191: 455–462
25. Senior RM, Skogen WF, Griffin GL, Wilner GD (1986) Effects of fibrinogen derivatives upon the inflammatory response. Studies with human fibrinopeptide B. J Clin Invest 77: 1014–1019
26. Persson K, Russell W, Morgelin M, Herwald H (2003) The conversion of fibrinogen to fibrin at the surface of curliated Escherichia coli bacteria leads to the generation of proinflammatory fibrinopeptides. J Biol Chem 278: 31884–31890
27. Hamaguchi M, Morishita Y, Takahashi I, et al (1991) FDP D-dimer induces the secretion of interleukin-1, urokinase-type plasminogen activator, and plasminogen activator inhibitor-2 in a human promonocytic leukemia cell line. Blood 77: 94–100
28. Robson SC, Shephard EG, Kirsch RE (1994) Fibrin degradation product D-dimer induces the synthesis and release of biologically active IL-1 beta, IL-6 and plasminogen activator inhibitors from monocytes in vitro. Br J Haematol 86: 322–326
29. Lee ME, Rhee KJ, Nham SU (1999) Fragment E derived from both fibrin and fibrinogen stimulates interleukin-6 production in rat peritoneal macrophages. Mol Cells 9: 7–13
30. Lee ME, Kweon SM, Ha KS, Nham SU (2001) Fibrin stimulates microfilament reorganization and IL-1beta production in human monocytic THP-1 cells. Mol Cells 11: 13–20

31. Olexa SA, Budzynski AZ, Doolittle RF, Cottrell BA, Greene TC (1981) Structure of fragment E species from human cross-linked fibrin. Biochemistry 20: 6139 – 6145
32. Vali Z, Scheraga HA (1988) Localization of the binding site on fibrin for the secondary binding site of thrombin. Biochemistry 27: 1956 – 1963
33. Bach TL, Barsigian C, Yaen CH, Martinez J (1998) Endothelial cell VE-cadherin functions as a receptor for the beta15 – 42 sequence of fibrin. J Biol Chem 273: 30719 – 30728
34. Petzelbauer P, Zacharowski PA, Miyazaki Y, et al (2005) The fibrin-derived peptide Bbeta15 – 42 protects the myocardium against ischemia-reperfusion injury. Nat Med 11: 298 – 304
35. Atar D, Petzelbauer P, Schwitter J, et al (2009) Effect of intravenous FX06 as an adjunct to primary percutaneous coronary intervention for acute ST-segment elevation myocardial infarction results of the F.I.R.E. (Efficacy of FX06 in the Prevention of Myocardial Reperfusion Injury) trial. J Am Coll Cardiol 53: 720 – 729
36. Roesner JP, Petzelbauer P, Koch A, et al (2009) Bbeta15 – 42 (FX06) reduces pulmonary, myocardial, liver, and small intestine damage in a pig model of hemorrhagic shock and reperfusion. Crit Care Med 37: 598 – 605
37. Groger M, Pasteiner W, Ignatyev G, et al (2009) Peptide Bbeta(15 – 42) preserves endothelial barrier function in shock. PLoS One 4: e5391
38. Wiedemann D, Schneeberger S, Friedl P, et al (2010) The fibrin-derived peptide Bbeta(15 – 42) significantly attenuates ischemia-reperfusion injury in a cardiac transplant model. Transplantation 89: 824 – 829

III Acute Respiratory Failure

Heparin-induced Thrombocytopenia in the ICU: An Overview

II

Y. Sakr

Introduction

Heparin, a negatively charged glycosaminoglycan (3000 – 30,000 Da), is an anticoagulant released by mast cells and basophils during the normal clotting process [1]. Heparin is widely used for the treatment and prophylaxis of thromboembolic diseases in medical and surgical patients [1]. Heparin-induced thrombocytopenia (HIT) is one of the most serious adverse events associated with this drug. HIT is an immune-mediated, prothrombotic complication that occurs with unfractionated heparin (UFH) and to a lesser extent with low-molecular-weight heparin (LMWH) [2]. The fundamental paradox of HIT results from a platelet-activating immune response triggered by the interaction of heparin with a specific platelet protein, platelet factor 4 (PF4) [3].

In this chapter, we review current knowledge about the pathophysiology, epidemiology, clinical manifestations, and treatment of HIT in the intensive care unit (ICU).

Pathophysiology of HIT

Heparin causes mild platelet aggregation *in vivo*, especially in patients with activated platelets, resulting in increased platelet sequestration in the spleen and thrombocytopenia [1]. Thrombocytopenia can be triggered via non-immune and immune mechanisms. Clinically, two types of HIT can be differentiated: HIT type I, a benign non-immune condition; and HIT type II, an immune-mediated syndrome caused by an antibody to the PF4/heparin complex.

Non-immune HIT, or HIT type I, is a self-limiting condition without any major complications that occurs in 10 – 30 % of patients within 4 days after exposure to heparin. Heparin binds to PF4 with high affinity and inhibits adenylcyclase. This leads to a decrease in intracellular cyclic adenosine monophosphate (cAMP) levels with subsequent reduction in the platelet activation threshold and mild platelet aggregation and thrombocytopenia [4, 5]. HIT type I may occur in patients with sepsis, burn injuries, and vascular diseases, probably due to platelet hyperreactivity in these conditions [4, 5]. Thrombocytopenia in HIT type I is usually mild and platelet counts rarely decrease below 100,000/μl [6]. Heparin administration should be continued and no specific therapy is required.

Immune-mediated HIT type II is a disorder initiated by an immunological response to heparin exposure and is characterized by an absolute or relative thrombocytopenia with a paradoxically increased incidence of thrombosis (**Fig. 1**)

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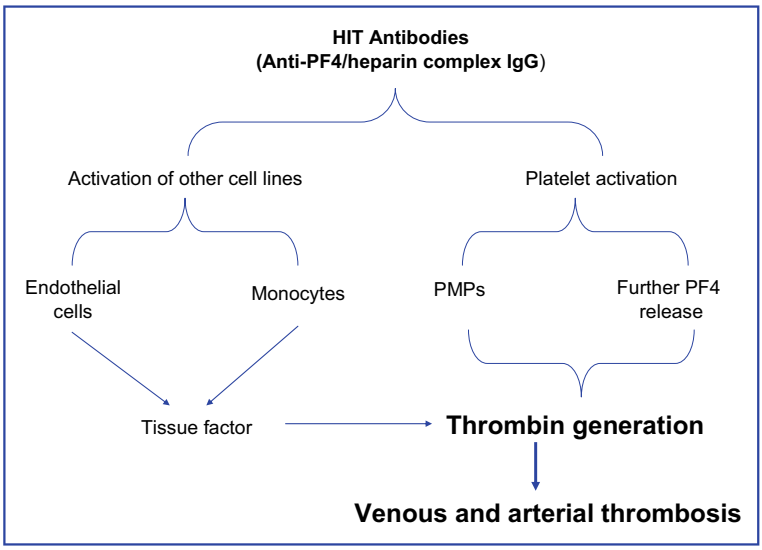

Fig. 1. Schematic representation of the pathogenesis of HIT (see text for details). From [5] with permission. PF: platelet factor; PMPs: platelet microparticles.

[1]. The major antigen responsible for this syndrome is PF4, which is synthesized by megakaryocytes and stored in platelet α-granules. Upon platelet activation, PF4 is released and binds anionic glycosaminoglycans on cell surfaces. The main function of PF4 is to inhibit the formation of megakaryocytes and angiogenesis, as well as modulating the immune response. Considerable amounts of PF4 are released after trauma, inflammation, surgical trauma, and in neoplasm [7]. In HIT type II, heparin infusion displaces PF4 and produces structural changes on it, leading to the formation of a PF4/heparin complex. This complex is recognized as a 'foreign' antigen and triggers an immune response, which is characterized by the release of IgG antibodies that bind to the PF4/heparin complexes with subsequent clustering of the platelet Fc-receptors (FcγRIIa, FcγRIIIa) resulting in platelet activation. This may lead to overt arterial thrombosis, historically, called "the white clot syndrome". Activated platelets can also fragment into prothrombotic microparticles and stimulate venous thrombosis [5, 8]. In addition, HIT antibodies may bind to Fc receptors on monocytes which produces significant quantities of tissue factor, stimulating thrombosis [5, 9]. HIT antibodies may promote thrombosis through platelet adhesion to the vessel wall and formation of platelet-leukocyte aggregates [5, 10]. Davidson et al. [11] reported elevated levels of von Willebrand factor and soluble thrombomodulin in patients with HIT type II, suggesting that endothelial cell damage with the consecutive loss of its physiologic antithrombotic properties may contribute to the thrombotic risk.

Heparin molecules bind PF4 in proportion to the length of the polysaccharide chain. This explains the higher frequency of HIT among patients treated with UFH than among those treated with LMWH [12]. The amount of anti-PF4/heparin antibodies produced is determined not only by the dose and structure of heparin but also by the amount of circulating PF4. In some clinical situations, such as cardiac surgery, the relatively abundant circulating PF4 and heparin

increase the risk of immunization [7]. PF4 bound *in vivo* to cell surface glycosaminoglycans can be immunogenic and could explain why healthy individuals may be positive for anti-PF4/heparin antibodies [13]. In fact, not all patients who have heparin antibodies develop platelet activation and clinically relevant HIT. After termination of heparin therapy, the platelet count increases within 4 to 14 days [14]. HIT antibodies are transient, generally disappearing within 4 months. [15]

HIT type II is the most important clinical entity and will be discussed in the following sections. For simplicity, we will refer to HIT type II simply as HIT.

Epidemiology

The frequency of HIT in heparin-exposed patients is highly variable. Heparin preparation is one influential factor with bovine UFH being the most common trigger followed by porcine UFH [12]. HIT occurs less commonly in patients receiving LMWH. The incidence of HIT is 1–5 % when UFH is used but < 1 % with LMWH [12]. Females are more likely to develop HIT than males and postoperative patients have a higher incidence of HIT than have medical ICU patients [16]. Heparin dosage also plays an important role. Prophylactic doses of heparin increase the risk of antibody formation, whereas clinical manifestations occur more in patients receiving therapeutic doses [16]. Only a small proportion, at most 5 % to 30 %, of patients who form HIT-IgG will develop clinical HIT [12, 17].

The incidence of HIT varies from 0 % in pregnant women receiving LMWH to 5 % in patients undergoing orthopedic surgery receiving UFH [18]. Despite the relatively high prevalence of anti-PF4/heparin antibodies in patients undergoing cardiac surgery, the incidence of HIT in this patient population is about 2.4 % [18]. The formation of anti-PF4/heparin antibodies varies from 2 to 5 % in cardiology patients, from 15 to 30 % in patients undergoing orthopedic surgery, and up to 30 to 70 % in patients undergoing cardiac surgery [19]. Several studies have assessed the frequency of HIT in ICU patients [3]; the incidence of HIT in ICU patients is generally less than 2 %.

Clinical Manifestations

HIT is a clinicopathological syndrome with one or more clinical events (thrombocytopenia with or without thrombosis) temporally related to heparin administration and caused by HIT antibodies [20]. The clinical manifestations of HIT are discussed below.

Onset

In patients with HIT, thrombocytopenia typically occurs 5–10 days after initiation of heparin therapy (typical onset HIT) as the immune system requires several days to produce sufficient amounts of anti-PF4/heparin antibodies [21]. Thrombocytopenia that occurs more than 10 days after exposure to heparin is probably caused by other factors, such as sepsis. In some exceptional cases, invasive procedures, such as surgical interventions, may promote seroconversion and release of PF4 after long periods of exposure to heparin [21].

In the so called 'rapid onset' HIT, thrombocytopenia occurs within 24 hours of exposure to heparin, mostly due to the presence of anti-PF4/heparin antibodies after prior exposure to heparin within the previous 100 days [15]. The onset of HIT in these cases is usually accompanied by fever, shivering, and skin lesions at the injection sites within 30 minutes after heparin administration [3]. Some patients also develop acute respiratory or cardiac dysfunction, manifested as hypertension, tachycardia, angina pectoris, or dyspnea. These manifestations may suggest pulmonary embolism because of the sudden pronounced platelet activation [3, 15].

In some patients, HIT may occur after termination of heparin therapy. Thrombotic events or low platelet counts may draw attention to the presence of HIT. This 'delayed onset' HIT is associated with large numbers of anti-PF4/heparin antibodies, which lead to platelet activation in the absence of heparin [3]. This entity may be clinically relevant in patients who are discharged early from the hospital after surgical interventions.

Thrombocytopenia

Thrombocytopenia is the first sign of HIT in 85 – 90 % of patients who have a decrease in platelet count below 150,000/μl or a reduction of more than 50 % from the baseline platelet count [3]. Platelet count usually falls to values between 40,000 to 80,000/μl. In only 5 – 10 % of cases, does the platelet count reach a nadir below 20,000/μl [22], and in such cases other possible causes of thrombocytopenia should be considered.

Thrombocytopenia is a common laboratory abnormality in critically ill patients. Prospective data from 329 adult surgical ICU patients during one year showed that 41.3 % had a platelet count less than 150,000/μl at some point [23]. The most common etiology of thrombocytopenia in critical illness is sepsis (around 48 %), although 25 % of ICU patients have more than one cause [24]. Drug-induced thrombocytopenia must be considered, since several medications can cause thrombocytopenia and critically ill patients usually receive numerous medications [25]. Possible causes of thrombocytopenia are shown in **Box 1**.

Box 1. Differential diagnosis of thrombocytopenia in the ICU

Sepsis and healthcare-associated infections
Drug-induced thrombocytopenia: e.g., GP IIb/IIIa inhibitor, thrombolytic agents, and antibiotics (e.g., vancomycin)
Perioperative fluid resuscitation
Disseminated intravascular coagulation (DIC)
Massive transfusion
Intravascular devices: ECMO, IABP, LVAD and pulmonary catheter
Liver disease/hypersplenism
Pulmonary embolism
Immune thrombocytopenias
Diabetic ketoacidosis
Cancer-associated DIC, primary bone marrow disorder
Antiphospholipid syndrome and systemic lupus erythematosis
EDTA-induced pseudothrombocytopenia

ECMO: extracorporeal membrane oxygenation; IABP: intra-aortic balloon pump; LVAD: left ventricular assist device; EDTA: ethylenediaminetetraacetic acid

Thrombotic Complications

HIT is associated with thrombotic complications in 30–70 % of cases. These may develop without significant thrombocytopenia in 15 % of patients [18]. In patients with symptomatic deep vein thrombosis (DVT) after initiation of heparin therapy, HIT cannot be excluded even in the absence of thrombocytopenia. Thrombotic events occur around three days before the onset of thrombocytopenia in 40 % of HIT patients [26]. The risk of thrombosis correlates, however, to the magnitude of relative thrombocytopenia [26].

The most common thrombotic complications in patients with HIT include DVT (50 %) and pulmonary embolism (25 %) [27]. Other less common complications include myocardial infarction, cardiovascular accidents, arterial occlusive lower limb ischemia, sinus vein thrombosis, mesenteric venous or arterial occlusion, and skin necrosis [28]. Venous thrombosis is 4 to 10 times higher than arterial thrombosis [3, 27].

Other Complications of HIT

The risk of bleeding in patients with HIT is relatively low, even at a platelet count of less than 20,000/μl [3]. However, bleeding can occur due to thrombocytic dysfunction, such as in patients with uremia. Wester et al. [29] compared 20 patients with HIT to 20 ICU patients without HIT as a control group. Although patients with HIT had a higher incidence of bleeding than the control group (85 vs. 35 %), bleeding in the HIT patients occurred under heparin therapy and was not directly related to thrombocytopenia.

In a median of 8 days after the onset of heparin therapy, 10 to 20 % of patients with HIT develop skin lesions in the form of erythematous nodules, subcutaneous plaques, or necrotic lesions [30]. Skin lesions occur equally after treatment with UFH or LMWH [30].

Scoring System for HIT

The ‘4 T’s’ scoring system is based on thrombocytopenia, timing of onset, thrombosis, and absence of other causes (**Table 1**) and allows evaluation of the pretest probability of HIT [31]. Patients with low pretest scores (< 4 points) are unlikely to be positive for HIT antibodies (0 to 1.6 %), whereas patients with intermediate (4–5 points) and high (> 5 points) scores are more likely to test positive (21.4 % to 100 %) [32]. The evaluation of this scoring system showed a high negative predictive value in the general population and in ICU patients, with low scores being suitable for ruling out HIT in most clinical situations [32].

Laboratory Diagnosis of HIT

In patients with suspected HIT, diagnosis can be established by laboratory testing for the presence of HIT antibodies. Two types of assays are available: Functional and antigen assays.

Table 1. The 4 T's score [32]

4 T Category	Score 2	1	0
Thrombocytopenia	Platelet count decrease > 50 % or platelet nadir ≥ 20 × 10^9/L	Platelet count decrease 30–50 % or platelet nadir 10–19 × 10^9/L	Platelet count decrease < 30 % or platelet nadir < 10 × 10^9/L
Time to platelet count decrease*	Clear onset between days 5–10 or platelet count decrease ≤ 1 day (prior heparin exposure within 100 days)	Consistent with decrease between days 5–10, but not clear (e.g., missing platelet counts); onset after day 10	Platelet count decrease < 4 days without recent exposure
Thrombosis or other sequelae	New thrombosis (confirmed); skin necrosis; acute systemic reaction postintravenous heparin	Progressive or recurrent thrombosis; non-necrotizing (erythematous) skin lesions; suspected thrombosis (not proven)	None
Other causes of thrombocytopenia	None apparent	Possible	Definite

* First day immunizing heparin exposure considered day zero; the day the platelet count begins to decrease is considered the day of onset of thrombocytopenia.

Functional Assays

These assays are based on *in vitro* activation of platelets as evidence for the presence of relevant IgG-HIT antibodies [20]. Heparin-induced platelet activation (HIPA) and serotonin release assays (SRA) are examples of these tests. Washed platelets from healthy volunteers are mixed with patient serum and then incubated with low and high concentrations of heparin. In the presence of HIT antibodies, platelets are activated in low concentrations of heparin. This activation can be detected using radioactive serotonin (e.g., SRA) or visually (e.g., HIPA) [19].

The strength of functional assays is their very high specificity, if the appropriate controls are performed. Whether these tests can reach 100 % sensitivity depends on the 'gold standard' against which they are compared. Moreover, functional assays are technically demanding (selected platelet donors, washed platelets, internal controls, radioactivity), have a high turn-around time, and are performed by only a minority of experienced laboratories [19].

Antigen Assays

Enzyme-linked immunoassays (ELISA) are the tests most commonly used to detect HIT antibodies. These assays non-specifically detect IgG, IgA, and IgM antibodies against PF4/heparin. The results are analyzed photometrically and an optical density higher than 0.4 is considered as positive [3]. ELISA is highly sensitive due to its ability to detect a broad range of HIT antibodies. However, the specificity of ELISA is lower compared to functional assays [3].

Particle gel immunoassay (PaGIA) is another antigen assay that may be used to detect HIT antibodies. The ID-heparin/PF4 antibody test (ID-Micro Typing System DiaMed®) is a PaGIA, in which a PF4/heparin-coated synthetic polymer is

used. The agglutination of HIT antibodies in patient serum leads to the formation of bands on the gel matrix. The results can be obtained after 20 minutes. The sensitivity and specificity of this test lies between the functional tests and the ELISA [33]. PaGIA may be used, therefore, as a rapid screening test, pending the results of functional assays [33].

The particle immunofiltration assay (PIFA) is another screening test which involves the use of PF4-coated colored polymer particles. This test, however, has relatively low performance in terms of specificity and sensitivity [34].

Interpretation of the Results of Laboratory Assays

As mentioned above, antigen assays are highly sensitive. These tests can be used, therefore, to exclude the presence of HIT. However, positive results do not confirm the diagnosis or reflect the risk of thrombotic events [35]. Increasing the ELISA optical density threshold from 0.4 to 1 may increase the specificity of ELISA from 65 to 83 % [36]. The combination of functional and antigen assays has the highest performance in terms of specificity and sensitivity [3]. Laboratory assays may help to establish the diagnosis of HIT. However, not all PF4/heparin antibodies are pathologic. Only a subset of patients with positive antigen assays has platelet activating antibodies, of which only a few patients develop thrombocytopenia and subsequent thrombosis [37]. Hence, this spectrum can be described as an 'iceberg model', with clinical HIT as the tip of the iceberg [37]. The diagnosis of HIT should be established taking into consideration clinical manifestations and laboratory evidence [38].

Management of Patients with HIT

General Measures

If there is a clinical suspicion of HIT, all heparin should be stopped, including heparin used to 'flush' intravascular catheters, and regional use for dialysis and to coat catheters [16, 19]. In patients with strongly suspected or confirmed HIT who do not have active bleeding, prophylactic platelet transfusions are not indicated because this will lead to subsequent platelet activation and increased risk of thrombosis without a net increase in platelet count [16].

Alternative Anticoagulation

The highest risk of new, progressive, or recurrent thrombosis occurs in the first few days after stopping heparin. Alternative therapeutic anticoagulation should be initiated based on a high clinical suspicion and not delayed while awaiting confirmatory laboratory testing or because of thrombocytopenia [39]. When treatment was delayed pending laboratory confirmation of the diagnosis within a clinical trial setting, the incidence of new thrombosis was approximately tenfold higher than during the subsequent period of treatment with a direct thrombin inhibitor [40]. Therapeutic options include direct thrombin inhibitors and factor Xa inhibitors. Oral thrombin and factor Xa inhibitors, such as dabigatran, rivaroxaban und apixaban, are not yet approved in patients with HIT [18]. The choice of alternative anticoagulant depends upon availability, associated medical conditions, and the preference of the medical staff.

Heparinoids

These are direct factor Xa inhibitors, of which danaproid is the only available preparation established for use in patients with HIT. Danaproid is a mixture of low molecular sulphated gylcosaminoglycans: Heparan, dermatan, and chondroitin sulfate [18]. It inhibits thrombin formation primarily through inhibition of factor Xa. The anti-Xa activity of danaparoid has a half-life of 24 hours. The bioavailability reaches almost 100 % after intravenous or subcutaneous administration with a reliable dose-response curve. Anti-Xa levels (target, 0.5 – 0.8 anti-Xa U/ml) may be used to guide danaparoid therapy. Monitoring anti-factor Xa activity is important in patients with renal dysfunction, as danaparoid is partially excreted in the urine [3]. To avoid overdosage, monitoring of factor Xa activity is also recommended in patients with extremely low or high body weight, life-threatening thrombosis, bleeding complications, and in critically ill patients with marked organ dysfunction or comorbidity [3].

Cross reactivity with HIT IgG antibody may occur in less than 10 % of cases and cannot be predicted by *in vitro* testing prior to onset of therapy [41]. Danaparoid blocks HIT antibody-induced platelet aggregation and thromboxane B2 production and has been shown to be an effective alternative anticoagulant in patients with HIT [41]. In some instances, HIT IgG antibody's cross reaction may have clinical consequences. Laboratory testing for cross reactivity should be reserved, however, for suspected cases, such as those who develop thrombotic complications during danaparoid therapy or when thrombocytopenia persists for more than 4 days after onset of therapy. Another anticoagulant should be considered if the diagnosis is confirmed [3, 41]. The disadvantage of danaparoid therapy is its relatively prolonged kinetics in the absence of a specific antidote. Overdosage, as manifested by increased anti factor Xa activity (> 2 IE/ml) may lead to serious bleeding complications and increased mortality rates [4]. Adequate dosing and monitoring of patients at risk is, therefore, mandatory to avoid subsequent complications. Danaparoid was withdrawn from the US market in April 2002, but remains available for treatment and/or prevention of HIT-thrombosis in several other jurisdictions, e.g., Canada, Europe, Japan, Australia, and New Zealand.

Direct thrombin inhibitors

These substances directly inhibit thrombin. Lepirudin, argatroban und bivalirudin are available for use in patients with HIT.

- Lepirudin: Lepirudin is a recombinant hirudin (found in the saliva of the medicinal leech, *Hirudo medicinalis*) derived from genetically produced yeasts. It is approved and available in the USA, Canada, Europe, and Australia for treatment of thrombosis complicating HIT [42]. Lepirudin binds to thrombin and inhibits its prothrombotic activity. The activated partial thromboplastin time (aPTT) should be targeted at 1.5 to 2.0 times the patient's baseline aPTT or the mean laboratory normal range. After intravenous administration, lepirudin reaches a peak level within 15 minutes and plasma levels maintain a steady state for 1 – 2 hours [3, 43]. To avoid overdosage and bleeding complications some authors suggest starting intravenous infusion without bolus administration, unless fulminant thrombosis is present [3]. Dose adjustment is required in patients with renal dysfunction, as the drug undergoes renal elimination.

In 30 % of patients who are treated with lepirudin, anti-hirudin IgG antibodies may develop. This was not found to be associated with higher risk of thrombosis, bleeding, or anaphylactic reactions, thus, lepirudin administration should not be discontinued for this reason [3]. Anaphylactic reactions due to lepirudin therapy are rarely observed. The risk of anaphylaxis can be reduced by avoiding bolus doses [3]. The risk of bleeding was also found to be increased with simultaneous use of acetylsalicylic acid [44]. Therefore, acetylsalicylic acid therapy should be avoided during concomitant therapy with direct thrombin inhibitors.

- Argatroban: Argatroban is a synthetic L-arginine derivative. It reversibly inhibits both soluble and clot-bound thrombin and has a half-life of 50 minutes after intravenous administration. The infusion rate should be adjusted to target the aPTT at 1.5 to 3 times of initial levels. Reduced infusion rates are appropriate in patients with heart failure, multiple organ system failure, severe anasarca, and during the early post-cardiac surgery period. In patients with hepatic dysfunction, the half-life increases up to 6 hours, as argatroban undergoes hepatobiliary excretion [3]. This is particularly relevant in ICU patients because of the common occurrence of hepatic perfusion abnormalities in the ICU setting [3, 45]. Argatroban is contraindicated in patients with liver cell failure [3, 45].

  The advantage of argatroban over LMWH and danparoid is the absence of cross reactivity, as argatroban does not posses molecular similarity to heparin. In addition, antibody formation does not occur, which is an advantage compared to lepirudin [46]. Nevertheless, the incidence of thromboembolic complications was shown to be higher in patients treated with argatroban than in those who were treated with lepirudin or danaparoid. This was explained, however, by the shorter duration of argatroban therapy compared to lepirudin [40].
- Bivalirudin: Bivalirudin is a synthetic congener of hirudin. It exerts its anticoagulant effect through direct thrombin inhibition. The half-life of bivalirudin is 25 minutes after intravenous administration and increases to up to 4 hours in patients with renal failure undergoing dialysis. Only 20 % of the drug is excreted in the urine, whereas 80 % undergoes enzymatic proteolysis [47]. Bivalirudin therapy can be monitored by aPTT or the activated clotting time (ACT). In the absence of a specific antidote, hemofiltration, hemodialysis, or plasmapharesis may be effective therapeutic options [48]. This drug is approved in the USA, Canada, Europe, Australia, New Zealand, and Latin America for anticoagulation during percutaneous transluminal coronary intervervention (PCI); in the USA it is also approved for PCI with provisional use of glycoprotein IIb/IIIa antagonist therapy, and for patients with, or at risk of HIT (or HIT with thrombotic complications) undergoing PCI; it is also approved in Canada for patients with, or at risk of HIT (or HIT with thrombosis syndrome) undergoing cardiac surgery. In Germany, bivalirudin is not approved in HIT patients but is used 'off-label' in special situations, such as anticoagulation during cardiac surgery in patients with HIT [47].

  The anticoagulant effect of bivalirudin is similar to other available alternative anticoagulants with a reduced risk of bleeding [47]. In patients with renal or hepatic dysfunction, bivalirudin therapy is advantageous, as it undergoes enzymatic proteolysis in addition to renal excretion. Cross reactivity with HIT antibodies has not been reported [3].

Fondaparinux

Fondaparinux is a synthetic, heparin analog, pentasaccharide anticoagulant. It enhances factor Xa inhibition by binding to antithrombin III. The half-life is 18 hours, so that it should be administered only once per day [49]. The dose response curve is linear. Fondaparinux undergoes predominant renal excretion and is, therefore, contraindicated in patients with terminal renal failure [50]. The anticoagulant effect of fondaparinux is more potent than enoxaparin [49]. The risk of bleeding is not increased as compared to LMWH [49].

Patients treated with fondaparinux develop anti-PF4/heparin antibodies with a similar frequency to those treated with LMWH [12], but fondaparinux-induced HIT appears to be exceptionally rare. This is probably because of its short polysaccharide chain of 10–12 saccharides and subsequently weak platelet activating potential [50]. In the USA, fondaparinux is approved in patients with HIT for prophylaxis and treatment of thromboembolic diseases. In Germany, this drug is approved for prophylaxis after major orthopedic surgery. The anti-factor Xa activity of fondaparinux can be useful in patients under warfarin therapy who require alternative anticoagulation preoperatively. The risk of microvascular thrombosis and lower limb gangrene is increased in some patients with HIT who receive concomitant therapy with warfarin and direct thrombin inhibitors (*vide infra*) [50]. Fondaparinux can be used, therefore, in the transient phase until warfarin therapy is withdrawn, to reduce the risk of thromboembolic complications in these patients [50]. The use of fondaparinux in ICU patients with renal insufficiency and multiorgan failure is not recommended because of the significant risk of accumulation [3].

Heparin and Vitamin K Antagonist Therapy in Patients with HIT

To avoid possible bleeding complications with alternative anticoagulants in the absence of specific antidotes, patients with known HIT may be treated with heparin for short periods, such as those undergoing surgery using a heart-lung machine [6]. However, this should only be considered when heparin has not been administered within the previous 100 days to avoid the occurrence of rapid onset HIT. In addition, the presence of anti-HIT antibodies should be excluded and use of heparin should be avoided during the perioperative period [6].

Vitamin K antagonist therapy is contraindicated in patients with HIT because of the increased risk of thrombosis in the presence of thrombocytopenia. In these patients, vitamin K antagonist therapy may induce lower limb venous gangrene or severe skin necrosis. This occurs a few days after the onset of vitamin K antagonist therapy [39, 51]. Treatment with vitamin K antagonists is associated with a rapid decrease in protein C concentration, which has a short half-life of 6 hours, whereas serum levels of procoagulant coagulation factors (Factors II, VII, IX, X) remain high during the first days of therapy. This imbalance between pro- and anticoagulant favors a prothrombotic state [4]. Use of vitamin K antagonist therapy should be postponed until the platelet count has recovered substantially and, thereafter, started at a low dose [16]. Alternative anticoagulants should be used during thrombocytopenia and should be continued until the platelet count has reached a stable plateau and the international normalized ratio (INR) has reached the intended target range, with a minimal overlap of 5 days [14, 16]. For patients receiving a vitamin K antagonist at the time of diagnosis of HIT, use of vitamin K is recommended [16, 39, 51].

The Challenge of Diagnosis and Treatment of HIT in the ICU

Anti-thrombosis prophylaxis is a keystone in the management of critically ill patients. In German ICUs, 99 % of patients receive prophylactic anticoagulants, 88 % receive LMWH and 45 % receive UFH during the ICU stay [52]. HIT is, therefore, a major concern in ICU patients. Nevertheless, thrombocytopenia is a common occurrence in 30 – 50 % of ICU patients, so that diagnosis of HIT represents a major challenge [53]. Common reasons for thrombocytopenia in these patients include sepsis, adverse effects of drugs, transfusion reactions, and major surgical procedures [54]. The development of thrombotic complications under heparin therapy is, therefore, a better indicator of a diagnosis of HIT than uncomplicated thrombocytopenia [3]. Repeated occlusion of hemodialysis filters and necrotic or erythematous skin lesions at the site of heparin injections may also be an important sign of HIT [3, 53]. In this context, the use of HIT scores, such as the 4 T's score, may be helpful in establishing the diagnosis (*vide supra*). In uncomplicated cases with a low probability of HIT, heparin administration should not be discontinued and further laboratory testing is not required. In patients where HIT is moderately or strongly suspected, heparin administration should be stopped pending the results of laboratory testing, and alternative anticoagulation should be initiated [3]. Even though platelet activation (functional) assays are more specific for detecting HIT antibodies than antigen tests, neither test is completely specific for HIT, which is considered a clinicopathological syndrome (*vide supra*).

Summary and Conclusion

HIT is an immune-mediated, prothrombotic complication that occurs with UFH and to a lesser extent with LMWH. HIT is a clinicopathologic syndrome with one or more clinical events (thrombocytopenia with or without thrombosis). The diagnosis of HIT can be established by laboratory testing for the presence of HIT antibodies. The combination of functional and antigen assays has the highest performance in terms of specificity and sensitivity. Alternative therapeutic anticoagulation should be initiated based on high clinical suspicion and not delayed while waiting for confirmatory laboratory testing or because of thrombocytopenia. Therapeutic options include direct thrombin inhibitors and factor Xa inhibitors. The choice of alternative anticoagulant depends upon availability, associated medical conditions, and preferences of the medical staff. The diagnosis of HIT in the ICU is a major challenge as thrombocytopenia is prevalent in these patients and generally caused by conditions other than HIT. In this context, the use of the 4 T's score may be helpful in establishing the diagnosis and management of these patients.

References

1. Thong CL, Kam PCA (2005) Heparin-induced thrombocytopenia. Curr Anaesth Crit Care 16: 143 – 150
2. Greinacher A, Eichler P, Lietz T, Warkentin TE (2005) Replacement of unfractionated heparin by low-molecular-weight heparin for postorthopedic surgery antithrombotic prophylaxis lowers the overall risk of symptomatic thrombosis because of a lower frequency of heparin-induced thrombocytopenia. Blood 106: 2921 – 2922

3. Selleng K, Warkentin TE, Greinacher A (2007) Heparin-induced thrombocytopenia in intensive care patients. Crit Care Med 35: 1165 – 1176
4. Picker SM, Gathof BS (2004) [Heparin induced thrombocytopenia. A frequently unrecognised complication after major orthopedic surgery]. Orthopade 33: 1300 – 1308
5. Battistelli S, Genovese A, Gori T (2010) Heparin-induced thrombocytopenia in surgical patients. Am J Surg 199: 43 – 51
6. Greinacher A, Warkentin TE (2006) Recognition, treatment, and prevention of heparin-induced thrombocytopenia: review and update. Thromb Res 118: 165 – 176
7. Amiral J, Peynaud-Debayle E, Wolf M, Bridey F, Vissac AM, Meyer D (1996) Generation of antibodies to heparin-PF4 complexes without thrombocytopenia in patients treated with unfractionated or low-molecular-weight heparin. Am J Hematol 52: 90 – 95
8. Aster RH (1995) Heparin-induced thrombocytopenia and thrombosis. N Engl J Med 332: 1374 – 1376
9. Shoenfeld Y, Praprotnik S, Levy Y, et al (2000) Pathogenic anti-endothelial cell antibodies: classification to anti-microvascular EC and anti-macrovascular EC antibodies. Isr Med Assoc J (2 Suppl): 24 – 25
10. Khairy M, Lasne D, Amelot A, et al (2004) Polymorphonuclear leukocyte and monocyte activation induced by plasma from patients with heparin-induced thrombocytopenia in whole blood. Thromb Haemost 92: 1411 – 1419
11. Davidson SJ, Wadham P, Rogers L, Burman JF (2007) Endothelial cell damage in heparin-induced thrombocytopenia. Blood Coagul Fibrinolysis 18: 317 – 320
12. Warkentin TE, Cook RJ, Marder VJ, et al (2005) Anti-platelet factor 4/heparin antibodies in orthopedic surgery patients receiving antithrombotic prophylaxis with fondaparinux or enoxaparin. Blood 106: 3791 – 3796
13. Arepally GM, Hursting MJ (2008) Platelet factor 4/heparin antibody (IgG/M/A) in healthy subjects: a literature analysis of commercial immunoassay results. J Thromb Thrombolysis 26: 55 – 61
14. Hassan Y, Awaisu A, Aziz NA, Aziz NH, Ismail O (2007) Heparin-induced thrombocytopenia and recent advances in its therapy. J Clin Pharm Ther 32: 535 – 544
15. Lubenow N, Kempf R, Eichner A, Eichler P, Carlsson LE, Greinacher A (2002) Heparin-induced thrombocytopenia: temporal pattern of thrombocytopenia in relation to initial use or reexposure to heparin. Chest 122: 37 – 42
16. Warkentin TE, Greinacher A, Koster A, Lincoff AM (2008) Treatment and prevention of heparin-induced thrombocytopenia: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 133: 340S-380S
17. Warkentin TE, Sheppard JA, Moore JC, Moore KM, Sigouin CS, Kelton JG (2005) Laboratory testing for the antibodies that cause heparin-induced thrombocytopenia: how much class do we need? J Lab Clin Med 146: 341 – 346
18. Warkentin TE (2007) Heparin-induced thrombocytopenia. Hematol Oncol Clin North Am 21: 589 – 607
19. Shantsila E, Lip GY, Chong BH (2009) Heparin-induced thrombocytopenia. A contemporary clinical approach to diagnosis and management. Chest 135: 1651 – 1664
20. Warkentin TE, Chong BH, Greinacher A (1998) Heparin-induced thrombocytopenia: towards consensus. Thromb Haemost 79: 1 – 7
21. Warkentin TE, Crowther MA (2007) When is HIT really HIT? Ann Thorac Surg 83: 21 – 23
22. Greinacher A, Eichler P, Lubenow N, Kwasny H, Luz M (2000) Heparin-induced thrombocytopenia with thromboembolic complications: meta-analysis of 2 prospective trials to assess the value of parenteral treatment with lepirudin and its therapeutic aPTT range. Blood 96: 846 – 851
23. Cawley MJ, Wittbrodt ET, Boyce EG, Skaar DJ (1999) Potential risk factors associated with thrombocytopenia in a surgical intensive care unit. Pharmacotherapy 19: 108 – 113
24. Vanderschueren S, De Weerdt A, Malbrain M, et al (2000) Thrombocytopenia and prognosis in intensive care. Crit Care Med 28: 1871 – 1876
25. Drews RE (2003) Critical issues in hematology: anemia, thrombocytopenia, coagulopathy, and blood product transfusions in critically ill patients. Clin Chest Med 24: 607 – 622
26. Greinacher A, Farner B, Kroll H, Kohlmann T, Warkentin TE, Eichler P (2005) Clinical fea-

tures of heparin-induced thrombocytopenia including risk factors for thrombosis. A retrospective analysis of 408 patients. Thromb Haemost 94: 132–135
27. Linkins LA, Warkentin TE (2008) The approach to heparin-induced thrombocytopenia. Semin Respir Crit Care Med 29: 66–74
28. Pohl C, Klockgether T, Greinacher A, Hanfland P, Harbrecht U (1999) Neurological complications in heparin-induced thrombocytopenia. Lancet 353: 1678–1679
29. Wester JP, Haas FJ, Biesma DH, Leusink JA, Veth G (2004) Thrombosis and hemorrhage in heparin-induced thrombocytopenia in seriously ill patients. Intensive Care Med 30: 1927–1934
30. Warkentin TE (2005) Heparin-induced thrombocytopenia. Dis Mon 51: 141–149
31. Warkentin TE, Heddle NM (2003) Laboratory diagnosis of immune heparin-induced thrombocytopenia. Curr Hematol Rep 2: 148–157
32. Lo GK, Juhl D, Warkentin TE, Sigouin CS, Eichler P, Greinacher A (2006) Evaluation of pretest clinical score (4 T's) for the diagnosis of heparin-induced thrombocytopenia in two clinical settings. J Thromb Haemost 4: 759–765
33. Schallmoser K, Drexler C, Rohde E, et al (2009) The particle gel immunoassay as a rapid test to rule out heparin-induced thrombocytopenia? J Thorac Cardiovasc Surg 137: 781–783
34. Greinacher A, Gopinadhan M, Gunther JU, et al (2006) Close approximation of two platelet factor 4 tetramers by charge neutralization forms the antigens recognized by HIT antibodies. Arterioscler Thromb Vasc Biol 26: 2386–2393
35. Shaheed G, Malkovska V, Mendoza J, et al (2007) PF4 ENHANCED assay for the diagnosis of heparin-induced thrombocytopenia in complex medical and surgical patients. Crit Care Med 35: 1691–1695
36. Parker RI (2007) Measurement of heparin-dependent platelet antibodies in the diagnosis of heparin-induced thrombocytopenia: fact or fiction? Crit Care Med 35: 1784–1785
37. Warkentin TE (2003) Heparin-induced thrombocytopenia: pathogenesis and management. Br J Haematol 121: 535–555
38. Warkentin TE (1999) Heparin-induced thrombocytopenia: a clinicopathologic syndrome. Thromb Haemost 82: 439–447
39. Warkentin TE, Greinacher A (2004) Heparin-induced thrombocytopenia: recognition, treatment, and prevention: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 126: 311S-337S
40. Lubenow N, Eichler P, Lietz T, Greinacher A (2005) Lepirudin in patients with heparin-induced thrombocytopenia – results of the third prospective study (HAT-3) and a combined analysis of HAT-1, HAT-2, and HAT-3. J Thromb Haemost 3: 2428–2436
41. Tardy-Poncet B, Wolf M, Lasne D, et al (2009) Danaparoid cross-reactivity with heparin-induced thrombocytopenia antibodies: report of 12 cases. Intensive Care Med 35: 1449–1453
42. Warkentin TE (2003) Management of heparin-induced thrombocytopenia: a critical comparison of lepirudin and argatroban. Thromb Res 110: 73–82
43. Greinacher A (2004) Lepirudin: a bivalent direct thrombin inhibitor for anticoagulation therapy. Expert Rev Cardiovasc Ther 2: 339–357
44. Tardy-Poncet B, Tardy B, Reynaud J, et al (1999) Efficacy and safety of danaparoid sodium (ORG 10172) in critically ill patients with heparin-associated thrombocytopenia. Chest 115: 1616–1620
45. Keegan SP, Gallagher EM, Ernst NE, Young EJ, Mueller EW (2009) Effects of critical illness and organ failure on therapeutic argatroban dosage requirements in patients with suspected or confirmed heparin-induced thrombocytopenia. Ann Pharmacother 43: 19–27
46. Lewis BE, Wallis DE, Berkowitz SD, et al (2001) Argatroban anticoagulant therapy in patients with heparin-induced thrombocytopenia. Circulation 103: 1838–1843
47. Warkentin TE, Greinacher A, Koster A (2008) Bivalirudin. Thromb Haemost 99: 830–839
48. Koster A, Dyke CM, Aldea G, et al (2007) Bivalirudin during cardiopulmonary bypass in patients with previous or acute heparin-induced thrombocytopenia and heparin antibodies: results of the CHOOSE-ON trial. Ann Thorac Surg 83: 572–577
49. Lobo B, Finch C, Howard A, Minhas S (2008) Fondaparinux for the treatment of patients with acute heparin-induced thrombocytopenia. Thromb Haemost 99: 208–214

50. Warkentin TE (2008) Fondaparinux versus direct thrombin inhibitor therapy for the management of heparin-induced thrombocytopenia (HIT)--bridging the River Coumarin. Thromb Haemost 99: 2 – 3
51. Warkentin TE (2006) Should vitamin K be administered when HIT is diagnosed after administration of coumarin? J Thromb Haemost 4: 894 – 896
52. Hilbert P, Teumer P, Stuttmann R (2008) [Prevention of thromboembolism in German intensive care units : Results of a nationwide survey.]. Anaesthesist 57: 242 – 250
53. Crowther MA, Cook DJ, Meade MO, et al (2005) Thrombocytopenia in medical-surgical critically ill patients: prevalence, incidence, and risk factors. J Crit Care 20: 348 – 353
54. Baldwin ZK, Spitzer AL, Ng VL, Harken AH (2008) Contemporary standards for the diagnosis and treatment of heparin-induced thrombocytopenia (HIT). Surgery 143: 305 – 312

Iron Deficiency in Critically Ill Patients: Highlighting the Role of Hepcidin

II

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Introduction

Iron is a paradoxical element, essential for living organisms but also potentially toxic. Indeed, iron has the ability to readily accept and donate electrons, interconverting from soluble ferrous form (Fe^{2+}) to the insoluble ferric form (Fe^{3+}). This capacity allows iron to play a major role in oxygen transport (as the central part of hemoglobin) but also in electron transfer, nitrogen fixation or DNA synthesis, all essential reactions for living organisms. Indeed, iron deficiency is the main cause of anemia [1] as well as a cause of fatigue [2, 3] and decreased effort capacity [4, 5]. However, despite a high frequency of anemia among critically ill patients, with 60 to 66 % being anemic at intensive care unit (ICU) admission [6, 7], to date little is known about iron deficiency and iron metabolism in critically ill patients [8]. The interaction between inflammation and iron metabolism interferes with the usual iron metabolism variables and renders this metabolism difficult to investigate [9, 10].

The recent discovery of hepcidin (the master regulator of iron metabolism) has shed new light on the regulation of iron homeostasis and has helped our understanding of complex clinical situations, such as those observed in critically ill patients, where several regulatory circuits interfere with iron metabolism [11]. The purpose of this article is to review iron metabolism and anemia in critically ill patients as well as the role of hepcidin, and to discuss the indications for iron supplementation in these patients.

Iron Metabolism Overview and the Role of Hepcidin

Although iron is essential for life, it may also be toxic because of its capacity to react with oxygen and to promote the production of free radicals. This duality is found in human pathology: Iron deficiency (because of poor iron intake, abnormal blood losses etc...) presents with anemia and fatigue; whereas iron overload (mainly in hereditary hemochromatosis and following repeated blood transfusions) induces multiple organ dysfunctions (including liver fibrosis, cirrhosis, cardiomyopathy, diabetes...). This explains why iron homeostasis must be finely tuned to avoid both deficiency and excess.

Iron turnover in the organism occurs almost in a closed circuit (**Fig. 1**). Indeed, global iron turnover through losses (because of bleeding or cell desquamation) and dietary uptake (by duodenal cells) is only 1 to 2 mg per day, compared to approximately 3 to 4 g of iron contained in the organism. In fact, most of the iron

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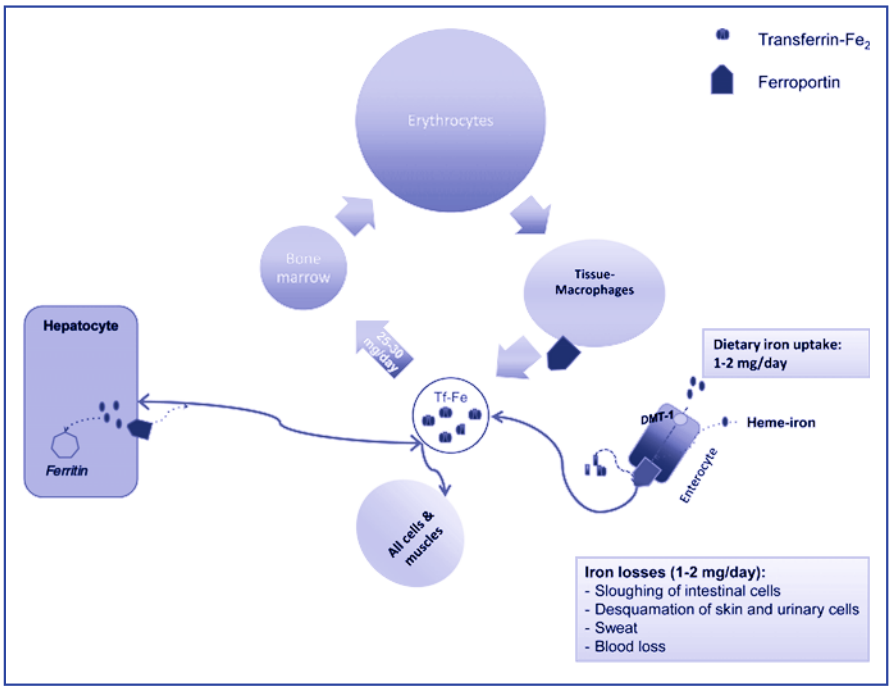

Fig. 1. Distribution of iron in the body. Erythrocytes contain almost two thirds of all body iron. Any blood loss may thus lead to direct iron loss. Serum iron, representing less than $1/10^3$ of the total iron content, is very limited at any time compared to the daily amount of iron needed for erythropoiesis. Hepatocytes and tissue macrophages are the main sites of iron storage. Iron is absorbed by intestinal cells through the duodenal metal transporter (DMT-1 apical transporter) and exported into the blood circulation via ferroportin.

available for erythropoiesis comes from the catabolism of senescent red blood cells (RBCs) by macrophages in the reticuloendothelial system (called eythrophagocytosis). As shown in **Figure 1**, more than two-thirds of the body's iron content is incorporated into hemoglobin, either in bone marrow erythroid progenitors or in circulating RBCs. Once aged, these RBCs are internalized and hemoglobin is degraded in tissue macrophages. Iron is then transferred to the macrophage cytosol and either released into the blood flow or stored in ferritin molecules. In the plasma, transferrin binds newly released iron to allow its mobilization from storage sites (mainly the spleen and to a lesser extent the liver) to utilization sites (mainly the bone marrow). Erythropoiesis requires about 25 to 30 mg of iron daily. It has to be stressed that the amount of iron present in the plasma at any time is small (about 3 mg) compared to the daily amount of iron needed for erythropoiesis. Iron metabolism is therefore finely tuned, with hepcidin being central to its regulation [12].

Hepcidin is a small 25 amino acid peptide mainly produced by the liver. It is produced as an 84 amino acid pre-pro-peptide. Pro-hepcidin has been shown to be biologically inactive. Hepcidin acts by binding to ferroportin, which is the sole known iron exporter [13]. The binding of hepcidin to ferroportin induces its internalization and degradation in the cytosol, which prevents the release of

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intracellular iron [13]. Ferroportin is mainly expressed in macrophages and duodenal cells, allowing, respectively, iron recycling (after eythrophagocytosis) and iron absorption from the digestive lumen (after internalization of iron through natural resistance-associated macrophage protein [nRAMP]/duodenal metal transporter [DMT1]). Induction of hepcidin synthesis may thus lead to iron-restricted erythropoiesis (by inhibiting the release of iron from macrophages to the bone marrow) and to dietary iron deficiency (by inhibiting the uptake of iron from the digestive duodenal cells). Hepcidin acts as a 'hyposideremic' hormone, aimed at inhibiting iron absorption and reducing the level of iron in the blood.

Because hepcidin plays this central role in iron metabolism regulation, its synthesis is finely regulated (**Fig. 2**) [11, 12]. Hepcidin synthesis is induced by iron overload and inflammation, whereas iron deficiency, hypoxia and erythroid expansion repress its synthesis. The molecular mechanisms implicated in these complex regulations are not fully understood (see [12] for review), but the induction of hepcidin synthesis by inflammation has been shown to be interleukin (IL)-6 dependent [14]. This interaction between hepcidin and inflammation

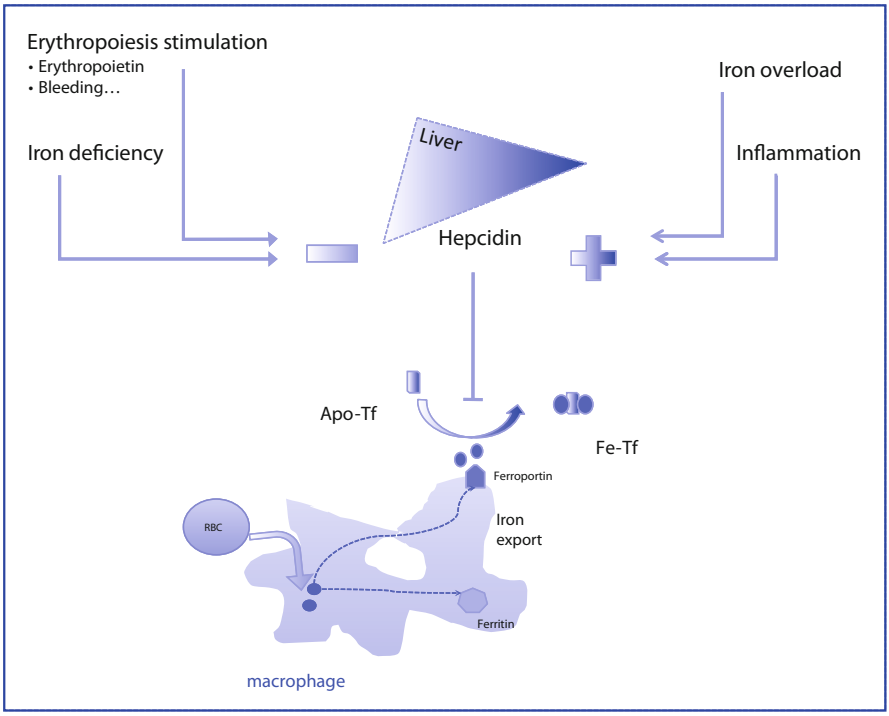

Fig. 2. Regulation of iron metabolism in anemia of the critically ill patient. Two opposite stimuli regulate hepcidin, which is the master regulator of iron metabolism. Hepcidin binds to ferroportin, inducing its internalization and destruction, thus avoiding iron export. Inflammation induces hepcidin synthesis, while iron deficiency, blood spoliation and erythropoiesis stimulation repress it. A low hepcidin level is required to allow iron export and its utilization for erythropoiesis. Apo-Tf: apotransferrin; Tf-Fe: transferrin bound iron

makes hepcidin the principal agent responsible for the iron-restricted erythropoiesis observed during chronic diseases, ultimately leading to the 'anemia of chronic disease' (or anemia of inflammation) [15, 16]. On the other hand, hepcidin synthesis is repressed by both iron deficiency and stimulation of erythropoiesis [11, 12]. Although the precise mechanisms involved in the repression of hepcidin are not fully understood, it appears that matriptase 2, a membrane-bound serine protease expressed in hepatocytes, seems to play a key role in repressing hepcidin synthesis in iron deficiency conditions [17]. Repression of hepcidin by erythropoiesis stimulation is even less well understood, but seems to involve bone marrow erythropoietic activity rather than erythropoietin itself [18, 19]. Hypoxia-inducible factor (HIF) or CCAAT enhancer binding protein-alpha pathways have also been proposed [12]. In human pathology, little is known. Growth differentiation factor 15, a member of the transforming growth factor (TGF)-β family produced by late erythroblasts, has been found in high levels in patients with beta-thalassemia syndromes and has been shown to repress hepcidin synthesis [20]. These two opposite stimuli are found in the anemia of critically ill patients, as discussed below.

Implication of Iron Metabolism in the Anemia of the Critically Ill: Hepcidin as a Diagnostic Tool?

Anemia is not only very frequent among critically ill patients, it is also associated with increased transfusion rates and worse outcomes (increased length of stay, increased mortality) [6, 7]. However, recent recommendations have led to a decrease in transfusion triggers [21]. Nowadays, anemia is present at ICU discharge in at least 75 % of all patients when considering their last measured hemoglobin levels [22]. Furthermore, anemia may also be prolonged after discharge, with a median time to recovery of 11 weeks and more than half of the patients still anemic 6 months after ICU discharge [23]. There is, therefore, need for a better understanding of the mechanisms of anemia in the critically ill and an evaluation of therapeutic options.

The two main contributing factors for anemia in the critically ill are inflammation and iron deficiency, which have opposite effects on iron metabolism (see above). Until recently, inflammation, rather than iron deficiency, was considered to play the major role. Indeed, the iron profile of critically ill patients constantly shows hallmarks of anemia of inflammation. However, this topic has not been considered a matter of great interest in the past, with few studies undertaken [9]. Inflammation is frequent in critical illness, whatever the underlying pathology. The anemia of critically ill patients is indeed similar to the anemia of inflammation, with blunted erythropoietic response and activation of RBC destruction by macrophages [15, 24]. Low serum iron and high ferritin levels constitute the typical iron profile of critically ill patients and are indicative of an inflammatory iron profile [25, 26]. Because ferritin synthesis is induced by inflammation (through IL-1) independently of the level of iron stores, elevated ferritin levels are no longer indicative of iron stores in the context of inflammation [10]. Thus, despite an iron profile that mimics iron overload (with high ferritin levels), iron deficiency may exist in these critically ill patients.

Indeed, daily blood losses are far from negligible, either through repeated blood sampling [6, 27], surgical site bleeding, other invasive procedures (drain-

Table 1. Biological variables of iron metabolism

	Iron deficiency	Anemia of inflammation	Iron deficiency and inflammation
Bone marrow iron	↘↘↘	↘	↘↘
Iron	↘↘	↘↘	↘↘
Transferrin	↗↗	↘↘	N to ↘
Transferrin saturation	↘↘	↘↘	↘↘
Ferritin	↘↘	↗↗	N to ↗
Percentage of hypochromic red blood cells	↗↗	N to ↗	↗↗
Reticulocyte hemoglobin content	↘↘	N or ↘	↘
Erythrocyte zinc protoporphyrin	↗↗	N to ↗	↗↗
sTfR	↗↗	↘↘	↗
sTfR/log ferritin	↗↗	↘	↗
Hepcidin	↘↘	↗↗	N to ↘
C-reactive Protein	N	↗↗	↗

sTfR: soluble transferrin receptor; N: normal; ↘: decreased; ↗ increased

age, catheter placement, renal replacement therapy...) or occult bleeding [26]. The median blood loss for anemic critically ill patients has been estimated to be as high as 128 ml per day [26]. This may represent a median iron loss as high as 64 mg per day. As daily iron intake is less than 20 fold iron losses, iron deficiency could easily appear in critically ill patients.

Iron deficiency may thus coexist with inflammation. In addition, iron deficiency is not infrequent in the general population [28], and also in the elderly [3, 29] or patients suffering from heart failure [30]. The frequency of iron deficiency on ICU admission may thus be around 35 % [31, 32]. However, the diagnosis of iron deficiency is difficult in the context of inflammation because the usual indicators of iron deficiency are no longer valid [9, 10]. Because inflammation induces ferritin synthesis, serum ferritin levels are no longer indicative of iron stores. New biological markers are thus required for the diagnosis of iron deficiency in the context of inflammation (**Table 1**) [10]. Below are the main biological markers that can be used:

- Percentage of hypochromic RBCs. These hypochromic RBCs result from iron-restricted erythropoiesis. Schematically, a value of > 10 % hypochromic erythrocytes (normal < 2.5 %) is indicative of iron-restricted erythropoiesis over the past 3 months (this being the RBC lifespan).
- Reticulocyte hemoglobin content. Reticulocyte hemoglobin content below 28 pg is also indicative of iron-restricted erythropoiesis over the past 2 to 3 days (this being the lifespan of reticulocytes). Recently, a low reticulocyte hemoglobin content on admission was shown to be associated with higher transfusion rates in critically ill patients [32].

- Erythrocyte zinc protoporphyrin (ZPP). During erythropoiesis, Fe is normally incorporated into protoporphyrin IX to form heme. In iron deficiency, zinc is substituted for iron, leading to the formation of ZPP. Increased erythrocyte ZPP is thus indicative of iron deficiency.
- Soluble transferrin receptor (sTfR). Transferrin receptors allow the internalization of iron into erythroid progenitor. Their synthesis is increased as bone marrow erythropoietic activity increases. When iron supply is insufficient, a truncated form of transferrin receptor appears in the serum. sTfR is thus indicative of iron-deficiency anemia. This marker is widely proposed, however there is no gold standard for its measurement.
- sTfR/log ferritin ratio (called the ferritin index). This is proposed as a marker to differentiate between anemia of inflammation and the combined situation of iron deficiency and anemia of inflammation, taking into account the "uncovered need for iron" on the one hand and the "iron stores" on the other [15].

Complex algorithms combining all these variables have been proposed for the diagnosis of iron deficiency in the presence of inflammation [10, 15]; however, none are clinically validated and the cut-off values for each variable are unknown. Moreover, all but sTfR cannot be used after recent blood transfusion.

Being central to iron metabolism, hepcidin may be a marker of iron deficiency, even in the presence of inflammation. Indeed, using animal models, we and others have demonstrated that hepcidin can be repressed despite inflammation [33–35] and that this repression is associated with spleen iron mobilization [34]. These observations reinforce the concept that iron deficiency may coexist with anemia of inflammation [15]. Measurement of hepcidin concentrations may thus be helpful for the diagnosis of iron deficiency in the context of inflammation. Additionally, many hepcidin assays have been recently developed [36]. Most studies evaluating the use of hepcidin concentrations to diagnose iron deficiency during inflammation have used ELISA-based values showing virtually undetectable levels [35] or normal values [37, 38] of hepcidin despite inflammation (supposed to increase hepcidin synthesis). Measurement of hepcidin concentrations could be accurate in the diagnosis of iron deficiency in critically ill anemic patients using a cut-off value of less than 130 ng/l [38].

Is There a Place for Iron Supplementation or Treatment in Critically Ill Patients?

Because iron deficiency may coexist with inflammation in critically ill patients [9, 10, 32, 38] and because iron may be mobilized from spleen stores in the presence of inflammation [34, 35], one could propose that iron be given to critically ill patients.

Because blood transfusion is not an option to fully correct the anemia in critically ill patients [6, 21], the use of alternatives such as erythropoiesis-stimulating agents or iron has been suggested. Erythropoiesis-stimulating agents have already been studied in the critically ill. They have not been shown to be useful [39] and are beyond the scope of this review. In addition, iron deficiency may concern up to 40 % of critically ill patients [10, 31, 32, 38]. Iron may thus be needed not only for erythropoiesis but also to correct all the disorders associated with iron deficiency, having been shown to improve functional capacity in women [40] and in

cardiac patients [41]. However, iron is also a toxic compound with the ability to induce oxidative stress or to promote bacterial growth and may thus not be suitable in the ICU context. Indeed, free iron may induce oxidative stress through the Fenton reaction. Large amounts of iron, exceeding the transferrin iron-binding capacity, may thus be toxic by inducing the release of free iron and causing oxidative stress. This probably explains the increased mortality associated with large amounts of iron administration (around the DL50) observed in an animal model of peritonitis [42]. However, no increase in oxidative stress has been demonstrated in human practice [43]. There is also a link between iron and infection, with iron being needed for bacterial growth. The decrease in serum iron concentration may be a defense mechanism against bacterial proliferation. However, bacteria have developed mechanisms for iron acquisition including the release of siderophores. The respective affinity for iron between transferrin and siderophores is probably what matters [44]. In clinical studies, this link between iron and infection has essentially been supported by experimental data on microorganisms and retrospective studies in hemodialysis patients showing an association between hyperferritinemia and the likelihood of infection. However, available observational studies in postoperative or critically ill patients show no association between intravenous iron administration and risk of infection [45]. Furthermore, iron deficiency is associated with impaired immunity [46] and may, therefore, be responsible for increased susceptibility to infection [32] as well as being associated with increased length of stay in the ICU [31].

Iron may thus be suggested to correct iron deficiency, even in the presence of inflammation, similar to its proposed use in the treatment of patients with cancer-induced anemia [15, 47]. Iron may be given using either intravenous or enteral routes. For the latter, ferrous iron is used. Iron absorption requires a mildly acidic medium (i.e., without concomitant use of proton pump inhibitors) and ascorbic acid. However, absorption may be reduced by inflammation because of the decrease in ferroportin levels induced by hepcidin, or because of frequent gastrointestinal adverse effects. The intravenous route allows administration of much higher doses with few adverse effects (with the notable exception of anaphylactic shock following iron dextran injections) and no difficulty of absorption. A recent meta-analysis showed that non-dextran iron was superior to enteral iron for the correction of anemia, with few adverse effects [48]. However, the only available study of intravenous iron showed no beneficial effect on erythropoiesis when used without erythropoiesis-stimulating agents [25]. The only study of iron deficiency treatment in critically ill patients is the study by Pieracci et al., which showed a reduced transfusion rate in patients with baseline iron deficiency treated with enteral iron supplementation (ferrous sulfate 325 mg three times daily) [49]. In this study, oral iron supplementation was not associated with an increased risk of infection.

Iron may therefore be proposed either to correct iron deficiency and/or to enhance the response to erythropoiesis-stimulating agents in critically ill patients, but further studies are needed to rule out the potential risks of iron treatment (i.e., oxidative stress induction, increased risk of infection) and to define the best route of administration. In **Figure 3**, we propose an algorithm for iron deficiency diagnosis and treatment. We believe that iron should be given to critically ill patients only in cases of iron deficiency, at best defined according to a low hepcidin level. The dose of iron needed may be assessed using the following formula:

$$\text{iron deficit} = \text{body weight (kg)} \times (\text{target Hb} - \text{actual Hb}) \times 2.4.$$

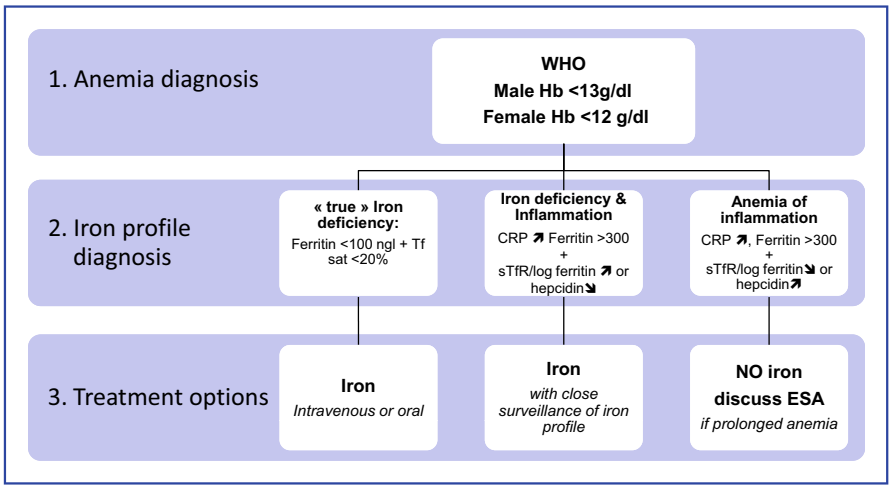

Fig. 3. Algorithm for diagnosis and treatment of iron deficiency (proposal not yet supported by clinical trial evidence). ESA: erythropoiesis-stimulating agents; CRP: C-reactive protein; sTfR: soluble transferrin receptor

Because elevated iron concentrations induce the synthesis of hepcidin, which in turn may reduce iron availability, the total dose of iron should be given using fractionated injections. Further clinical studies are needed to validate these propositions.

Conclusion

The discovery of hepcidin sheds new light on our knowledge of iron metabolism and may enable easier recognition of iron deficiency in the presence of inflammation in critically ill patients. This opens new areas of research exploring the role of iron treatment for these patients.

References

1. Clark SF (2008) Iron deficiency anemia. Nutr Clin Pract 23: 128–141
2. Patterson AJ, Brown WJ, Powers JR, Roberts DC (2000) Iron deficiency, general health and fatigue: results from the Australian Longitudinal Study on Women's Health. Qual Life Res 9: 491–497
3. Schultz BM, Freedman ML (1987) Iron deficiency in the elderly. Baillieres Clin Haematol 1: 291–313
4. Zhu YI, Haas JD (1997) Iron depletion without anemia and physical performance in young women. Am J Clin Nutr 66: 334–341
5. Zhu YI, Haas JD (1998) Altered metabolic response of iron-depleted nonanemic women during a 15-km time trial. J Appl Physiol 84: 1768–1775
6. Vincent JL, Baron JF, Reinhart K, et al (2002) Anemia and blood transfusion in critically ill patients. JAMA 288: 1499–1507
7. Corwin HL, Gettinger A, Pearl RG, et al (2004) The CRIT Study: Anemia and blood transfusion in the critically ill--current clinical practice in the United States. Crit Care Med 32: 39–52

8. Piagnerelli M, Vincent JL (2004) Role of iron in anaemic critically ill patients: it's time to investigate! Crit Care 8: 306 – 307
9. Darveau M, Denault AY, Blais N, Notebaert E (2004) Bench-to-bedside review: iron metabolism in critically ill patients. Crit Care 8: 356 – 362
10. Pieracci FM, Barie PS (2006) Diagnosis and management of iron-related anemias in critical illness. Crit Care Med 34: 1898 – 1905
11. Nicolas G, Chauvet C, Viatte L, et al (2002) The gene encoding the iron regulatory peptide hepcidin is regulated by anemia, hypoxia, and inflammation. J Clin Invest 110: 1037 – 1044
12. Hentze MW, Muckenthaler MU, Galy B, Camaschella C (2010) Two to tango: regulation of Mammalian iron metabolism. Cell 142: 24 – 38
13. Nemeth E, Tuttle MS, Powelson J, et al (2004) Hepcidin regulates cellular iron efflux by binding to ferroportin and inducing its internalization. Science 306: 2090 – 2093
14. Nemeth E, Rivera S, Gabayan V, et al (2004) IL-6 mediates hypoferremia of inflammation by inducing the synthesis of the iron regulatory hormone hepcidin. J Clin Invest 113: 1271 – 1276
15. Weiss G, Goodnough LT (2005) Anemia of chronic disease. N Engl J Med 352: 1011 – 1023
16. Andrews NC (2004) Anemia of inflammation: the cytokine-hepcidin link. J Clin Invest 113: 1251 – 1253
17. Ramsay AJ, Hooper JD, Folgueras AR, Velasco G, Lopez-Otin C (2009) Matriptase-2 (TMPRSS6): a proteolytic regulator of iron homeostasis. Haematologica 94: 849 – 849
18. Pak M, Lopez MA, Gabayan V, Ganz T, Rivera S (2006) Suppression of hepcidin during anemia requires erythropoietic activity. Blood 108: 3730 – 3735
19. Vokurka M, Krijt J, Sulc K, Necas E (2006) Hepcidin mRNA levels in mouse liver respond to inhibition of erythropoiesis. Physiol Res 55: 667 – 674
20. Tanno T, Bhanu NV, Oneal PA, et al (2007) High levels of GDF15 in thalassemia suppress expression of the iron regulatory protein hepcidin. Nat Med 13: 1096 – 1101
21. Hill SR, Carless PA, Henry DA, et al (2002) Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion. Cochrane Dat Syst Rev: CD002042
22. Walsh TS, Lee RJ, Maciver CR, et al (2006) Anemia during and at discharge from intensive care: the impact of restrictive blood transfusion practice. Intensive Care Med 32: 100 – 109
23. Bateman AP, McArdle F, Walsh TS (2009) Time course of anemia during six months follow up following intensive care discharge and factors associated with impaired recovery of erythropoiesis. Crit Care Med 37: 1906 – 1912
24. Corwin HL, Krantz SB (2000) Anemia of the critically ill: "acute" anemia of chronic disease. Crit Care Med 28: 3098 – 3099
25. van Iperen CE, Gaillard CA, Kraaijenhagen RJ, Braam BG, Marx JJ, van de Wiel A (2000) Response of erythropoiesis and iron metabolism to recombinant human erythropoietin in intensive care unit patients. Crit Care Med 28: 2773 – 2778
26. von Ahsen N, Muller C, Serke S, Frei U, Eckardt KU (1999) Important role of nondiagnostic blood loss and blunted erythropoietic response in the anemia of medical intensive care patients. Crit Care Med 27: 2630 – 2639
27. Wisser D, van Ackern K, Knoll E, Wisser H, Bertsch T (2003) Blood loss from laboratory tests. Clin Chem 49: 1651 – 1655
28. Looker AC, Dallman PR, Carroll MD, Gunter EW, Johnson CL (1997) Prevalence of iron deficiency in the United States. JAMA 277: 973 – 976
29. Smieja MJ, Cook DJ, Hunt DL, Ali MA, Guyatt GH (1996) Recognizing and investigating iron-deficiency anemia in hospitalized elderly people. CMAJ 155: 691 – 696
30. Jankowska EA, Rozentryt P, Witkowska A, et al (2010) Iron deficiency: an ominous sign in patients with systolic chronic heart failure. Eur Heart J 31: 1872 – 1880
31. Bellamy MC, Gedney JA (1998) Unrecognised iron deficiency in critical illness. Lancet 352:1903
32. Fernandez R, Tubau I, Masip J, Munoz L, Roig I, Artigas A (2010) Low reticulocyte hemoglobin content is associated with a higher blood transfusion rate in critically ill patients: a cohort study. Anesthesiology 112: 1211 – 1215
33. Huang H, Constante M, Layoun A, Santos MM (2009) Contribution of STAT3 and SMAD4 pathways to the regulation of hepcidin by opposing stimuli. Blood 113: 3593 – 3599
34. Lasocki S, Millot S, Andrieu V, et al (2008) Phlebotomies or erythropoietin injections

allow mobilization of iron stores in a mouse model mimicking intensive care anemia. Crit Care Med 36: 2388 – 2394
35. Theurl I, Aigner E, Theurl M, et al (2009) Regulation of iron homeostasis in anemia of chronic disease and iron deficiency anemia: diagnostic and therapeutic implications. Blood 113: 5277 – 5286
36. Kroot JJ, Kemna EH, Bansal SS, et al (2009) Results of the first international round robin for the quantification of urinary and plasma hepcidin assays: need for standardization. Haematologica 94: 1748 – 1752
37. Cheng PP, Jiao XY, Wang XH, Lin JH, Cai YM (2010) Hepcidin expression in anemia of chronic disease and concomitant iron-deficiency anemia. Clin Exp Med (in press)
38. Lasocki S, Baron G, Driss F, et al (2010) Diagnostic accuracy of serum hepcidin for iron deficiency in critically ill patients with anemia. Intensive Care Med 36: 1044 – 1048
39. Zarychanski R, Turgeon AF, McIntyre L, Fergusson DA (2007) Erythropoietin-receptor agonists in critically ill patients: a meta-analysis of randomized controlled trials. CMAJ 177: 725 – 734
40. Brutsaert TD, Hernandez-Cordero S, Rivera J, Viola T, Hughes G, Haas JD (2003) Iron supplementation improves progressive fatigue resistance during dynamic knee extensor exercise in iron-depleted, nonanemic women. Am J Clin Nutr 77: 441 – 448
41. Anker SD, Comin Colet J, Filippatos G, et al (2009) Ferric carboxymaltose in patients with heart failure and iron deficiency. N Engl J Med 361: 2436 – 2448
42. Javadi P, Buchman TG, Stromberg PE, et al (2004) High-dose exogenous iron following cecal ligation and puncture increases mortality rate in mice and is associated with an increase in gut epithelial and splenic apoptosis. Crit Care Med 32: 1178 – 1185
43. Driss F, Vrtovsnik F, Katsahian S, et al (2005) Effects of intravenous polymaltose iron on oxidant stress and non-transferrin-bound iron in hemodialysis patients. Nephron Clin Pract 99: c63 – 67
44. Marx JJ (2002) Iron and infection: competition between host and microbes for a precious element. Best Pract Res Clin Haematol 15: 411 – 426
45. Hoen B, Paul-Dauphin A, Kessler M (2002) Intravenous iron administration does not significantly increase the risk of bacteremia in chronic hemodialysis patients. Clin Nephrol 57: 457 – 461
46. Dallman PR (1987) Iron deficiency and the immune response. Am J Clin Nutr 46: 329 – 334
47. Auerbach M, Ballard H, Glaspy J (2007) Clinical update: intravenous iron for anaemia. Lancet 369: 1502 – 1504
48. Notebaert E, Chauny JM, Albert M, Fortier S, Leblanc N, Williamson DR (2007) Short-term benefits and risks of intravenous iron: a systematic review and meta-analysis. Transfusion 47: 1905 – 1918
49. Pieracci FM, Henderson P, Rodney JR, et al (2009) Randomized, double-blind, placebo-controlled trial of effects of enteral iron supplementation on anemia and risk of infection during surgical critical illness. Surg Infect (Larchmt) 10: 9 – 19

The Next Generation of ALI Genetics: Insights into Pathophysiology

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III

Introduction

The last few years have seen an explosion in the publication of gene association studies, particularly genome wide analyses, giving insight into the molecular underpinnings of disease [1, 2]. For acute lung injury (ALI), the field of genetics is just beginning to move past its infancy, from candidate gene studies to higher throughput, hypothesis-generating designs. As a phenotype, ALI can be challenging to study given the lack of available pedigrees for family-based analyses, the necessity for a severe environmental insult such as sepsis, pneumonia, trauma, or aspiration, and the heterogeneity of the populations at-risk for the syndrome and those who manifest it [3]. The search to identify genetic risk factors for ALI susceptibility or outcome draws input from molecular advances as well as from large epidemiological studies with carefully phenotyped critically ill subjects, and these efforts in tandem have recently produced exciting results. In this chapter, we will discuss the most recent developments in the effort to identify genetic risk factors contributing to ALI susceptibility or outcome, and will highlight the more novel techniques applied to this question. A glossary of genetic terms is provided (**Box**).

General Considerations in Designing ALI Genetic Studies

Because ALI requires both severe environmental exposure and an individual predilection to manifest the syndrome, it is known as a complex genetic trait [4]. The lack of ALI pedigrees has traditionally limited the available methodology for studying this trait to genetic association studies, where the frequency of variants within a candidate gene are compared between ALI cases and non-cases [5] using either cohort or case-control designs.

Many investigators have chosen a case-control approach, defining cases of ALI and comparing them to either population-based controls or critically ill subjects at risk for ALI. As genetic studies become increasingly high-throughput, there is demand for extremely large control populations – in excess of 1000 subjects – thus finding sufficient at-risk controls may be difficult. Nonetheless, the use of at-risk controls is preferred, as it avoids the potential for misclassification in outcome due to the controls never being exposed to an ALI-potentiating event. Furthermore, the use of at-risk controls lends construct validity that the outcome being studied is actually lung injury, rather than simply identifying genetic associations with critical illness. However, even at-risk controls may be prone to

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Box: Glossary

Single nucleotide polymorphism (SNP): A substitution at a single base pair of DNA. These are the most frequent genetic variations observed.

Non-synonymous coding SNP (cSNP): A single base-pair substitution resulting in a change in the protein sequence. Generally these substitutions are deleterious on the fitness of the gene product.

Insertion/deletion polymorphism (indel): A variation in which one or more bases are inserted or deleted compared to the reference sequence. These can be as small as 1 base pair (the 4G/5G *PAI-1* indel) or can be greater than 250 base pairs (*ACE* indel).

Intron: The portion of the DNA which does not code for messenger RNA (mRNA) and thus will not change the protein coding sequence.

Exon: The protein coding (mRNA-coding) sequence of the DNA.

Promoter region: Regulatory region upstream (5′) of the transcription initiation site for the gene's mRNA which controls gene expression/transcription.

Intergenic region: DNA sequence which has not been annotated to any known gene or gene product

Splice variant: Many proteins have different isoforms, which may result from different exons being included in the final gene product. Splice variants arise when an exon is skipped while forming mRNA.

3′ Untranslated Region (3′ UTR): A region of DNA which follows the protein coding region, and has been recognized to affect the translation of mRNA into protein.

Linkage disequilibrium (LD): Non-random assortment of alleles, such that 2 (or more) markers appear to segregate together more frequently than would be expected based on each allele's frequency alone. Factors contributing to LD include genomic position, recombination rate, mutation rate, selection, non-random mating, genetic drift, and population structure.

selection bias. An alternative study design that limits bias due to selection of controls is the cohort study design. Cohort studies are often more costly and must enroll for a longer duration to reach enough meaningful outcomes, but ensure that cases and non-cases are drawn from comparable populations. Applying the case-control or cohort design, epidemiological studies can use either focused approaches aimed at specific candidate genes, or larger scale approaches that incorporate varying degrees of *a priori* hypotheses. Specific methodologies of each approach are presented in **Table 1**.

An additional consideration in the design of genetic studies is the ancestral populations from which subjects arise, and ensuring proper accounting for population substructure [6]. The bulk of published ALI genetic literature has been performed in subjects of European ancestry, as is evident in **Table 2**. Because genetic variation is actually much greater within rather than between ancestral populations [7], it will be important for future studies to test the genetic associations found among Europeans with ALI in African, Asian, and admixed populations. To do this, the medical community must greatly improve the enrollment of non-European subjects with and at risk for ALI.

Table 1. Study designs to address the genetic risk factors for ALI susceptibility or outcome.

Study Design	What is tested?	What are the results?	Potential shortcomings
Hypothesis – driven methodologies			
Candidate Gene Association	Variation in DNA at specific sites (few loci)	OR for association between genetic variant and phenotype	• Inefficient selection of gene or gene variant • Low throughput • Needs replication • Functional significance?
Multiplexed Candidate Gene	Variation in DNA at many (50K) loci in 1,000s of priority genes	OR for association between many variants and phenotype • May include LD information • May inform about subjects ancestry	• Multiple comparisons • Limited to genes & variants selected • No accepted statistics • Needs replication • Functional significance?
Hypothesis – free methodologies (Generate new candidate genes)			
Microarray Gene Expression	Transcript abundance (mRNA) of ~20,000 global genes	List of genes with significant fold-change in expression between conditions; • Strong evidence for functional significance • Can be analyzed for pathway enrichment	• Multiple comparisons • QA: other reasons for altered expression? • Only informative about transcriptional regulation • Requires further confirmation (*in vitro* or *in vivo*)
GWA Study	Variation in DNA at 500K – 1.5M loci; with LD, captures ~80 % of person's genetic variation	OR for association of locus with phenotype • Can analyze results as gene-based or pathway-based • Informative about ancestry, allows adjustment for population structure	• Multiple comparisons • Miss rare variants • May miss small (but real) associations • Rely on annotation to determine gene region • Requires replication • Functional significance?
Gene Expression + Gene Association	Pairs changes in transcript abundance with changes in DNA sequence	eQTL (expression quantitative trait loci); genetic variants associated with change in expression level of transcribed gene; can describe both cis and trans effects;† strong evidence for functional significance	• Expression depends on the cell type/tissue type studied • QA: gene expression • Multiple comparisons • May miss non-transcriptional regulation • If targeted gene expression or targeted genotyping, may miss meaningful variation
Exome or GW Sequencing	DNA sequence of all exons or of the entire genome • Each person has ~300,000 variants, 15 % unique to the individual/not previously described	Identify rare changes in sequence between individual and reference • Exome: coding sequence only • GW: genome wide, ~6GB sequence	• Expensive • Massive data generation • Separating signal from noise; which variants are meaningful? • Uncertain if helpful in complex, multigenic traits

GWA: genome-wide association; eQTL: expression quantitative trait loci; LD: linkage disequilibrium; OR: odds ratio; QA: quality assurance; † When discussing gene regulation, *cis* acting elements are regions of DNA in the genomic vicinity of the gene they regulate, potentially within the promoter of the gene. By contrast, *trans* acting elements are often sequences which code for a distinct protein or small molecule which in turn can regulate transcription of the gene of interest and tend to be genomically distant from the regulated gene (ie, different chromosomes). In general, far less is understood about *trans* regulation, and unless studies combine gene expression with an assessment of genetic variation, these relationships are difficult to appreciate.

Table 2. Genetic variants associated with ALI/ARDS or ALI/ARDS mortality. Functional associations include mRNA or protein changes demonstrated either *in vitro* or *in vivo* to be associated with the genotype listed. Ancestry refers to the ancestral population of study subjects. Please see glossary for a description of the genetic terms.

Gene	Variant(s)	Functional Association?	Ancestry	Reference
Variants associated with ALI susceptibility				
IL-6	G-174C 3 SNP haplotype 6 SNP haplotype	Promoter SNP Unknown Unknown	European	[13, 14, 17]
IL-10	G-1082A	Promoter	European	[26]
FAS	3 SNP haplotype	eQTL, ↑ mRNA expression	European	[21]
MBL2	Exon 1 54BB	nsCoding SNP, ↓ plasma MBL	European	[12]
SFTPB	T+1580C Intron 4 indel	nsCoding SNP intronic; splice variant	European Multiethnic	[10, 16, 17]
PBEF	T-1001G C-1543T	Promoter Promoter (protective)	European	[34]
MYLK	3 SNPs, 3 haplotypes	nsCoding SNPs Unknown	European, African	[24, 16, 17]
Non-replicated associations in the following genes: ANGPT2, IL-8, MIF, TNFA, NRF2, NFKBIA, FTL, HMOX2				[16, 17, 28]
Variants associated with ALI mortality or severity				
VEGFA	C+936T	3′ UTR; T allele ↓ plasma VEGF	European	[27]
SOD3	4 SNP haplotype	Unknown	European	[25]
ACE	Intron 16 indel	Intron; ↑ plasma ACE level	European, Asian	[11]
PAI-1	4G/5G indel	Promoter, ↑ mRNA expression	European	[22, 23]
Non-replicated associations in the following genes: NFKB1, PLAU, F5, TNFA				[16, 17]

SNP: single nucleotide polymorphism; indel: insertion/deletion; eQTL: expression quantitative trait loci

Candidate Gene Studies

Candidate gene association studies typically begin with an investigator's hypothesis that a specific gene or gene family influences the development or course of a disease. For ALI, in which the chief molecular mechanisms are believed to include cytokine or neutrophil-mediated inflammation, oxidant stress, endothelial and epithelial injury, mechanotransduction injury, coagulopathy, and altered iron homeostasis [8, 9], many candidate gene studies have centered on genes in these pathways. Such studies can yield fruitful associations as presented in **Table 2** [10–14], but they are predicated on a correct hypothesis about which candidate gene is important and on genotyping either the 'functional' or meaningful variant or a marker in linkage disequilibrium with it. Because the contribution of each individual genetic variant is likely quite small, especially for common genetic variants, it can be difficult to power studies appropriately to detect an effect [4, 15]. With these limitations, and given the modest power of most ALI cohorts or case-control populations to date, relatively few genetic variants have demonstrated a

reproducible association with ALI or its outcomes [16, 17]. **Table 2** highlights those candidates with strong evidence for an association with ALI, as well as genetic associations which have not been replicated. Importantly, as the molecular understanding of ALI pathogenesis advances, new potential candidate genes are continuously introduced. Similarly, genes not previously recognized to play crucial roles in the mechanisms described above may emerge, and be appealing candidates for genetic investigation.

A relatively recent development has been the ability to multiplex large numbers of candidate gene variants together on one chip, so that each sample is simultaneously tested for many variants in many genes. Such chips can either be customized to a researcher's specifications or investigators may purchase single nucleotide polymorphism (SNP) array chips designed to interrogate certain families of genes. Our group used one such commercially available chip, the Illumina® 50K humanCVD beadchip, assaying 50K SNPs in approximately 2000 candidate genes prioritized for pulmonary, vascular, inflammatory, or metabolic pathways, and found ALI associations that have replicated in external populations [18, 19]. This high-throughput approach is an efficient screen of the variation in numerous potential candidates, although the large number of comparisons (50K) demands both a stringent alpha threshold for statistical significance and replication in another population [20].

Recent Candidate Gene Studies in ALI

In the past year, several new candidates affecting ALI susceptibility or outcome have emerged (**Table 2**). A haplotype in the *FAS* gene was found to associate with ALI in the ARDS network population compared to healthy controls and then replicated its association in a sepsis cohort followed prospectively for ALI [21]. The same haplotype was also found to associate with higher levels of lipopolysaccharide-(LPS)-stimulated *FAS* mRNA expression, suggesting that this haplotype contains a functional genetic variant [21]. Two separate groups reported an association between the 4G allele of a common insertion/deletion (indel) polymorphism in the plasminogen activator inhibitor-1 (*PAI-1*) gene promoter and worse outcomes for patients with pneumonia and severe sepsis [22, 23]. This variant, which is present in approximately 45 % of the Caucasian population, reportedly increases interleukin-driven expression of *PAI-I* mRNA 6-fold relative to the dominant 5G allele [22]. Further candidate gene associations are summarized in **Table 2** [12, 24–28].

Gene and Pathway-based Analyses

Another strategy to identify new candidate genes focuses not on individual genetic variants which associate with the disease, but considers instead all of the potential variants within either one gene or a family of interacting genes and selects those with statistically overrepresented variation in the disease state relative to controls. As an initial screen, these techniques produce a gene list which can then undergo further evaluation either *in vitro*, for mechanistic elucidation, or for replication in human populations. The most common way to obtain the gene list is by microarray gene expression profiling, which compares the tran-

script abundance of a global set of genes between two experimental (or patient) populations, to identify genes with differential regulation. Gene expression profiling can be performed on human, animal, or cell culture subjected to different conditions, and results are generally filtered for genes showing at least a 1.5 or 2-fold change in mRNA level [29]. Bioinformatic tools are used to annotate the genes according to their biological pathway [30], molecular functions, or cellular localization [31], and statistical tools can be applied to suggest enrichment of different annotation categories [32]. Genes and pathways demonstrating markedly different regulation in experimental lung injury in ALI subjects versus control conditions or populations may give insight to novel mechanisms at play in the development or progression of lung injury, and may lend functional significance to gene variants already identified.

Grigoryev and colleagues utilized gene expression from multiple animal and *in vitro* studies of ventilator-induced lung injury (VILI) and filtered for orthologous genes demonstrating consistent effects across species [33]. Their results highlighted a number of genes and pathways already hypothesized to be at play during ALI, but more importantly identified novel candidates, such as *PBEF*, which had not previously been associated with ALI and which have since yielded consistent associations with ALI [16, 34]. Other authors have employed gene expression methodology to identify ALI susceptibility between mouse strains [35], to identify gene products that are differentially expressed in early versus late stages of ARDS [36], or to describe a genetic signature potentially differentiating sepsis with ARDS from sepsis alone [37].

The strength of gene expression analysis is its ability to detect novel biological processes or pathways potentially mechanistically involved in discriminating between 2 groups [38]. However, several cautions apply (**Table 1**). By comparing thousands of gene expression levels simultaneously between 2 (or more) groups, one would anticipate hundreds of transcript level imbalances to occur purely by chance alone. In all gene expression studies, details of the study design and quality assurance methodology are of paramount importance. Gene expression changes may erroneously reflect a batch effect of having been performed on different days or in different labs; may reflect a different baseline transcript level rather than a differential response to injury; or may reflect an unrecognized confounder (such as age or gender). These methodological concerns can be overcome in animal studies by careful design, use of animals with an identical genetic background (such as inbred mice), and by adequate replication. However, with heterogeneous human samples and typically small sample sizes, it can be challenging to draw inferences about why transcript abundance varies between groups.

Another potential source of bias is the use of mRNA derived from whole blood samples – reflecting an unquantified mix of different circulating cell lineages – versus selecting only specific cell types related to the disease under study. Oncologic studies have the advantage of using tumor cells for their analyses; however, it remains unknown whether the findings from peripheral blood are as relevant as lung tissue or bronchoalveolar lavage (BAL)-obtained cells in ALI studies. Microarray expression studies are a valuable method to discover new genes and pathways involved in ALI pathogenesis, but similar to genetic association studies, their findings necessitate replication and functional assessment.

Genome-wide Association Studies

Over the past 10 years, genotyping and multiplexing technology has advanced greatly to the point where it has become not only possible, but affordable to test simultaneously over a million genetic markers on each sample. These high density genotyping platforms are designed to sample the genetic variation in every region of each chromosome of the genome and thus are termed "whole genome" scans. By combining knowledge of the linkage disequilibrium between genotyped markers along with the recombination rate across various regions of the genome [39], genome-wide association (GWA) platforms leverage so-called "tagging SNPs" to generate a complete map of the genome. Tagging SNPs are SNPs that represent a block of genetic variants which tend to be inherited together. Thus GWA platforms genotype 500K–1 million markers but are informative about the approximately 6 giga-base sequence of each individual.

GWAs take a hypothesis-free approach and sample across the genome rather than in specific genes, and thus are a powerful method to discover genetic risk factors in loci that previously had not been identified as candidate genes (**Table 1**). The results from GWAs depict the association of a phenotype as a function of genomic locus, typically graphed as a Manhattan plot (**Fig. 1**), where the y-axis is the negative log of the p-value for the association and the x-axis is chromosomal position. A very strong association will have not only a peak with a very high –(log p), but will also demonstrate lesser degrees of association between the phenotype and markers in linkage disequilibrium with the peak marker. Once a genomic locus is identified and, ideally, replicated in a second population, the next steps are to identify which genes or regulatory regions reside in the region of association, and then to perform deep sequencing to determine the 'functional' variant driving the association. With increasing numbers of GWA being performed, the majority of replicated GWA hits appear to be intronic or even intergenic, far from any recognized protein coding sequence [40]. This observation suggests that the traditional conception of genetics (DNA is transcribed to mRNA; mRNA is translated to amino acid sequence; amino acids constitute the protein and assume a conformational structure) may be overly simplistic. Rather, there are likely regulatory mechanisms that we do not yet understand whereby intergenic or intronic variation may influence transcription, translation, post-translational modification, or protein conformation.

Both the promise and the limitations of GWA stem from the enormous number of genetic variants (500K–1.5 million) assayed. Increasing the number of genetic variants tested allows finer resolution, or a much greater characterization of the variation between the case and control populations. However, the number of simultaneous tests also greatly increases the probability of an apparent statistical imbalance happening purely by chance. To overcome the multiple comparison issue, GWA studies use a very conservative alpha level to declare statistical significance, typically 5E-08 [41]. Furthermore, even when genome-wide significance appears to be met, replication of the association in additional populations is essential [15, 40, 42]. Furthermore, GWA studies require very large numbers of subjects to offset the large amounts of unshared variation between unrelated individuals and to find commonality despite inherently heterogeneous traits [15, 41]. For most complex genetic traits in which the phenotype is believed to be multigenic and penetrance is incomplete, a minimum case population of approximately 600 is recommended [41].

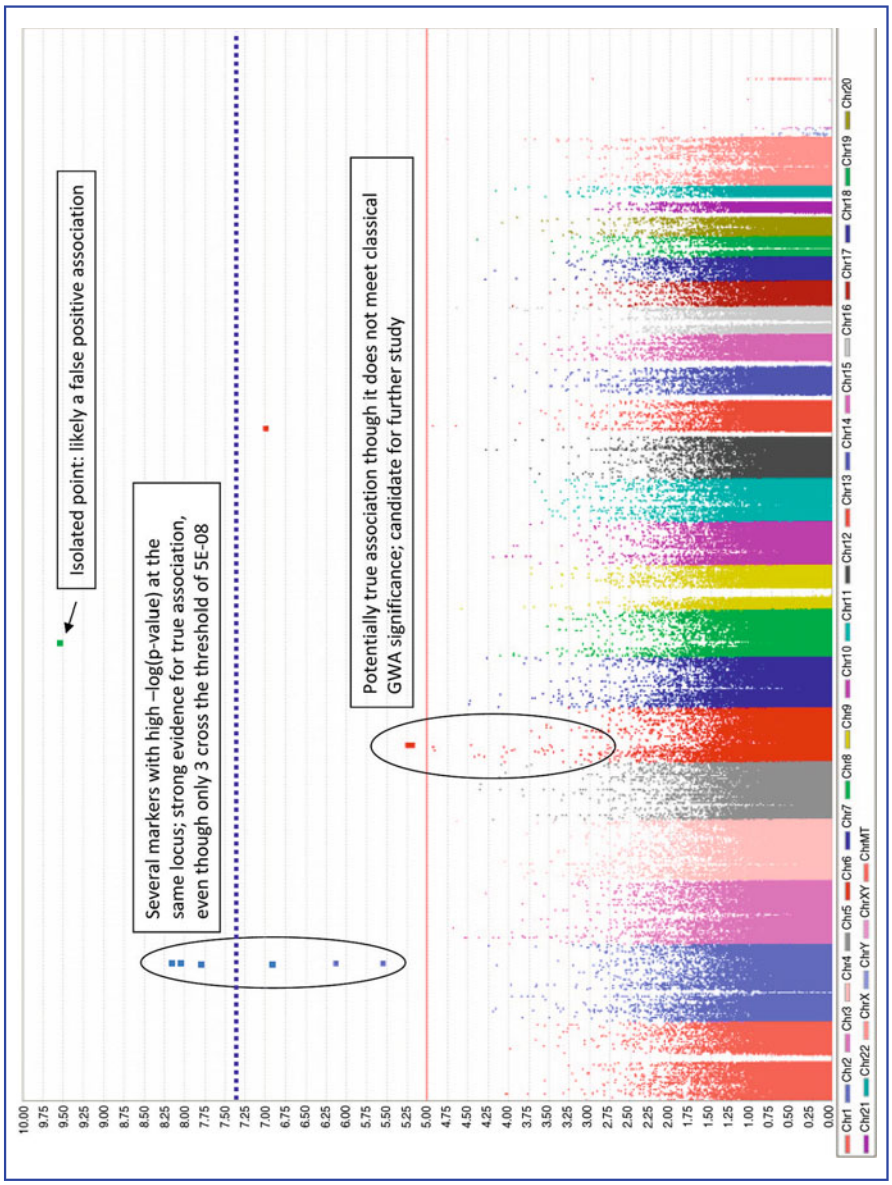

Fig. 1. A representative Manhattan plot depicting the genome wide associations between a hypothetical phenotype and positions along chromosomes 1 – 23. The x-axis is chromosomal position beginning with chromosome 1 and ending with the sex chromosomes and mitrochondrial DNA. The y-axis graphs the inverse log (p-value) for the χ^2 test of association with the phenotype, such that $p = 0.05$ would be plotted at 1.3, $p = 0.00001$ would be plotted at 5 (red line), and p< 5E-08 would be graphed above 7.3 (blue dashed line). Convincing associations have not only one high peak such as the green box within chromosome 8, but rather demonstrate a trail of associations leading up to the point (blue and red squares, circled), fleshing out the virtual building of a skyscraper on the Manhattan plot.

Although not yet published, the first GWA of subjects with ALI compared to population controls has been performed by our group, and has been presented in abstract form [43]. This was a multistage study using 600 trauma-associated ALI cases and over 2000 population-based controls, and while no variants met the stringent level for genome-wide significance in the discovery phase, a number of variants with putative functional effects replicated in a small replication phase. This study is important in illustrating the feasibility of multicenter collaborative efforts aimed at ALI GWA studies. It seems likely that further GWA studies will follow, and the community of researchers involved in ALI genetics is poised to collaborate in order to generate sufficient power for these investigations [44].

Future Directions in ALI Genomics

Several additional methodologies may also soon be applied in ALI. As it has been argued that rare variants – polymorphisms occurring in < 5 % or even < 1 % of the population – substantially contribute to disease burden [40, 45], there is interest in moving from genotyping 'tags' or markers of common variation to directly sequencing either the protein coding sequences of DNA (the 'exome', or all exons in the genome) or the entire genome, and analyzing the base-by-base genetic sequence for each individual [46]. This novel strategy has the potential to greatly increase the number of identified deleterious polymorphisms, most of which are exceedingly rare, and thus the challenge will be filtering results to identify the potentially disease-causing variants from the genetic noise. In addition, quality control becomes paramount, as even a system with 99.9999 % fidelity in genotyping a human genome will result in thousands of errors [38]. Redundant sequencing – typically 30x – is thus a hallmark of GW or exome sequencing. Exome resequencing has been successful in identifying the cause of a rare Mendelian disorder [47]; time will tell if it is equally useful in complex genetic traits, where the multiple genes or multiple variants within multiple genes are the more likely scenario.

Another major development likely to be adopted in ALI genetics is to further interrogate expression quantitative trait loci (eQTLs), or the genetic variants responsible for altered levels of gene expression [48]. As it becomes clear that gene regulation is at least as important as the actual DNA sequence, one creative approach has been to combine an assessment of mRNA level, also termed the transcript abundance, with DNA genotyping. By pairing these techniques, investigators may determine which genetic variants drive the gene expression for various transcripts. Study designs may vary in whether global gene expression is measured, typically using microarray platforms which assess transcript levels of approximately 20,000 genes, versus a targeted number of genes measured by polymerase chain reaction (PCR), and in whether the genotyping is limited or genome wide.

Studying sepsis and ALI, Wurfel and colleagues demonstrated that a number of polymorphisms in Toll-like receptor (TLR) 1-related genes were associated with dramatic variation in inflammatory responses to various TLR stimuli [49]. One hypermorphic variant in particular, in *TLR1*, was also shown to be associated with sepsis-associated mortality and organ dysfunction (including ALI) [49]. Dixon and colleagues performed simultaneous GWA with a global gene expression assay of lymphoblastoid cell lines to identify numerous eQTLs for over

20,000 genes [50]. The search for additional eQTLs, potentially driving variation in the transcripts of pulmonary endothelial cells or alveolar epithelial cells, might point to pharmacologic targets for the future.

Conclusion

It is encouraging that over 20 genetic variants have now demonstrated an association with either ALI or ALI outcomes, and 11 of these associations have been replicated. The scientific community is increasingly recognizing the importance of collaboration to pool samples and replicate findings, which will undoubtedly yield important results in the near future [43, 44]. With advances leading to more detailed molecular understanding of ALI pathogenesis, incorporation of genetic information to 'personalize' ALI care or define more specific ALI phenotypes is a realistic goal. As costs and assay times continue to contract while capacity expands, genomic risk factors may yet become part of our clinical care.

References

1. Murphy A, Chu JH, Xu M, et al (2010) Mapping of numerous disease-associated expression polymorphisms in primary peripheral blood CD4+ lymphocytes. Hum Mol Genet 19: 4745–4757
2. Maller J, George S, Purcell S, et al (2006) Common variation in three genes, including a noncoding variant in CFH, strongly influences risk of age-related macular degeneration. Nat Genet 38: 1055–1059
3. Meyer NJ, Garcia JG (2007) Wading into the genomic pool to unravel acute lung injury genetics. Proc Am Thorac Soc 4: 69–76
4. Frazer KA, Murray SS, Schork NJ, Topol EJ (2009) Human genetic variation and its contribution to complex traits. Nat Rev Genet 10: 241–251
5. Gong MN (2009) Gene association studies in acute lung injury: replication and future direction. Am J Physiol Lung Cell Mol Physiol 296: L711–712
6. Coop G, Pickrell JK, Novembre J, et al (2009) The role of geography in human adaptation. PLoS Genet 5: e1000500
7. Kruglyak L, Nickerson DA (2001) Variation is the spice of life. Nat Genet 27: 234–236
8. Ware LB, Matthay MA (2000) The acute respiratory distress syndrome. N Engl J Med 342: 1334–1349
9. Lagan AL, Melley DD, Evans TW, Quinlan GJ (2008) Pathogenesis of the systemic inflammatory syndrome and acute lung injury: role of iron mobilization and decompartmentalization. Am J Physiol Lung Cell Mol Physiol 294: L161–174
10. Lin Z, Pearson C, Chinchilli V, et al (2000) Polymorphisms of human SP-A, SP-B, and SP-D genes: association of SP-B Thr131Ile with ARDS. Clin Genet 58: 181–191
11. Marshall RP, Webb S, Bellingan GJ, et al (2002) Angiotensin converting enzyme insertion/deletion polymorphism is associated with susceptibility and outcome in acute respiratory distress syndrome. Am J Respir Crit Care Med 166: 646–650
12. Gong MN, Zhou W, Williams PL, Thompson BT, Pothier L, Christiani DC (2007) Polymorphisms in the mannose binding lectin-2 gene and acute respiratory distress syndrome. Crit Care Med 35: 48–56
13. Flores C, Ma SF, Maresso K, Wade MS, Villar J, Garcia JG (2008) IL6 gene-wide haplotype is associated with susceptibility to acute lung injury. Transl Res 152: 11–17
14. Sutherland AM, Walley KR, Manocha S, Russell JA (2005) The association of interleukin 6 haplotype clades with mortality in critically ill adults. Arch Intern Med 165: 75–82
15. Zondervan KT, Cardon LR (2007) Designing candidate gene and genome-wide case-control association studies. Nat Protoc 2: 2492–2501
16. Flores C, Pino-Yanes Mdel M, Villar J (2008) A quality assessment of genetic association studies supporting susceptibility and outcome in acute lung injury. Crit Care 12: R130

17. Gao L, Barnes KC (2009) Recent advances in genetic predisposition to clinical acute lung injury. Am J Physiol Lung Cell Mol Physiol 296: L713–725
18. Meyer NJ, Li M, Shah CV, et al (2009) Large scale genotyping in an African American trauma population identifies angiopoietin-2 variants associated with ALI. Am J Respir Crit Care Med 179: A3879 (abst)
19. Meyer NJ, Sheu CC, Li M, et al (2010) IL1RN polymorphism is associated with lower risk of acute lung injury in two separate at-risk populations Am J Respir Crit Care Med 181: A1023 (abst)
20. Chanock SJ, Manolio T, Boehnke M, et al (2007) Replicating genotype-phenotype associations. Nature 447: 655–660
21. Glavan BJ, Holden TD, Goss CH, et al (2011) Genetic variation in the FAS gene and associations with acute lung injury. Am J Respir Crit Care Med (in press)
22. Sapru A, Hansen H, Ajayi T, et al (2009) 4G/5G polymorphism of plasminogen activator inhibitor-1 gene is associated with mortality in intensive care unit patients with severe pneumonia. Anesthesiology 110: 1086–1091
23. Madach K, Aladzsity I, Szilagyi A, et al (2010) 4G/5G polymorphism of PAI-1 gene is associated with multiple organ dysfunction and septic shock in pneumonia induced severe sepsis: prospective, observational, genetic study. Crit Care 14:R79
24. Christie JD, Ma SF, Aplenc R, et al (2008) Variation in the myosin light chain kinase gene is associated with development of acute lung injury after major trauma. Crit Care Med 36: 2794–2800
25. Arcaroli JJ, Hokanson JE, Abraham E, et al (2009) Extracellular superoxide dismutase haplotypes are associated with acute lung injury and mortality. Am J Respir Crit Care Med 179: 105–112
26. Gong MN, Thompson BT, Williams PL, et al (2006) Interleukin-10 polymorphism in position -1082 and acute respiratory distress syndrome. Eur Respir J 27: 674–681
27. Medford AR, Keen LJ, Bidwell JL, Millar AB (2005) Vascular endothelial growth factor gene polymorphism and acute respiratory distress syndrome. Thorax 60: 244–248
28. Su L, Zhai R, Sheu CC, et al (2009) Genetic variants in the angiopoietin-2 gene are associated with increased risk of ARDS. Intensive Care Med 35: 1024–1030
29. dos Santos CC, Okutani D, Hu P, et al (2008) Differential gene profiling in acute lung injury identifies injury-specific gene expression. Crit Care Med 36: 855–865
30. Kanehisa M, Goto S (2000) KEGG: kyoto encyclopedia of genes and genomes. Nucleic Acids Res 28: 27–30
31. Ashburner M, Ball CA, Blake JA, et al (2000) Gene ontology: tool for the unification of biology. The Gene Ontology Consortium. Nat Genet 25: 25–29
32. Huang DW, Sherman BT, Lempicki RA (2008) Systematic and integrative analysis of large gene lists using DAVID bioinformatics resources. Nat Protocols 4: 44–57
33. Grigoryev DN, Ma SF, Irizarry RA, Ye SQ, Quackenbush J, Garcia JG (2004) Orthologous gene-expression profiling in multi-species models: search for candidate genes. Genome Biol 5: R34
34. Ye SQ, Simon BA, Maloney JP, et al (2005) Pre-B-cell colony-enhancing factor as a potential novel biomarker in acute lung injury. Am J Respir Crit Care Med 171: 361–370
35. Leikauf GD, Pope-Varsalona H, Concel VJ, et al (2010) Functional genomics of chlorine-induced acute lung injury in mice. Proc Am Thorac Soc 7: 294–296
36. Wang Z, Beach D, Su L, Zhai R, Christiani DC (2008) A genome-wide expression analysis in blood identifies pre-elafin as a biomarker in ARDS. Am J Respir Cell Mol Biol 38: 724–732
37. Howrylak JA, Dolinay T, Lucht L, et al (2009) Discovery of the gene signature for acute lung injury in patients with sepsis. Physiol Genomics 37: 133–139
38. Feero WG, Guttmacher AE, Collins FS (2010) Genomic medicine--an updated primer. N Engl J Med 362: 2001–2011
39. Frazer KA, Ballinger DG, Cox DR, et al (2007) A second generation human haplotype map of over 3.1 million SNPs. Nature 449: 851–861
40. McClellan J, King MC (2010) Genetic heterogeneity in human disease. Cell 141: 210–217
41. McCarthy MI, Abecasis GR, Cardon LR, et al (2008) Genome-wide association studies for complex traits: consensus, uncertainty and challenges. Nat Rev Genet 9: 356–369

42. Keating BJ, Tischfield S, Murray SS, et al (2008) Concept, design and implementation of a cardiovascular gene-centric 50 k SNP array for large-scale genomic association studies. PLoS ONE 3: e3583
43. Christie JD, Wurfel MM, O'Keefe GE, et al (2010) Genome wide association (gwa) identifies functional susceptibility loci for acute lung injury Am J Respir Crit Care Med 181: A1025. (abst)
44. Wurfel MM, Christiani D, Christie JD, et al (2009) Genetic risks for ALI in the ARDSnet and iSPAAR consortium. Grant award from the National Heart Lung and Blood Institute of the National Institutes of Health
45. Manolio TA, Collins FS, Cox NJ, et al (2009) Finding the missing heritability of complex diseases. Nature 461: 747–753
46. Ng PC, Kirkness EF (2010) Whole genome sequencing. Methods Mol Biol 628: 215–226
47. Ng SB, Buckingham KJ, Lee C, et al (2010) Exome sequencing identifies the cause of a mendelian disorder. Nat Genet 42: 30–35
48. Cookson W, Liang L, Abecasis G, Moffatt M, Lathrop M (2009) Mapping complex disease traits with global gene expression. Nat Rev Genet 10: 184–194
49. Wurfel MM, Gordon AC, Holden TD, et al (2008) Toll-like receptor 1 polymorphisms affect innate immune responses and outcomes in sepsis. Am J Respir Crit Care Med 178: 710–720
50. Dixon AL, Liang L, Moffatt MF, et al (2007) A genome-wide association study of global gene expression. Nat Genet 39: 1202–1207

Use of B-type Natriuretic Peptides in Acute Exacerbation of Chronic Obstructive Pulmonary Disease Requiring Ventilatory Support

F. Dachraoui, L. Ouanes-Besbes, and F. Abroug

III

Introduction

Chronic obstructive pulmonary disease (COPD) is expected to become the third leading cause of death by 2020 [1]. Acute exacerbation of COPD is the most frequent reason for emergency room attendance and hospital admission. It accounts for most of the burden related to the disease, including healthcare costs, social impact, and mortality [2]. Biomarkers, such as natriuretic peptides, have the advantage of being easy to obtain at affordable cost. B-type natriuretic peptide (BNP) is a 32-amino acid peptide that is released following the cleavage of pro-BNP into the biologically active BNP, and the inactive amino terminal NT-proBNP [3]. BNP and NT-proBNP are closely correlated to each other and change in parallel. NT-pro BNP has a longer half-life than BNP with plasma levels 2 – 10 times higher than those of BNP [4]. Both are detectable in plasma and, therefore, have the potential to serve as indicators of heart failure. BNP and NT-proBNP are released into the bloodstream in response to ventricular increase in volume or pressure. BNP is the sole biologically active peptide. It increases myocardial relaxation and opposes the activation of the renin-angiotensin-aldosterone system with effects against vasoconstriction, sodium retention, and diuretic effects [3]. The diagnostic usefulness of measuring plasma levels of BNP and NT-proBNP in patients presenting to the emergency department (ED) with dyspnea is now well established [5]. High levels of natriuretic peptides accurately reflect left ventricular (LV) dysfunction and help distinguish acute dyspnea due to acute cardiac dysfunction from that of pulmonary origin. This paradigm has been extended to the setting of acute LV dysfunction superimposed on pre-existing or simultaneous right ventricular (RV) stress and/or hypoxemia. Circulating natriuretic levels are indeed above normal when hypoxemia, RV stress, or pulmonary hypertension are present [6]. Recent studies conducted in stable COPD patients or during acute exacerbations requiring ventilatory assistance, have shown that levels of natriuretic peptides remain accurate in the diagnosis of coexisting left heart dysfunction in stable COPD patients, during acute severe exacerbation, and during weaning difficulties from mechanical ventilation.

COPD and congestive heart failure (CHF) have common determinants (smoking and chronic inflammation) and are highly prevalent in the elderly where they can co-exist in the same patient. Indeed, the prevalence of COPD ranges from 20 to 32 % in patients with CHF [7 – 11], while in COPD patients the odds ratio of prevalence of CHF was 3.8 compared with age-matched controls without COPD [12]. Accordingly, unrecognized acute heart failure might be a cause of acute exacerbation of COPD, or a cause of weaning difficulties in COPD patients [8,

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13–19]. Recognition of this non-infectious cause of acute exacerbation of COPD precludes the use of antibiotics in such patients, and accelerates recovery by adequate treatment of heart failure. On the other hand, COPD patients ventilated for acute exacerbation are frequently difficult to wean from mechanical ventilation, related in many instances to overt LV dysfunction [20, 21].

The aim of this chapter is to appraise recent publications that have evaluated the diagnostic performance of natriuretic peptide levels in acute exacerbations of COPD, assessing their contribution to the diagnosis of the mechanism of exacerbation, and identification of weaning difficulties of cardiac origin.

Natriuretic Peptides in the Diagnosis of Left Heart Failure in COPD Patients

Measurement of plasma levels of natriuretic peptides is a sensitive and specific test to identify the cardiovascular or pulmonary origin of acute dyspnea. This issue has recently been reviewed using meta-analytic statistics [5]. Nine studies [22–30], mainly published between 2002 and 2004, which assessed the performance of either BNP or NT-proBNP in the diagnosis of heart failure in patients presenting with dyspnea to the ED were included in this meta-analysis [5]. All eligible studies used a cohort design where diagnosis of heart failure was based on the interpretation of available clinical data including echocardiography results. This meta-analysis clearly showed that in patients presenting with acute dyspnea, BNP and NT-proBNP have similar diagnostic performance characteristics, with clinical value. Specifically, their high sensitivity and low negative likelihood ratio, indicate that these peptides can be used to rule-out heart failure as a cause of acute dyspnea in the acute clinical setting. The pooled estimate of combined sensitivity of BNP and NT-proBNP assays was 0.96 (95 % CI 0.95, 0.98). The combined negative likelihood ratio was 0.07 (95 % CI: 0.04, 0.12) suggesting a high performance in ruling-out heart failure. However, the combined specificity of 0.69 (95 % CI: 0.56, 0.82) was lower than the combined sensitivity, as was the combined positive likelihood ratio, which was quite low at 3.28 (95 % CI: 2.34, 4.61). However, there is no easily identifiable optimal cut-off value for each peptide. Currently, cut-off levels of 100 pg/ml for BNP and 450 pg/ml for NT-proBNP are recommended for ruling in a diagnosis of acute CHF. Levels of 50 pg/ml for BNP and 300 pg/ml for NT-proBNP are accurate in ruling out the diagnosis of acute CHF in ED attendees with dyspnea [4, 6].

In addition to LV stress, BNP secretion might be secondary to hypoxemia, which impedes natriuretic peptide clearance in COPD patients [31]. Moreover, pulmonary hypertension and RV stress, which are usually present in COPD exacerbations, are associated with the release of peptides from the right ventricle [32]. Accordingly, BNP levels are five-fold greater in stable COPD patients than in healthy controls [33]. These levels are even higher in hypoxemic COPD patients, and in those with pulmonary hypertension [34–36].

Several studies have evaluated the accuracy of natriuretic peptide measurements in the diagnosis of CHF among COPD patients. Morrison et al. evaluated the performance of BNP measurements in the diagnosis of a cardiac origin of acute dyspnea in 321 patients presenting to the emergency department [37]. Among the subset of patients with a history of lung disease (asthma or COPD) but whose current complaint of dyspnea was due to CHF (diagnosed using the

Framingham criteria), BNP levels were markedly elevated. In contrast, BNP levels were only slightly elevated in patients with uncomplicated COPD or asthma [37].

In an ancillary report from the Breathing Not Properly (BNP) multicenter study, McCullough et al. assessed the accuracy of BNP in identifying new-onset heart failure in the subset of patients with COPD and/or asthma, who presented to the ED with dyspnea [38]. The diagnosis of CHF was adjudicated by independent cardiologists who were blinded to BNP results. Eighty-seven of 417 patients (20.9 %) had CHF. These patients had significantly higher levels of BNP. A cut-off of 100 pg/ml had good accuracy for ruling out a diagnosis of CHF (negative likelihood ratio, 0.09).

Rutten et al. compared the ability of different BNP assays to identify heart failure in 200 stable COPD patients (aged ≥ 65 years) [39]. A final diagnosis of heart failure was established on the basis of history, physical examination, and echocardiographic results. Unrecognized heart failure was diagnosed in 51 of 200 included COPD patients (25.5 %). BNP and NT-proBNP assays performed equally for diagnosing heart failure. All assays were much better at excluding than detecting heart failure. The optimal cut-off points to rule-out heart failure were 35 pg/ml for BNP and 125 pg/ml for NT-proBNP. Due to low positive predictive values, the overall diagnostic ability of the BNP assays was moderate in identifying heart failure patients with moderate LF dysfunction (i.e., LV ejection fraction [LVEF] < 30 – 45 %), and poor for identifying those with isolated diastolic heart failure. Of interest, there was no relationship between severity of COPD (assessed by GOLD classification) and the presence of heart failure. Instead, BNP levels increased with severity of LV dysfunction (evaluated by decreasing LVEF).

Abroug et al. assessed the accuracy of NT-proBNP in the diagnosis of left heart dysfunction in the specific setting of severe COPD exacerbation requiring ventilatory support, which usually associates severe hypoxemia, hypercapnia, acute right heart failure and pulmonary hypertension [13]. These authors included 148 consecutive patients without known CHF history, who were admitted to the ICU with severe exacerbation of COPD necessitating ventilatory support [13]. In these patients, left heart failure was diagnosed by an expert panel on the basis of clinical history, physical examination, and the results of transthoracic echocardiographic examination. Patients had severe COPD as indicated by the median forced expiratory volume (FEV, 0.7 l/sec) and the frequency of core pulmonale (40 %). All patients had ventilatory assistance either with non-invasive ventilation (63 %) or after tracheal intubation (37 %).

According to the experts' classification, left heart dysfunction was definitely present in 31 % patients and possible in an additional 13 %. It was excluded in the remaining 56 %. The area under the receiver operating characteristic (ROC) curve, which estimates the overall accuracy of NT-proBNP, was 0.95. NT-proBNP performed better to rule-out the association of left heart failure than to rule-in this diagnosis. The optimal cut-off point of NT-proBNP to rule-out the diagnosis of left heart failure was 1000 pg/ml, which had a negative likelihood ratio of 0.08. The proBNP cut-off point of 2500 pg/ml was quite accurate to rule-in the diagnosis of associated left heart failure with a positive likelihood ratio of 5.16. This study also showed that, in contrast to its good accuracy for the diagnosis of left heart failure, NT-proBNP levels performed poorly in the diagnosis of right heart failure in severe exacerbation of COPD (AUC= 0.53, NS). This finding was also confirmed by the multivariate analysis which disclosed the presence of left heart failure (and not of right heart failure) as a cause of increased NT-proBNP in this setting.

BNP and NT-proBNP in the Diagnosis of Left Heart Dysfunction in Difficult-To-Wean COPD Patients

Natriuretic peptide measurement has also proved useful in detecting left heart failure or dysfunction that impedes weaning from mechanical ventilation in COPD patients intubated for severe exacerbation. Ventilator-dependent COPD patients may potentially develop acute cardiac dysfunction during the attempt to restore spontaneous breathing [40]. This is usually due to the cardiovascular stress induced by the shift from positive to negative intrathoracic pressures during disconnection from the ventilator [16, 17]. Grasso et al. performed a study to evaluate the value of serial measurements of plasma NT-proBNP to detect acute cardiac dysfunction during weaning failure in difficult to wean patients with COPD [41]. These authors prospectively identified 19 patients who were mechanically ventilated for acute exacerbation of COPD and who had weaning difficulties (defined by failure in three consecutive spontaneous breathing trials [SBTs]), and without any prior history of CHF. NT-proBNP was measured at baseline (under mechanical ventilation), 2 hours, and 24 hours after a SBT. The diagnosis of heart failure was adjudicated by one cardiologist and one intensivist who were blind to the results of NT-proBNP levels. Diagnosis of heart failure was made on the basis of clinical and echocardiographic data (LV systolic and diastolic function, and pattern of LV wall motion). Upon the shift from mechanical ventilation to spontaneous breath, left heart dysfunction was uncovered in eight of the 19 included patients. Baseline NT-proBNP plasma levels were significantly higher in the group with acute cardiac dysfunction during the weaning trial (median 5000 pg/ml) than in the other group (median 1705 pg/ml). Compared with baseline, the NT-proBNP plasma level was significantly higher two hours after the start of the SBT in the eight patients with acute cardiac dysfunction during the weaning trial, whereas it remained unchanged in the other 11 patients. In comparison with anamnestic, cardiovascular (rate-pressure product, heart rate), or respiratory variables (frequency/tidal volume [f/V_T]), NT-proBNP levels were the sole indicator of the cardiovascular origin of weaning difficulties. Of interest, baseline NT-proBNP was not disclosed as a predictor of the cardiac origin of the weaning failure. The operative characteristics of a NT-proBNP cut-off of 198 pg/ml were of potential clinical interest both to rule-in or to rule-out the cardiac origin of weaning difficulties in COPD patients (specificity 91 % and positive predictive value 87.5 %, sensitivity 87.5 % and negative predictive value 91 %). The small sample size of the study precluded definitive conclusions regarding the accuracy of change in NT-proBNP plasma levels between mechanical ventilation and spontaneous breathing. This study should also not be regarded as definitively excluding the diagnostic utility of baseline NT-proBNP levels in the identification of patients with potential weaning difficulties related to LV dysfunction.

In this context, Mekontso-Dessap et al. conducted a prospective cohort study devised to explore the potential of plasma BNP to predict the failure of weaning from mechanical ventilation in a general population of a single medical ICU. This study showed that a baseline BNP level of 275 pg/ml had an accuracy of 85 % for this objective [42]. However, the study was not devised to address this question in the specific subset of COPD patients (which represented only 26 among 102 included patients).

More recently, Chien et al. [43] conducted a study similar to that of Mekontso-Dessap et al. [42] in a general ICU population. They found that rather than base-

line BNP levels, it was the increase (between the start and the end of a two-hour SBT) of these levels by less than 20 % that was able to predict extubation success with the best operative characteristics. Both studies provide an indication for the potential of BNP measurements to aid clinical decision making regarding whether or not to extubate a patient, but application in the specific setting of COPD patients, where the prevalence of LV failure is higher than in the general population and heart-lung interactions are more frequent and deeper, warrants further studies.

III

Natriuretic Peptide Performance as Prognostic Indicators in COPD Exacerbation Requiring Ventilatory Support

Natriuretic peptides have emerged in recent years as potential prognostic markers and independent predictors of outcome in unselected ICU patients [44, 45], in patients with septic shock [46], and in pulmonary diseases like pulmonary fibrosis [47].

We assessed the potential prognostic information derived from natriuretic peptide levels at ICU admission in patients with severe acute exacerbation of COPD requiring ventilatory support whether invasive or non-invasive (unpublished data). We measured NT-proBNP levels on ICU admission in 304 patients (mean age = 66 ± 10 years, 83 % men) who were consecutively admitted for severe adverse exacerbation of COPD (mean pH at admission: 7.29 ± 0.05) ascribed mainly to infectious origin (tracheobronchitis in 82 %), and requiring ventilatory support. Non-invasive ventilation was started in 68 % while the remaining 32 % underwent intubation on admission. Overall, ventilatory support lasted for 7.7 ± 5.2 days. The mean ICU stay was 11.7 ± 7.5 days with an overall ICU mortality of 17 %.

NT-proBNP levels were significantly higher in patients who eventually died compared to survivors (median [IQR] 9600 [16000] vs 746 [2292] pg/ml, $p < 0.0001$). The area under the ROC curve was 0.82 (**Fig. 1**). A cut-off value of

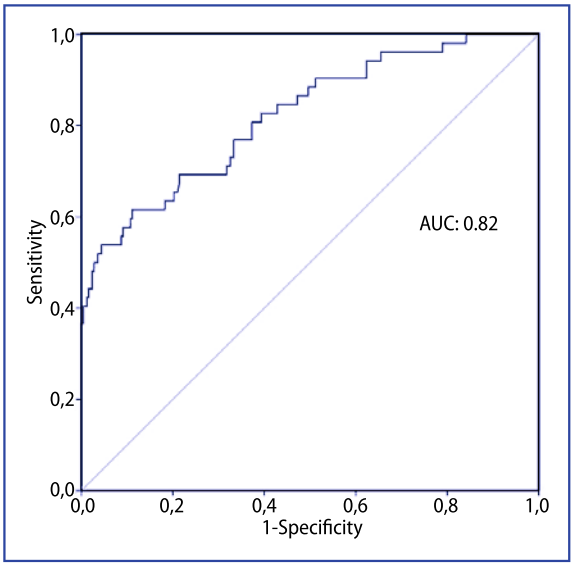

Fig. 1. Area under ROC curve for prediction of ICU mortality by NT-proBNP measurement at ICU admission.

2500 pg/ml predicted ICU mortality with 75 % specificity and a positive likelihood ratio of 2.7.

Conclusion

III

Elevated plasma levels of natriuretic peptides (BNP or NT-proBNP) are accurate in the diagnosis of coexisting left heart dysfunction in patients with COPD whether they are stable or during acute exacerbation. Thresholds are, however, more elevated than those reported in patients without chronic pulmonary disease. Moreover, natriuretic peptide measurement seems a promising tool to relate difficulties in weaning from mechanical ventilation to left heart dysfunction in COPD patients. Natriuretic peptides also carry valuable capabilities to identify COPD patients admitted to the ICU with a bad prognosis.

References

1. Murray CJ, Lopez AD (1997) Alternative projections of mortality and disability by cause 1990–2020: Global Burden of Disease Study. Lancet 349: 1498–1504
2. Mannino DM, Homa DM, Akinbami LJ, Ford ES, Redd SC (2002) Chronic obstructive pulmonary disease surveillance--United States, 1971–2000. MMWR Surveill Summ 51: 1–16
3. Daniels LB, Maisel AS (2007) Natriuretic peptides. J Am Coll Cardiol 50: 2357–2368
4. Maisel A (2006) The coming of age of natriuretic peptides: the emperor does have clothes! J Am Coll Cardiol 47: 61–64
5. Worster A, Balion CM, Hill SA, et al (2007) Diagnostic accuracy of BNP and NT-proBNP in patients presenting to acute care settings with dyspnoea: A systematic review. Clin Biochem 41: 250–259
6. Le Jemtel TH, Padeletti M, Jelic S (2007) Diagnostic and therapeutic challenges in patients with coexistent chronic obstructive pulmonary disease and chronic heart failure. J Am Coll Cardiol 49: 171–180
7. Rutten FH, Cramer MJ, Lammers JW, Grobbee DE, Hoes AW (2006) Heart failure and chronic obstructive pulmonary disease: An ignored combination? Eur J Heart Fail 8: 706–711
8. Rutten FH, Moons KG, Cramer MJ, et al (2005) Recognising heart failure in elderly patients with stable chronic obstructive pulmonary disease in primary care: cross sectional diagnostic study. BMJ 331: 1379
9. Havranek EP, Masoudi FA, Westfall KA, Wolfe P, Ordin DL, Krumholz HM (2002) Spectrum of heart failure in older patients: results from the National Heart Failure project. Am Heart J 143: 412–417
10. Masoudi FA, Havranek EP, Krumholz HM (2002) The burden of chronic congestive heart failure in older persons: magnitude and implications for policy and research. Heart Fail Rev 7: 9–16
11. Braunstein JB, Anderson GF, Gerstenblith G, et al (2003) Noncardiac comorbidity increases preventable hospitalizations and mortality among Medicare beneficiaries with chronic heart failure. J Am Coll Cardiol 42: 1226–1233
12. Curkendall SM, DeLuise C, Jones JK, et al (2006) Cardiovascular disease in patients with chronic obstructive pulmonary disease, Saskatchewan Canada cardiovascular disease in COPD patients. Ann Epidemiol 16: 63–70
13. Abroug F, Ouanes-Besbes L, Nciri N, et al (2006) Association of left-heart dysfunction with severe exacerbation of chronic obstructive pulmonary disease: diagnostic performance of cardiac biomarkers. Am J Respir Crit Care Med 174: 990–996
14. Lemaire F, Teboul JL, Cinotti L, et al (1988) Acute left ventricular dysfunction during unsuccessful weaning from mechanical ventilation. Anesthesiology 69: 171–179
15. Rutten FH, Cramer MJ, Grobbee DE, et al (2005) Unrecognized heart failure in elderly patients with stable chronic obstructive pulmonary disease. Eur Heart J 26: 1887–1894

16. Richard C, Teboul JL (2005) Weaning failure from cardiovascular origin. Intensive Care Med 31: 1605 – 1607
17. Teboul JL, Richard C (2006) How to diagnose weaning-induced pulmonary edema? Intensive Care Med 32: 938
18. Monnet X, Teboul JL, Richard C (2007) Cardiopulmonary interactions in patients with heart failure. Curr Opin Crit Care 13: 6 – 11
19. Jubran A, Mathru M, Dries D, Tobin MJ (1998) Continuous recordings of mixed venous oxygen saturation during weaning from mechanical ventilation and the ramifications thereof. Am J Respir Crit Care Med 158: 1763 – 1769
20. MacIntyre NR, Cook DJ, Ely EW Jr, et al (2001) Evidence-based guidelines for weaning and discontinuing ventilatory support: a collective task force facilitated by the American College of Chest Physicians; the American Association for Respiratory Care; and the American College of Critical Care Medicine. Chest 120: 375S-395S
21. Alia I, Esteban A (2000) Weaning from mechanical ventilation. Crit Care 4: 72 – 80
22. Lainchbury JG, Campbell E, Frampton CM, et al (2003) Brain natriuretic peptide and n-terminal brain natriuretic peptide in the diagnosis of heart failure in patients with acute shortness of breath. J Am Coll Cardiol 42: 728 – 735
23. Maisel AS, Krishnaswamy P, Nowak RM, et al (2002) Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. N Engl J Med 347: 161 – 167
24. Dao Q, Krishnaswamy P, Kazanegra R, et al (2001) Utility of B-type natriuretic peptide in the diagnosis of congestive heart failure in an urgent-care setting. J Am Coll Cardiol 37: 379 – 385
25. Ray P, Arthaud M, Lefort Y, Birolleau S, Beigelman C, Riou B (2004) Usefulness of B-type natriuretic peptide in elderly patients with acute dyspnoea. Intensive Care Med 30: 2230 – 2236
26. Villacorta H, Duarte A, Duarte NM, et al (2002) The role of B-type natriuretic peptide in the diagnosis of congestive heart failure in patients presenting to an emergency department with dyspnoea. Arq Bras Cardiol 79: 569 – 572, 564 – 568
27. Barcarse E, Kazanegra R, Chen A, Chiu A, Clopton P, Maisel A (2004) Combination of B-type natriuretic peptide levels and non-invasive hemodynamic parameters in diagnosing congestive heart failure in the emergency department. Congest Heart Fail 10: 171 – 176
28. Bayes-Genis A, Santalo-Bel M, Zapico-Muniz E, et al (2004) N-terminal probrain natriuretic peptide (NT-proBNP) in the emergency diagnosis and in-hospital monitoring of patients with dyspnoea and ventricular dysfunction. Eur J Heart Fail 6: 301 – 308
29. Jose JV, Gupta SN, Selvakumar D (2003) Utility of N-terminal pro-brain natriuretic peptide for the diagnosis of heart failure. Indian Heart J 55: 35 – 39
30. Logeart D, Saudubray C, Beyne P, et al (2002) Comparative value of Doppler echocardiography and B-type natriuretic peptide assay in the etiologic diagnosis of acute dyspnoea. J Am Coll Cardiol 40: 1794 – 1800
31. Klinger JR, Arnal F, Warburton RR, Ou LC, Hill NS (1994) Downregulation of pulmonary atrial natriuretic peptide receptors in rats exposed to chronic hypoxia. J Appl Physiol 77: 1309 – 1316
32. Nagaya N, Nishikimi T, Okano Y, et al (1998) Plasma brain natriuretic peptide levels increase in proportion to the extent of right ventricular dysfunction in pulmonary hypertension. J Am Coll Cardiol 31: 202 – 208
33. Bozkanat E, Tozkoparan E, Baysan O, Deniz O, Ciftci F, Yokusoglu M (2005) The significance of elevated brain natriuretic peptide levels in chronic obstructive pulmonary disease. J Int Med Res 33: 537 – 544
34. Lang CC, Coutie WJ, Struthers AD, Dhillon DP, Winter JH, Lipworth BJ (1992) Elevated levels of brain natriuretic peptide in acute hypoxaemic chronic obstructive pulmonary disease. Clin Sci (Lond) 83: 529 – 533
35. Bando M, Ishii Y, Sugiyama Y, Kitamura S (1999) Elevated plasma brain natriuretic peptide levels in chronic respiratory failure with cor pulmonale. Respir Med 93: 507 – 514
36. Ishii J, Nomura M, Ito M, et al (2000) Plasma concentration of brain natriuretic peptide as a biochemical marker for the evaluation of right ventricular overload and mortality in chronic respiratory disease. Clin Chim Acta 301: 19 – 30
37. Morrison LK, Harrison A, Krishnaswamy P, Kazanegra R, Clopton P, Maisel A (2002) Util-

ity of a rapid B-natriuretic peptide assay in differentiating congestive heart failure from lung disease in patients presenting with dyspnoea. J Am Coll Cardiol 39: 202 – 209
38. McCullough PA, Hollander JE, Nowak RM, et al (2003) Uncovering heart failure in patients with a history of pulmonary disease: rationale for the early use of B-type natriuretic peptide in the emergency department. Acad Emerg Med 10: 198 – 204
39. Rutten FH, Cramer MJ, Zuithoff NP, et al (2007) Comparison of B-type natriuretic peptide assays for identifying heart failure in stable elderly patients with a clinical diagnosis of chronic obstructive pulmonary disease. Eur J Heart Fail 9: 651 – 659
40. Ouanes-Besbes L, Ouanes I, Dachraoui F, Dimassi S, Mebazaa A, Abroug F (2011) Weaning difficult-to-wean chronic obstructive pulmonary disease patients: A pilot study comparing initial hemodynamic effects of levosimendan and dobutamine. J Crit Care (in press)
41. Grasso S, Leone A, De Michele M, et al (2007) Use of N-terminal pro-brain natriuretic peptide to detect acute cardiac dysfunction during weaning failure in difficult-to-wean patients with chronic obstructive pulmonary disease. Crit Care Med 35: 96 – 105
42. Mekontso-Dessap A, de Prost N, Girou E, et al (2006) B-type natriuretic peptide and weaning from mechanical ventilation. Intensive Care Med 32: 1529 – 1536
43. Chien JY, Lin MS, Huang YC, Chien YF, Yu CJ, Yang PC (2008) Changes in B-type natriuretic peptide improve weaning outcome predicted by spontaneous breathing trial. Crit Care Med 36: 1421 – 1426
44. Meyer B, Huelsmann M, Wexberg P, et al (2007) N-terminal pro-B-type natriuretic peptide is an independent predictor of outcome in an unselected cohort of critically ill patients. Crit Care Med 35: 2268 – 2273
45. Kotanidou A, Karsaliakos P, Tzanela M, et al (2009) Prognostic importance of increased plasma amino-terminal pro-brain natriuretic peptide levels in a large noncardiac, general intensive care unit population. Shock 31: 342 – 347
46. Sturgess DJ, Marwick TH, Joyce C, et al (2010) Prediction of hospital outcome in septic shock: a prospective comparison of tissue Doppler and cardiac biomarkers. Crit Care 14: R44
47. Song JW, Song JK, Kim DS (2009) Echocardiography and brain natriuretic peptide as prognostic indicators in idiopathic pulmonary fibrosis. Respir Med 103: 180 – 186

Acute Lung Injury in the ICU: Focus on Prevention

I. Galvin and N.D. Ferguson

III

Introduction

Acute lung Injury (ALI) is a syndrome characterized by the development of non-cardiogenic pulmonary edema and hypoxemia in response to a variety of predisposing acute illnesses and insults. Among patients admitted to hospital with predisposing conditions, those requiring intensive care likely have a particularly high risk of developing ALI [1]. The reported incidence of ALI occurring after admission to an intensive care unit (ICU), however, varies widely depending on the setting, study population, and study design [2–6]. A common confounding problem is distinguishing those who already have ALI at the time of ICU admission from those who develop it later. In studies of general ICU patients that have attempted to make this distinction, reported rates of ALI after ICU admission are between 5 and 20 % [2, 3].

ALI occurring after ICU admission is important for several reasons. First, the development of ALI is a serious complication for these patients; in addition to their original illness, they now acquire a condition that has few therapeutic options, significant mortality, and substantial survivor morbidity [7–9]. Second, late onset ALI carries a particularly poor prognosis with a higher mortality than patients admitted with ALI, and the number of days on mechanical ventilation before ALI onset is an independent predictor of mortality [10]. Third, and perhaps most importantly, if we can identify those at risk of developing ALI early enough, we may be able to alter their clinical course and so prevent ALI development and its associated morbidity. This window of intervention is clearly not open to us as intensivists when patients arrive with ALI at ICU admission, but we do have this opportunity for those patients already under our care in the ICU.

The 'two hit' model of ALI development describes a primary lung injury due to sepsis, pneumonia, etc, followed by a subsequent secondary insult resulting in further lung damage (**Fig. 1**) [11]. Many of these secondary insults are therapeutic interventions, including mechanical ventilation, blood products, and intravenous fluids [3, 6, 12–15]. An effective preventative strategy requires attention to both stages of this 'two hit' model. First stage prevention involves recognizing which primary insults are most strongly associated with development of ALI, so as to identify and define the at-risk population. Second stage prevention is about modifying therapeutic practice to reduce exposure to potentially injurious interventions.

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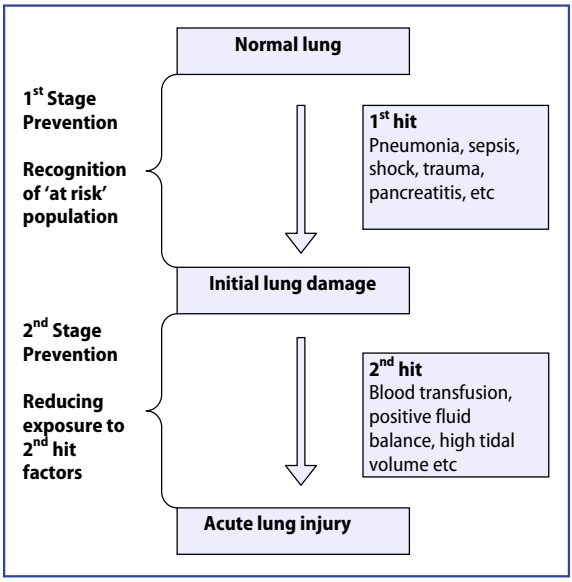

Fig. 1. Two hit model of acute lung injury development

Identifying the At-risk Population

The risk of developing ALI is not equally distributed among critically ill patients. It has long been recognized that certain acute illnesses carry a greatly increased risk of ALI [16, 17]. More recently there is emerging evidence that aside from acute conditions, particular premorbid characteristics influence the risk of ALI [18–21].

Acute Illnesses

There is substantial evidence supporting an increased rate of ALI with several predisposing acute illnesses [1, 4, 16, 17]. Many of these conditions are in themselves indications for admission to an ICU and are therefore particularly relevant to the risk of lung injury among the critically ill. Up to 44 % of patients admitted to an ICU with septic shock develop ALI [15]. Among patients with severe pneumonia, rates of ALI of nearly 47 % have been reported [1]. Conditions with a lesser but still substantial risk of lung injury include pancreatitis (33 %), requirement for massive transfusion (26 %), and multiple trauma (16 %) [1, 4]. In addition, although the numbers studied were small, over half of patients with pulmonary contusions or aspiration of gastric contents went on to develop ALI in one series [4].

Perhaps most concerning and of particular relevance in the context of the complex critically ill patient, is the finding that the risk of ALI increases linearly with the presence of increasing numbers of clinical predisposing conditions [1, 4] (**Fig. 2**).

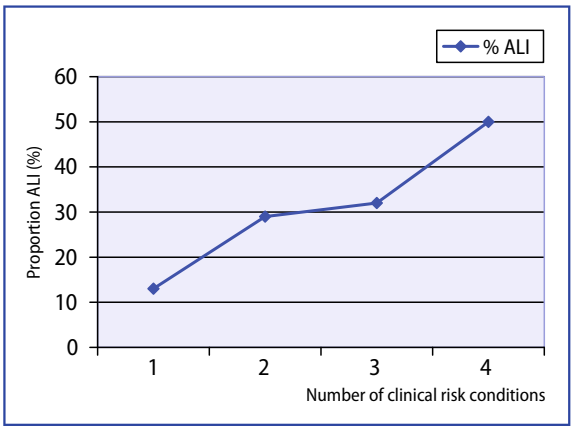

Fig. 2. Proportion of ALI according to number of clinical risk conditions. From [4] with permission

Premorbid Characteristics

There has been a recent resurgence of interest in the potential role of premorbid lifestyle choices and comorbidities in ALI development. Alcohol misuse has been implicated as a risk factor for ALI [18–20]. One of the first studies to demonstrate an association between alcohol misuse and ALI was a prospective observational study of over 350 critically ill patients, which showed that a history of alcohol abuse almost doubled the risk of lung injury [18]. The association between alcohol and ALI has been confirmed by a more recent study conducted by the same group [19]. Increased tissue vulnerability to oxidative stress because of chronic glutathione depletion has been proposed as a possible mechanism for alcohol-induced lung injury [20]. On the other hand, diabetes mellitus may have a protective effect against the development of ALI [21]. A prospective study of septic patients showed a reduced rate of ALI in diabetic as compared to non-diabetic patients [15]. The precise mechanisms are not yet defined and are likely to be mutifactorial. Whether the degree of glycemic control or intensity of insulin therapy has any effect on the risk of pulmonary injury remains to be established and may offer potential avenues for future risk reduction strategies.

Modifiable Therapeutic Practices

Clinical management can also influence a patient's risk of developing ALI. By definition, intensive care involves exposure to a high level and extent of medical treatment. Therefore, the population with the highest baseline clinical risk for ALI also includes those most likely to be exposed to interventions and practices that may further increase this risk. Changes in the way in which we treat the critically ill may substantially reduce the rate of ALI in these patients.

Mechanical Ventilation

Ventilator-induced lung injury (VILI) is essentially iatrogenic lung damage occurring due to a combination of mechanical disruption of the lung architecture and inflammatory changes caused by the distending and shearing forces of artificial

ventilation. The benefit of lower tidal volume ventilation to reduce the risk of VILI in those with established ALI is now well accepted. While the study that showed this benefit was performed in patients who already had ALI, it is important to remember that ALI itself is a heterogeneous condition and that the American-European Consensus Conference (AECC) definition of ALI lacks specificity [7, 22]. It is, therefore, likely that this study included a cohort with diverse pathophysiologies, many of whom did not have diffuse alveolar damage. This suggests that lower tidal volume ventilation may also have lung-protective effects in patients without established ALI.

Several studies of critically ill mechanically ventilated patients without ALI have demonstrated significant associations between ventilator settings and subsequent development of lung injury [12–14]. An observational study of over 300 patients ventilated for 48 h or more, found that 80 (24 %) patients who did not have ALI at the outset, developed it within 5 days of being ventilated [12]. The use of larger tidal volumes was significantly associated with the development of ALI (OR 1.3 for each ml above 6 ml/kg) (**Fig. 3**). This association was confirmed by the same group of investigators in a large international cohort who also showed that the proportion of patients who developed acute respiratory distress syndrome (ARDS) increased with tidal volumes above 700 ml and peak airway pressures above 30 cmH_2O [13].

The strength of the evidence implicating mechanical ventilation as a cause of ALI has lead to a debate on how best to ventilate patients who do not have ALI but are considered to be at risk [23–25] (**Table 1**). On the 'protectively ventilate all' side of the argument is the biological rationale that critically ill patients with an already heightened inflammatory response, altered capillary permeability, and primary lung injury, are particularly susceptible to VILI and so should be treated the same as those with established ALI [23]. The other side of the debate centers on the argument that lung protective ventilation has its own unwanted side effects, including hypercapnia-induced elevation of intracranial pressure and myocardial depression [24]. There is, however, general agreement that large tidal volumes should be avoided in patients considered to be at high risk of developing ALI [23–25]. Several questions remain unanswered, including: What is the ideal tidal volume in those at risk of ALI? To what extent should hypercapnia be tolerated in those without established ALI? What to do about the spontaneously

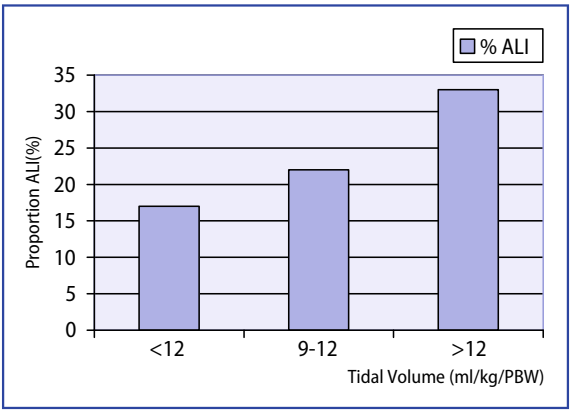

Fig. 3. Proportion of ALI according to tidal volume. PBW: predicted body weight. From [12] with permission

Table 1. Pros and cons of lower tidal volume ventilation in patients at risk of acute lung injury (ALI)

Pros	Cons
Proven mortality benefit in those with ALI.	Hypercapnia – Raised intracranial pressure, pulmonary hypertension, myocardial depression.
Reduced cytokine production.	Atelectasis – if not accompanied by moderate-high PEEP
Higher tidal volumes shown to be associated with increased risk of ALI.	Patients without established ALI do not have the characteristic 'baby lung' changes seen in ALI.
6 ml/kg tidal volumes are normal mammalian tidal volumes.	Patients may require more sedation +/– muscle relaxation.

breathing patient whose tidal volume exceeds 6 ml/kg? Deep sedation and muscle relaxation to achieve a target tidal volume may cause clinician discomfort in those with established ALI, let alone in those who have not yet developed the condition. One of the major challenges to providing answers to these questions is the extent to which individual opinion becomes the basis for decision making, in the absence of widely accepted evidence. This was highlighted recently by the premature termination of a randomized controlled trial of low tidal volume ventilation in patients without ALI, because of investigator discomfort with exposing the control arm to conventional tidal volumes [26].

Overall, given that we know that mechanical ventilation increases the risk of ALI, but we do not yet know how best to ventilate patients so as to minimize the risk, what should we do? There is obviously no easy answer to this question but there are some reasonable approaches. Individual risk of ALI needs to be taken into account when initiating mechanical ventilation. For high risk patients, smaller tidal volumes are probably more appropriate provided atelectasis and excessive acidosis are avoided or minimized. It is also worth remembering that low tidal volumes are in fact normal tidal volumes (based on healthy physiology) and that choosing tidal volume on the basis of actual rather than predicted body weight risks exposing women and shorter patients to potentially injurious volumes [25, 12]. Finally, it is important that we continue to seek to establish the ideal ventilator settings for these patients through both observational and randomized controlled trials.

Blood Products

There is now overwhelming evidence implicating blood products in the development of ALI [3, 6, 14, 15, 27] (**Table 2**). Zilberberg and colleagues showed that 67 % of patients with ARDS had received red cell transfusions as compared to 42 % of controls, and there was a dose response relationship between the quantity of blood transfused and the risk of ARDS, with the odds ratios increasing from 2 for one to two units to 3.9 for more than four units [27]. Gong and colleagues identified a significant association between packed red cell transfusion and ARDS development and perhaps more importantly a dose-dependent relationship between transfusion and mortality in ARDS [6]. Plasma rich products appear to carry the greatest risk of lung injury. A study of 841 critically ill patients showed that ALI was more likely to occur in those who received fresh frozen plasma (FFP) and platelets than in those who received red cells alone [3].

Table 2. Studies that have addressed the association between blood products and acute lung injury (ALI)

Author	Period	Design	Results
Gong [6]	1999 – 2002	Prospective observational	Red cell transfusion associated with an increased risk of ARDS (OR 1.52) and increased mortality in ARDS (OR 1.1 per unit transfused)
Zilberberg [27]	2000 – 2001	Retrospective case control	Red cell transfusion associated with increased risk of ARDS (OR 2 – 3.7)
Jia [14]	2001 – 2005	Retrospective	Transfusion of plasma associated with new onset ARDS (OR 1.26)
Khan [3]	2004 – 2005	Retrospective	ALI more likely in those who received FFP (OR 2.48) and platelets (OR 3.89) than in those receiving red cells alone (OR 1.39)
Yilmaz [34]	2005 – 2006	Before and after introduction of conservative tidal volume and transfusion protocol	Frequency of ALI decreased from 28 % – 10 %
Iscimen [15]	2004 – 2007	Prospective observational	Transfusion (OR 2.75) associated with development of ALI

ARDS: acute respiratory distress syndrome; FFP: fresh frozen plasma; OR: odds ratio

Transfusion-related acute lung injury (TRALI) is thought to be the end result of a series of events triggered by interaction between donor white blood cell antibodies and the corresponding recipient antigens. Biological response modifiers accumulated during storage of the blood products are also thought to play a role [28]. Both patient factors (1st hit) and transfusion factors (2nd hit) are likely to be important. A recent study showed that sepsis and chronic alcohol abuse were significant risk factors for TRALI as well as transfusion of plasma from female donors, numbers of pregnancies among donors, and numbers of units positive for anti-granulocyte and anti-HLA class II antibodies [28].

The increased awareness of the importance of blood constituents to the development of lung injury has led to international efforts to implement risk reduction policies for donated products. The UK National Transfusion Service has virtually eliminated high plasma volume components prepared from female donors, an initiative which seems to be yielding promising results [28, 29]. Similar policies were adopted by the American Association of Blood Banks in the United States in 2006 [30]. A survey performed 3 years later, revealed that these risk reduction measures are commonly implemented by most US blood centers but practices and procedures are not uniform [30].

While altering the constituents of donated blood to ameliorate the risk of ALI is an important part of overall ALI risk reduction, it is not and should not be the only approach. Consideration of recipient factors and clinical risk reduction are equally important. There are at least two current barriers in this regard. The first is a lack of evidence for certain transfusion practices. The second is an apparent lack of implementation of available evidence. The first issue was highlighted by a comprehensive review of the evidence for the use of FFP and platelets in the criti-

cally ill [31]. Having examined the literature in detail, the authors discovered that the current evidence for the use of FFP and platelets in the ICU consists largely of expert opinion, anecdotal experience, and extrapolation of findings from studies in cancer patients. There is a striking lack of good quality evidence as to the indications for using these products in the critically ill.

The second issue is one of knowledge translation. Despite the presence of high quality evidence in favor of a restrictive transfusion strategy [32] and the known link between blood products and lung injury [6], one study found that in established ARDS, 47 % of patients received a blood transfusion without evidence of either active bleeding or acute cardiac ischemia and 67 % were transfused above the recommended threshold of 7 g/dl [33].

Given the strength of the evidence for an association between blood products and ALI, reducing this risk alone is a large part of overall ALI risk reduction. Just how large this reduction may be was recently highlighted by a study comparing the frequency of ALI in critically ill patients before and after introduction of a combined low tidal volume/restrictive transfusion protocol [34]. The authors reported an 18 % reduction in the frequency of ALI after the protocol was implemented. This study is important for several reasons. It provides evidence that reduction in tidal volume and transfusion translates into actual reduction in ALI frequency. It also hints at the exciting possibility that multi-faceted interventions might have synergistic effects in ALI risk reduction, and finally it shows that substantial changes in clinical practice can be achieved through relatively simple interdisciplinary measures.

Fluid Balance

Increased extravascular lung water has been associated with worse outcome in patients with ARDS [35]. A large clinical trial comparing a conservative versus a liberal fluid protocol in ALI, found better lung function and fewer ventilated days in those in the conservative arm [36]. Subsequent secondary analysis of data from the ARDS Network tidal volume trial showed that a negative fluid balance on day 4 of ALI was associated with significantly lower mortality, independent of severity of illness [37]. However, this evidence does not tell which fluid management strategy is optimal in patients without established ALI, but with risk factors for its development. There are few studies directly addressing the role of fluid balance in ALI development. A retrospective analysis of 2583 mechanically ventilated patients showed that a high net fluid balance was a risk factor for ALI (odds ratio [OR] 1.3, 95 % confidence interval [CI] 1.1 – 1.6) [14]. However, patients who developed ALI and those who did not had large positive cumulative fluid balances (means of 10.6 and 6.7 liters, respectively), so these results may not accurately represent the risk associated with less positive fluid balances [14]. A recent study of patients with postoperative respiratory failure admitted to a surgical ICU reported a significant association between intraoperative fluid balance and subsequent ALI development [38]. However the numbers studied were small and the study was confined to surgical patients with respiratory failure, limiting its applicability to critically ill patients in general [38].

There is, therefore, a paucity of evidence to guide fluid management in the critically ill, so as to minimize the risk of ALI. This underscores the need for further research in this area. While awaiting more conclusive evidence, it is perhaps reasonable to avoid fluid overload in those considered to be at high risk of ALI. This does not, however, apply to the resuscitation period as discussed next.

Resuscitation Timelines

Iscimen and colleagues showed that delayed goal-directed resuscitation and delayed antibiotic treatment were significant risk factors for ALI development, among patients with septic shock [15]. Delayed antibiotic treatment was defined as failure to give adequate antibiotic treatment within 3 hours of the onset of septic shock. Delayed goal-directed resuscitation was defined as failure to achieve the following within the first 6 hours of the onset of septic shock: Central venous oxygenation saturation ≥ 70 % and/or a combination of central venous pressure > 8 mmHg, mean arterial blood pressure ≥ 65mmHg, urine output ≥ 0.5ml/kg/h and/or improvement in Glasgow Coma Scale (GCS), base deficit or lactate. The association between failure to achieve adequate resuscitation and subsequent development of ALI was very strong (OR 3.6, 95 % CI 1.5 – 8.6) [15]. It is important to note that the 6-hour window is a number chosen to represent a reasonable time frame in which to achieve resuscitation. The utility of this number lies in its relative rather than absolute interpretation, with the take home message being that resuscitation should be achieved without undue delay. As much of the resuscitation window is spent outside the ICU, the key to achieving these targets in practice is through good communication and collaboration with emergency department and ward staff.

Emerging Concepts and Possibilities

The following are some of the novel mechanisms that may play a role in the development of ALI, together with some potential preventative treatments (**Table 3**). Most studies of these areas have been confirmed to laboratory experiments and animal models; however, they have strong biological rationale and early human data are promising.

Table 3. Practical approach to reducing ALI risk in the critically ill

Modifiable Therapeutic Practice	Clinical Approach
Mechanical ventilation	Limit tidal volume to 6 – 8 ml/kg predicted body weight. Limit peak inspiratory pressure to < 30 cmH_2O. Use moderate PEEP as needed to avoid atelectasis.
Blood products	Limit the use of red cells to evidence based indications. Limit use of FFP and platelets to those who are actively bleeding.
Intravenous fluids	Maintain a neutral to negative fluid balance except in the presence of shock or in the resuscitation phase.
Resuscitation timelines	Achieve adequate repletion of circulating volume as soon as possible after the onset of shock. Prompt antibiotic treatment for suspected sepsis.
Amiodarone	Where possible, use alternative anti-arrhythmic. If amiodarone is required, use the minimally effective dose and duration.

Amiodarone

Amiodarone is a commonly used antiarrhythmic in critically ill patients. Adverse pulmonary effects occur in approximately 5 % of patients who receive amiodarone chronically [39]. Lung damage is thought to result from a combination of direct toxicity, immune mediated damage, and enzyme activation. Pathologically, amiodarone can produce many different patterns of tissue injury, including, lipoid pneumonia, eosinophilic pneumonia, fibrinous pneumonia, pulmonary nodules, and diffuse alveolar damage [39]. Since ALI is a clinical syndrome with no distinct pathological profile, it can be the end result of many of these processes. Amiodarone has been linked to the development of ARDS in postoperative patients and widespread lipoid pneumonia has been identified at post-mortem in patients who died of ARDS, having received amiodarone for more than 48 h [40, 41]. High inspired oxygen concentrations, higher cumulative dosages, iodinated contrast media, pre-existing lung disease, and older age have all been cited as increasing the likelihood of amiodarone-related pulmonary toxicity [39]. The role of amiodarone in ALI development requires further study. Observational studies may be key in the initial exploration of the link between this commonly used drug and ALI.

Gut Lymph Hypothesis of Multiple Organ Dysfunction

There is increasing evidence that in acute severe illness, the gut becomes a rich source of toxic substances and inflammatory mediators [42, 43]. Animal studies suggest that the mesenteric lymphatics play a central role in transporting these active factors to distant organs. This concept is called the 'gut lymph hypothesis' of multiple organ dysfunction and it has been implicated in the development of ALI [42, 43].

Deitch and colleagues used a primate model to determine under which circumstances mesenteric lymph is most likely to become toxic. They found that trauma and hemorrhagic shock produced lymph that caused lung injury in the animals studied and was cytotoxic to human cells [43]. Interestingly, lymph produced in the early phase of post-shock fluid resuscitation is particularly injurious to cells, suggesting that the ischemia-reperfusion process is central to the generation of toxic lymph [43]. The precise mechanism by which mesenteric lymph becomes toxic is unknown but gut ischemia, pancreatic protease-induced degradation of the mucus layer, bacterial translocation and release of inflammatory mediators are all thought to be important. It is likely that bowel ischemia and inflammation trigger a chain of events that result in the production of toxic lymph [44. 45]. As the lung is the first organ to be exposed to mesenteric lymph as it drains from the thoracic duct into the subclavian vein, it is not surprising that the lung is particularly vulnerable to the injurious effects of toxic lymph.

The important question is, what can we do clinically to reduce the toxicity of mesenteric lymph? One possibility comes from a clinical trial showing that early enteral nutrition (started within 6 hours of trauma-related shock) essentially prevented injury-related increases in gut permeability and reduced the incidence of subsequent organ failure compared to patients in whom enteral feeding was delayed by 24 hours or more [46]. Further clinical evidence purports possible beneficial effects of immune enhancing diets [47].

Anti–Platelet Therapy

A single center retrospective cohort study reported a reduced incidence of ALI in patients admitted to the ICU who were taking anti-platelet medication prior to admission to hospital [48]. Those taking drugs, such as aspirin and clopidrogel, had a much lower rate of ALI than those not taking these medications (12.7 versus 28 %), even when age and disease severity were taken into account. The authors suggest that anti-platelet medication may be protective against the development of ALI, but that further prospective studies are required [48]. Furthermore, in this study anti-platelet therapy was started before the onset of acute illness, therefore we do not know it has any protective effect if started after admission to hospital.

Activated Protein C

Activated protein C has several anti-inflammatory effects that may reduce the likelihood and severity of lung injury [49]. It prevents endothelial cell apoptosis and reduces macrophage activation. Much of the evidence for the role of activated protein C in attenuation of lung injury is from animal research [49]. Its practical application as a potential ALI-preventative agent in critically ill humans, including those with septic shock, remains to be established.

Conclusion

ALI is the end result of multiple insults superimposed on pre-existing lung damage, due to acute severe illness. Once established, the outcome is poor. It is, therefore, extremely important that we focus on preventing it from developing in the first instance. Patients admitted to the ICU have a high rate of ALI, with the risk being greatest for those with certain predisposing illnesses. Several of the treatments patients receive in the ICU further increase this risk. In light of this evidence, we need to reconsider the way in which we treat these patients and keep in mind our rationale and thresholds for using certain treatments. There is a pressing need for further research to guide the management of critically ill patients, so as to minimize their risk of lung injury. In the meantime, based on what we know already, there are several practical clinical approaches that are worth considering (**Table 3**).

References

1. Ferguson ND, Frutos- ivar F, Esteban A, et al (2007) Clinical risk conditions for acute lung injury in the intensive care unit and hospital ward: a prospective observational study. Crit Care 11: R96
2. The Irish Critical Care Trials Group (2008) Acute lung injury and acute respiratory distress syndrome in Ireland: a prospective audit of epidemiology and management. Crit Care 12: R30
3. Khan H, Belshar J, Yilmaz M, et al (2007) Fresh frozen plasma and platelet transfusions are associated with development of acute lung injury in critically ill medical patients. Chest 131: 1308 – 1314
4. Oliveria R, Filho A (2006) Incidence of acute lung injury and acute respiratory distress syndrome in the intensive care unit of a university hospital: a prospective observational study. J Bras Pneumol 32: 35 – 42

5. Brun-Buisson C, Minelli C, Bertolini G, et al (2004) Epidemiology and outcome of acute lung injury in European intensive care units. Results from the ALIVE Study. Intensive Care Med 30: 51 – 61
6. Gong M N, Taylor Thompson B, Williams P, Potheir L, Boyce PD, Christiani DC (2005) Clinical predictors of and mortality in acute respiratory distress syndrome: Potential role of red cell transfusion. Crit Care Med 33: 1191 – 1198
7. The Acute Respiratory Distress Syndrome Network (2000) Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and acute respiratory distress syndrome. N Engl J Med 342: 1301 – 1308
8. Rubenfeld GD, Herridge MS (2007) Epidemiology and outcomes of acute lung injury. Chest 131: 554 – 562
9. Herridge MS, Cheung AM, Tansey CM, et al (2003) One-year outcomes in survivors of acute respiratory distress syndrome. N Engl J Med 348: 683 – 693
10. Ferguson ND, Frutos–Vivar F, Esteban A , et al (2005) Airway pressures, tidal volumes and mortality in patients with acute respiratory distress syndrome. Crit Care Med 33: 21 – 30
11. Matthay MA, Zimmerman GA, Esmon C, et al (2003) Future research direction in acute lung injury: summary of a National Heart, Lung and Blood Institute working group. Am J Respir Crit Care Med 167: 1027 – 1035
12. Gajic O, Dara SI, Mendez JL, et al (2004) Ventilator associated lung injury in patients without acute lung injury at the onset of mechanical ventilation. Crit Care Med 32: 1817 – 1824
13. Gajic O, Frutos–ivar F, Esteban A,Hubmayer RD, Anzueto A (2005) Ventilator settings as a risk factor for acute respiratory distress syndrome. Intensive Care Med 31: 922 – 926
14. Jia X, Malhorta A, Saeed M, Mark RJ, Talmor D (2008) Risk factors for ARDS in patients receiving mechanical ventilation for > 48hrs. Chest 133: 853 – 861
15. Iscimen R, Cartin Ceba R, Yilmaz M, et al (2008) Risk factors for the development of acute lung injury in patients with septic shock: a prospective observational study. Crit Care Med 36: 1518 – 1522
16. Pepe PE, Potkin RT, Reus DH, Hudson LD, Carrico CJ (1982) Clinical predictors of acute respiratory distress syndrome. Am J Surg 144: 124 – 130
17. Fowler AA, Hamman RF, Good JT, et al (1993) Adult respiratory distress syndrome: risk with common predispositions. Ann Intern Med 98: 593 – 597
18. Moss M, Bucher B, Moore FA, Moore EE, Parsons PE (1996) The role of chronic alcohol abuse in the development of acute respiratory distress syndrome in adults. JAMA 275: 50 – 54
19. Moss M, Parsons PE, Steinberg KP, et al (2003) Chronic alcohol abuse is associated with an increased incidence of acute respiratory distress syndrome and severity of multiple organ dysfunction in patients with septic shock. Crit Care Med 31: 869 – 877
20. Esper A, Burnham EL, Moss M (2006) The effect of alcohol abuse on ARDS and multiple organ dysfunction. Minerva Anestesiol 72: 375 – 381
21. Honiden S, Gong MN (2009) Diabetes, insulin and development of acute lung injury. Crit Care Med 37: 2455 – 2464
22. Frutos-Vivar F, Ferguson ND, Esteban A (2006) Epidemiology of acute lung injury and acute respiratory distress syndrome. Semin Respir Crit Care Med 27: 327 – 336
23. Schultz MJ, Haitsma JJ, Slutsky AS, Gajic O (2007) What tidal volumes should be used in patients without acute lung injury? Anesthesiology 106: 1226 – 1231
24. Putensen C (2007) Tidal volumes in patients with normal lungs: One for all or the less, the better? Anesthesiol 106: 1085 – 1087
25. Schultz MJ (2008) Lung-protective mechanical ventilation with lower tidal volumes in patients not suffering from acute lung injury: A review of clinical studies. Med Sci Monit 14: RA22 – 26
26. Determann RM, Royakkers A, Wolthius EK, et al (2010) Ventilation with lower tidal volumes as compared to conventional tidal volumes for patients without acute lung injury: a preventative randomized controlled trial. Crit Care 14: R1
27. Zilberberg MD, Carter C, Lefebrve P, et al (2007) Red blood cells transfusion and the risk of acute respiratory distress syndrome among the critically ill: a cohort study. Crit Care 11: R63

III

28. Gajic O, Rana R, Winters JL, et al (2007) Transfusion related acute lung injury in the critically ill. Prospective nested case-control study. Am J Respir Crit Care Med 176: 886–891
29. Hume HA (2009) TRALI: moving towards prevention. Transfusion 49: 402–405
30. Kleinman S, Grossman B, Kopko P (2010) A national survey of transfusion-related acute lung injury risk reduction policies for platelets and plasma in the United States. Transfusion 50: 1312–1321
31. Gajic O, Dzik WH, Toy P (2006) Fresh frozen plasma and platelet transfusion for nonbleeding patients in the intensive care unit: Benefit or harm? Crit Care Med 34: S170–173
32. Herbert PC, Wells G, Blajchman MA, et al (1999) A multicentre, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion requirements in critical care investigators, Canadian Critical Care Trials Group. N Engl J Med 340: 409–417
33. Murphy DJ, Howard D, Muriithi A, et al (2009) Red blood cell transfusion practices in acute lung injury: What do patient factors contribute? Crit Care Med 36: 1935–1940
34. Yilmaz M, Keegan MT,Iscimen R,et al (2007) Protocol-guided limitation of large tidal volume ventilation and inappropriate transfusion. Crit Care 35: 1660–1666
35. Lewis CA, Martin GS (2004) Understanding and managing fluid balance in patients with acute lung injury. Curr Opin Crit Care 10: 13–17
36. Weidemann HP, Wheeler AP, Bernard GR, et al (2006) National Heart, Lung and Blood Institute ARDS Clinical Trials Network Comparison of two fluid management strategies in acute lung injury. N Engl J Med 354: 2564–2575
37. Rosenberg AL, Dechert RE, Park PK, Bartlett RH (2009) Review of a large clinical series: association of cumulative fluid balance on outcome in acute lung injury: a retrospective review of the ARDSnet tidal volume study cohort. J Intensive Care Med 24: 35–36
38. Hughes CG, Weavind L, Banerjee A, Mercaldo N, Schildcrout JS, Pandharipande PP (2010) Intraoperative risk factors for acute respiratory distress syndrome in critically ill patients. Anesth Analg 111: 464–467
39. Papiris SA, Triantafillidou C, Kolilekas L, Markoulaki D, Manali ED (2010) Amiodarone: review of pulmonary effects and toxicity. Drug Saf 33: 539–558
40. Greenspon AJ, Kidwell GA, Hurley W, Mannion J (1991) Amiodarone-related postoperative adult respiratory distress syndrome. Circulation 84: 407–415
41. Donaldson L, Grant IS, Naysmith MR, Thomas JS (1998) Acute amiodarone-induced lung toxicity. Intensive Care Med 24: 626–630
42. Johnston TD, Fischer R, ChenY, Reed RL (1993) Lung injury from gut ischemia: Insensitivity to portal blood flow diversion. J Trauma 35: 508–511
43. Dietch EA, Forsythe R, Anjara D, et al (2004) The role of lymph factors in lung injury, bone marrow suppression and endothelial cell dysfunction in a primate model of trauma–hemorrhagic shock. Shock 22: 221–228
44. Caputo FJ, Rupani B, Watkins AC, et al (2007) Pancreatic duct ligation abrogates the trauma hemorrhage induced gut barrier failure and the subsequent production of biologically active intestinal lymph. Shock 28: 441–446
45. Dietch EA. (2001) Role of the gut lymphatic in multiple organ failure. Curr Opin Crit Care 7: 92–98
46. Kompan L, Kremzar B, Gadzijev E, Prosek M (1999) Effects of early enteral nutrition on intestinal permeability and the development of multiple organ failure after multiple trauma. Intensive Care Med 25: 157–161
47. Galban C, Montejo JC, Mesejo A, et al (2008)An immune enhancing enteral diet reduces mortality rate and episodes of bacteremia in septic intensive care unit patients. Crit Care Med 28: 643–648
48. Erlich JM, Talmor DS, Cartin-Ceba R, Gajic O, Kor DJ (2011) Pre-hospitalization antiplatelet therapy is associated with a reduced incidence of acute lung injury: A population-based cohort study. Chest (in press)
49. Abraham E (2010) Inhaled activated protein C: A new therapy for the prevention of ventilator-induced lung injury? Crit Care 14: 144

IV Endotracheal Intubation

Rapid Sequence Intubation: Overview and Myths Versus Facts

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IV

Introduction

Endotracheal intubation is one of the skills in which emergency medicine, anesthesiology, and critical care physicians take pride. Outside the operating room (OR), it is performed daily in a variety of settings including pre-hospital, emergency departments (ED), and intensive care units (ICU). For emergency medicine physicians and intensivists, this was not the case as late as the 1970s, when medications used in the OR for intubation were not yet available. In 1979, Taryle and colleagues reported that complications occurred in 24 of 43 patients intubated in a university hospital ED. They called for improved training in endotracheal intubation outside of the OR, as well as use of OR approaches such as sedation and muscle relaxation [1]. The answer to this call came with expansion of training in intubation and introduction of rapid sequence intubation outside of the OR.

This expansion, in addition to the availability of newer more potent drugs, increased the success rate for intubations with a greater than 90 % success rate reported in most modern series [2]. This chapter is an overview of rapid sequence intubation with a description of current practices and the evidence behind them.

Why and What is Rapid Sequence Intubation?

Despite the similarities, airway control in the ED and ICU is not the same as planned intubation prior to general anesthesia. In fact, intubations in the ED and ICU are invariably performed emergently, typically without the chance to obtain an adequate history. Some patients are in a respiratory distress or cardiorespiratory arrest state. Other patients are agitated, in distress, and frequently not fasting. A rapid and effective mechanism is needed to sedate patients and achieve muscle relaxation prior to the procedure.

Rapid sequence intubation is the administration, after pre-oxygenation, of a potent hypnotic (induction agent), followed immediately by a rapidly acting neuromuscular blocking agent before endotracheal intubation [3]. Walls and Murphy describe in their "Manual of Emergency Airway Management" the 7 Ps of rapid sequence intubation: **P**reparation, **P**re-oxygenation, **P**retreatment, **P**aralysis with induction, **P**ositioning, **P**lacement, and **P**ost-intubation management [3].

1. **P**reparation is key. The operator needs to make sure that the necessary equipment is available. This includes a bag-valve mask connected to an oxygen

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delivery system, a suction catheter, endotracheal tubes of different sizes with intact cuff(s), a stylette, a syringe, and a laryngoscope with working blades of different sizes. In the experience of the authors, the routine use of surgical lubrication on the tip of the endotracheal tube also helps to facilitate the procedure. In addition, it is optimal if the patient has at least one secure and functioning intravenous catheter, and is connected to a cardiac monitor and pulse oximetry. It is also recommended that a 'secondary' setup be available for a surgical airway should it be required.

2. **P**reoxygenation with 100 % oxygen for 2–3 minutes should be performed, preferably by application of a bag-valve mask. It is best to avoid 'bagging' unless hypoxia develops or it becomes necessary between intubation attempts. The intent is to denitrogenize the lungs and to establish an oxygen reservoir, allowing the availability of several minutes of apnea time before hemoglobin saturation drops to less than 90 % [3]. Theoretically, saturations above 90 % should persist for up to 8 minutes in a healthy well pre-oxygenated adult, but frequently this is not the case as patients have pre-existing conditions such as pneumonia, chronic obstructive pulmonary disease (COPD), and pulmonary edema. Children, obese patients, and pregnant women desaturate much more rapidly because of their decreased functional residual capacity (FRC).
3. **P**retreatment is the administration of drugs to minimize the adverse effects associated with intubation or the patient's underlying comorbidities. This is discussed later in the text.
4. **P**aralysis with induction involves administration of a rapid-acting hypnotic followed by a paralyzing agent in order to achieve loss of consciousness and muscle relaxation. This will also be discussed in detail later in the text, with a focus on some of the induction and neuromuscular blocking agents.
5. **P**ositioning is paramount. This step is one of the most crucial for successful intubation. In order to achieve the best view of the epiglottis and vocal cords, the bed should be at the level of the operator's xiphoid bone. The head of the patient needs to be in a 'sniffing position' (as if sniffing air), with neck flexed and head extended [4]. Raising the occiput of the adult patient 5–10 cm with a towel or a similar device, then extending the head achieves this position. In the case of a child (more than one year of age), there is no need to elevate the occiput because of the proportionally larger size of the head. For an infant (less than 1 year of age), slight elevation of the shoulders will improve visualization. Cricoid pressure is routinely applied once the patient is unconscious. This maneuver will be discussed later in the text.
6. **P**lacement includes endotracheal intubation, inflation of the cuff, and confirmation of tube location. Visualization of the tube going through the vocal cords is the strongest support for initial proper placement. This should be combined with 5-point auscultation (bilateral anterior chest, bilateral mid-maxillary and epigastric), visualization of chest rise, calorimetric end-tidal CO_2 detection and, eventually, secondary confirmation with chest radiography to rule out main stem bronchus intubation [5]. In the event of a cardiac arrest and prolonged resuscitation, the esophageal detector device ('bulb') may be used instead of the CO_2 detector, as the latter is prone to false-negative results despite proper tracheal intubation. This is because of lack of circulation and gas exchange. Finally, the endotracheal tube should be secured.
7. **P**ost-intubation management and sedation is beyond the scope of this discussion.

Pre-hospital Rapid Sequence Intubation

A controversy exists as to the use of rapid sequence intubation in the pre-hospital setting. There were several papers in the 1990s and 2000s that attempted to shed light on this controversy. Some studies, such as the more recent one by Fakhry et al. in 2006 [6], found in a retrospective review of 175 patients transported by flight paramedics, that 169 (96.6 %) of patients were successfully intubated with rapid sequence intubation at the scene. The success rate was 70 % upon first attempt and 89 % by the second attempt and the rates of complications were under 5 %. The authors concluded that their high success and low complication rates were "comparable to rates for in-hospital airway management", and therefore that rapid sequence intubation was a safe and effective pre-hospital procedure [6]. Another study that looked at rapid sequence intubation performed by air transport personnel was by Pearson in 2003 [7]. Taking a slightly different approach, he compared variables in 70 patients intubated prior to the institution of a paramedic rapid sequence intubation protocol in 2001 and 70 patients who were intubated after institution of the rapid sequence intubation protocol. Success rate for first attempt was 65.7 % in the pre-rapid sequence intubation group compared with 79.3 % in the rapid sequence intubation group. The time between medication administration and intubation went from 5.1 minutes in the pre-rapid sequence intubation group to 2.1 minutes in the rapid sequence intubation group. There was no significant difference in the time spent on the scene [7]. It is important to consider outcomes beyond the intubation itself. Do patients intubated by paramedics experience comparable morbidity and mortality? In 2003, Davis et al. [8] matched each of 209 patients who had undergone paramedic rapid sequence intubation for traumatic brain injury with non-intubated hand-matched controls from their trauma registry. Each rapid sequence intubation patient and his/her controls were matched on the basis of age, sex and mechanism of injury as well as several measurements of injury severity scores. The rapid sequence intubation patients had higher mortality rates (33.0 %) when compared with controls (24.2 %) and a lower rate of "good outcomes" (45.5 % versus 57.9 %), defined as "discharge to home, rehabilitation, psychiatric facility, jail, or signing out against medical advice" [8].

It is difficult to conclude whether rapid sequence intubation should be performed in the current day pre-hospital setting. A better understanding of outcome differences and what specific factors are unique to pre-hospital, as opposed to hospital, conditions is needed. The studies which showed good success rates of rapid sequence intubation and intubation in the pre-hospital setting may have relied heavily on documentation of the operators themselves, i.e., the paramedics, potentially creating bias. Patients with respiratory distress for whom intubation could be delayed until they are brought to the ED, should be supplemented with 100 % oxygen or put on non-invasive positive pressure ventilation until they reach the hospital. This controversy does not apply to cardiac arrest (where rapid sequence intubation is not relevant) or to comatose patients with great concern for airway protection where the need for intubation at the scene is immediate.

Pretreatment

Pretreatment refers to administration of medications prior to hypnotic and paralyzing drugs to blunt the adverse effects of laryngoscopy and minimize the adverse effects of the drugs to follow [9]. Pretreatment is common practice based on the belief that stretching of the hypopharynx causes a 'pressor response', first described by King et al. in 1951 [10]. This response is mediated by the sympathetic nervous system and consists of an increase in blood pressure, heart rate, and increased risk of arrhythmias. Occasionally, parasympathetic responses are also elicited and manifest with bradycardia (mostly in children) or bronchoconstriction. Responses are usually transient and clinical significance is poorly defined. Succinylcholine is also linked to transient increase in intracranial pressure (ICP) in animals [11] and bradycardia.

A number of pretreatment agents have been studied or suggested. Below is a discussion of some of the more common agents used for pretreatment and the evidence behind their use.

1. Defasciculating agents: Fasciculation-brief twitches (visible under the skin) produced by the spontaneous firing of single motor units frequently occur after the administration of succinylcholine [12]. Some have postulated that fasciculations could potentially increase ICP, intraocular and intragastric pressures [13, 14]. Frequently, a 'defasciculating' dose ($1/10^{th}$ regular dose) of a non-depolarizing neuromuscular blocking agent (like vecuronium or rocuronium) is given a few minutes before administration of succinylcholine to prevent fasciculations. There are, however, few quality data to support this practice [3]. There is ongoing debate regarding the association between succinycholine and development of subsequent post-intubation myalgia, but this is more pertinent to elective anesthesia in the OR and not to the emergency rapid sequence intubation setting. We do not recommend the routine use of defasciculating doses of neuromuscular blocking agents outside of the OR as it adds more steps and risk for medication error to the already multi-step process of rapid sequence intubation.
2. Fentanyl: Endotracheal intubation is frequently associated with a sympathetic response, increase in blood pressure and pulse rate. These manifestations are usually transient and could be a compensatory physiologic response. Blunting this response is thought to be beneficial in select patient groups, including those with ischemic heart disease (with absence of hypotension), aneurysms, great vessel dissection, and intracranial hemorrhage. Any sedatives and hypnotics given at high doses can blunt this sympathetic response, but these agents can also cause hypotension. Fentanyl has been shown to have some sympathetic blunting effects at doses as low as 2 mcg/kg, and therefore for emergency rapid sequence intubation a dose of 2–3 mcg/kg is recommended. Caro and Bush recommend its use as pretreatment in the above clinical scenarios [9].
3. Lidocaine: Lidocaine is frequently used in rapid sequence intubation when intubating a patient with known or possible increased ICP. There are data to suggest that lidocaine at a dose of 1.5 mg/kg intravenously suppresses cough reflexes when administered as pretreatment before endotracheal intubation [15, 16]. There are less reliable data to support that lidocaine decreases ICP [17–19]. Since the drug is relatively safe and because data are conflicting, we

recommend its use in the setting of increased ICP, especially in the setting of a coughing patient. Lidocaine also has some bronchodilator characteristics and is recommended for routine use as a pretreatment drug in reactive airway disease [9]. Perhaps a better alternative for intubation in the presence of reactive airway disease is ketamine, a very potent bronchodilator, used as a single hypnotic agent without the need for pretreatment. Lidocaine should not be used as a bolus as it can cause seizures. Lidocaine is contraindicated in patients with amide anesthetic (...caine) allergy or in patients with high degree atrioventricular blocks/bradycardia [9].

4. Atropine: Atropine is still routinely used as a pretreatment agent in pediatric patients undergoing rapid sequence intubation. The common thought is that it blunts the parasympathetic effect of intubation and succinylcholine-induced bradycardia. There are no strong data to support its use in adults or children [20–22]. There are conflicting data regarding its benefit as a pretreatment agent in neonates and therefore its use is optional [9]. Succinylcholine should be used in sufficient doses and is frequently underdosed. The recommendation is 1.0–1.5 mg/kg in adults and children and 2.0 mg/kg in neonates. Underdosing frequently leads to administration of a second dose, which increases the risk of bradycardia, presumably due to an acetylcholine 'priming' mechanism [23, 24]. Atropine should be used following a first or second dose of succinylcholine should bradycardia develop [9].

Cricoid Pressure

In 1961, the British anesthesiologist Brian Sellick described a maneuver whereby cricoid pressure is applied during intubation in order to prevent regurgitation of gastric contents [25]. The concept behind 'Sellick's maneuver' is to collapse the posterior esophagus by applying firm pressure on the non-collapsible trachea. This was based on Sellick's own observational study of 26 high-risk anesthesia patients, where release of cricoid pressure in 3 out of 26 patients was followed by immediate reflux of gastric contents into the pharynx. This technique remains widely used in the United States and the United Kingdom and is heavily entrenched in the culture. In addition to Sellick's paper, which was published in *The Lancet* in 1961, a literature review on the topic only reveals two relevant studies [26]. Both papers are Canadian: One is a meta-analysis by Brimacombe and Bery from 1997 [27], and the other is a 2003 paper by Smith et al. [28]. The weakness in Sellick's observational study [25] was that it involved only a small number of patients, and was conducted in 1961 using anesthetic techniques available at that time.

Neither of the Canadian papers confirmed the perceived clinical benefit of cricoid pressure in reducing the incidence of aspiration during emergency rapid sequence intubation [26]. Criciod pressure has the potential to worsen laryngoscopic view [3], increase peak inspiratory pressure/decrease tidal volume, or cause complete obstruction during bag-mask ventilation [29]. There is a theoretical risk of moving the cervical spine in the setting of an injury, although this has not been adequately studied [3]. In conclusion, we summarize Walls' recommendations in his Manual of Emergency Airway Management: Sellick's maneuver lacks strong evidence to support its routine use. Perhaps, in cases where prolonged bag-mask ventilation is needed the "maneuver may minimize the volume of gases

passed down the esophagus to the stomach, possibly decreasing the likelihood of regurgitation" [3].

Paralysis with Induction

Various hypnotic agents (**Table 1**) and neuromuscular paralyzing agents (**Table 2**) are used in rapid sequence intubation. In the remainder of this chapter, we attempt to shed light on some of the most commonly used agents, etomidate, succinylcholine, midazolam and propofol.

Etomidate

Etomidate was introduced in the 1970s in Europe and in 1983 in the United States. It is a hypnotic anesthetic agent used in both the pediatric and adult populations. It is a very short-acting agent, which induces sleep in 30 seconds and lasts only 10 minutes if repeated doses are not administered. Etomidate is hydrolyzed in the liver and plasma to inactive metabolites and mostly eliminated renally. It works by causing depression of the reticular activating system (the part of the brain responsible for transition between sleep and wakeful states) specifically by acting at γ-aminobutyric acid (GABA) receptors. Among its most common side effects are nausea, vomiting, and myoclonic jerks [2].

There is much discussion in the literature over etomidate's effect on adrenal function as it has been found to decrease levels of cortisol and aldosterone production. Specifically, this occurs through an inhibition of 11-beta-hydroxylase, a critical enzyme in the path of production of these hormones from their precursor cholesterol, thus there is a blunted response to stimulation with adrenocorticotrophic hormone (ACTH) [30]. In a recent study by Jabre et al. of emergency intubations in France, patients were randomized to receive either etomidate or ketamine [31]. They detected no significant difference for the major endpoint, sequential organ failure assessment (SOFA) score, which rates organ function of six organ systems in the first three days of the patient's ICU stay. However, they did detect a difference in the rate of adrenal insufficiency, which was significantly higher in the etomidate group. The authors note that this effect on the adrenal axis was not associated with a significant difference in morbidity and mortality between the two groups [31]. Many other studies in the last two and a half decades have demonstrated this same effect on adrenal axis after a single bolus dose of etomidate for intubation (usually defined by cortisol levels in response to ACTH stimulation tests), but the clinical significance of this effect is still debated. The adrenal insufficiency after etomidate administration may be more frequent and have more consequence in the face of sepsis. Despite reports like the study by Cuthbertson et al. of 499 patients with sepsis, which demonstrated a higher 28-day mortality rate in those patients who received etomidate [32], other studies have not shown this effect. In a recent retrospective study of 224 ICU patients, half of whom had received etomidate during rapid sequence intubation, no increase in mortality, vasopressor use, length of stay in the ICU or number of ventilator-days was demonstrated [33]. In 2007, Ray and McKeown published a study that looked at 159 septic shock patients who received induction with etomidate or an alternative agent [34]. Fewer etomidate patients "required vasopressor agents at induction and less cardiovascular intervention was required than in patients given propofol,

Table 1. Hypnotic agents

Agent	Dose	Onset & Duration	Adverse Effects	Advantages	Disadvantages
Etomidate	0.3 mg/kg i.v.	Onset: 30 s Duration: 10 min	• pain on injection • nausea • vomiting • myoclonic jerks	• no compromise of hemodynamic stability	• may cause adrenal insufficiency, though it appears that there is no clinical significance and outcomes may be unchanged, even in the face of sepsis
Ketamine	1–2 mg/kg i.v.	Onset: 1 min Duration: 5–10 min	• postanesthesia emergence reactions – rare with doses used for RSI, treated with benzodiazepines	• high potency • rapid onset • short duration of action • causes relaxation of bronchial smooth muscle, thus advantageous in bronchospastic patients • preservation of laryngeal and pharyngeal reflexes	• not ideal for patients with intrancranial pathology due to tendency to increase ICP
Propofol	2 mg/kg i.v.	Onset: 1 min Duration: 5–10 min	• hypotension • myoclonus • tremors • hiccups • pain on injection	• short duration of action • Category B in pregnancy: drug of choice in RSI	• direct depression of blood pressure • myocardial depression • avoid rapid bolus
Midazolam	0.2–0.3 mg/kg	Onset: 1–2 min Duration: Approx 15–20 min		• minimal pain on injection • more potent, shorter half-life and less cardiorespiratory depression compared with diazepam	• decrease in systolic blood pressure, exaggerated in hypovolemic patients • Poor induction agent

RSI: rapid sequence intubation; ICP: intracranial pressure; i.v.: intravenous

Table 2. Paralyzing agents

Agent	Dose	Onset & Duration	Adverse Effects	Advantages	Disadvantages
Succinylcholine	1–1.5 mg/kg i.v. (adults and children) 2 mg/kg (infants)	Onset: 1 min Duration: 3–5 min	• muscle fasciculations • increased intraocular pressure • joint dislocation or displacement of skeletal fractures • malignant hyperthermia (very rare in ED)	• rapid onset • rapid degradation • most commonly used with reliable effects	• may cause hyperkalemia, leading to cardiac instability or arrest in patients with burns, trauma, critical illness or nervous system pathology • may cause transient increases in ICP, clinical significance not clearly demonstrated
Atracurium	0.5 mg/kg i.v.	Onset: 3 min Duration: 25–35 min	• flushing		• slow onset • long duration
Vecuronium	0.1 mg/kg i.v.	Onset: 3 min Duration: 30–35 min		• does not affect cardiac activity • does not cause increased ICP or IOP	• slow onset • long duration

ED: emergency department; i.v.: intravenous; ICP: intracranial pressure; IOP: intraocular pressure

thiopental, or other agents." They concluded that etomidate did not produce worse clinical outcomes in septic patients and could be beneficial because of its excellent cardiovascular profile [35]. We conclude that although there is a clearly demonstrated decrease in the adrenal gland production of cortisol in response to ACTH, it seems that clinical outcomes of patients receiving etomidate are unchanged when compared to those of patients receiving other induction agents. Another relevant question is "Should etomidate be used in rapid sequence intubation in patients who require reintubation within a short period of time after etomidate was used for the first intubation?" Further studies are needed to answer this question.

Succinylcholine

Succinylcholine is a neuromuscular blocking agent regularly used for muscle paralysis in rapid sequence intubation. Developed in the early 1950s, succinylcholine is a depolarizing agent which mimics acetylcholine and acts as an agonist of its receptors in the post-junctional neuromuscular membrane. While acetylcholine is rapidly hydrolyzed, succinylcholine takes significantly longer to be hydrolyzed, and thus keeps the membrane depolarized for a longer time. Though the depolarization continues, after brief fasciculation the muscles relax and cannot recover from relaxation until the membrane is capable of getting depolarized again. An intravenous bolus of 1 – 1.5 mg/kg should be given rapidly to ensure that total relaxation of the muscles occurs [2].

While a few small studies, starting with Halldin and Wahlin in 1959 [35], have reported that succinylcholine may cause increases in ICP, this remains a controversial potential effect of this agent. An example of one such study was that of Cottrell et al., in 1983. The study looked at the change in ICP in 17 cats that were divided into groups with either a normal or increased ICP before succinylcholine administration. Both groups, after administration of 1.5 mg/kg of succinylcholine, on average approximately doubled their ICP but this effect only lasted for 10 – 15 seconds [11]. A study by Minton et al. in 1986 considered 19 patients with baseline central nervous system pathology, in this case, brain tumors [36]. These authors, too, demonstrated an increase in ICP after succinylcholine administration, and that the increases in ICP were greater in those patients with worse cerebral edema. More recent studies in humans have failed to demonstrate such an effect of increased ICP after succinylcholine. Kovarick et al.'s 1994 study took 10 patients, all with intracranial pathology, administered succinylcholine and then measured ICP every minute over the course of 15 minutes, with no increases demonstrated [37]. Additionally, Kovarick et al. point out potential flaws in earlier studies such as that of Halldin and Wahlin who conducted their study on apneic patients [35] and McLesky et al. who demonstrating increased ICP after intubation was performed, but decreased ICP between succinylcholine administration and intubation [38]. Studies demonstrating increases in ICP after succinylcholine administration were predominantly in non-human subjects and/or human studies with small sample sizes, mostly with compromised central nervous systems. Effects were very transient and there was little to no discussion of clinical outcomes.

Another issue surrounding the use of succinylcholine is its potential to cause life-threatening hyperkalemia. Certain underlying conditions increase susceptibility to this adverse effect of succinylcholine, to include motor neuron defects,

chemical denervation (with muscle relaxants, drugs, or toxins), burn injury, trauma, tumor, infection/inflammation of the muscle and immobilization. The etiology of the hyperkalemia lies in a phenomenon common to all of these conditions, i.e., there is upregulation and expression of new isoforms of acetylcholine receptors throughout the muscle membrane. Upon depolarization by succinylcholine, there is a release of amounts of potassium significant enough to cause hyperkalemia [39]. Some recommend that succinylcholine be avoided 48–72 hours after trauma, burns and critical illness [40]. Others feel that this effect of exaggerated hyperkalemia takes several days to occur and that in the very acute phase of these conditions, succinylcholine need not be avoided since published data support that the hyperkalemic effect of succinylcholine first arises after 9 days in burns, 10 days in upper motor neuron lesions, 4 days in peripheral nerve lesions, 21 days in spinal cord injury, and 7 days in progressive neuropathies or sepsis [41]. New onset of electrocardiogram (EKG) changes due to succinylcholine-induced hyperkalemia are seen 2–5 minutes after succinylcholine is administered and, when this happens, the clinician should assume that these changes are succinylcholine-induced. Levels of 8 mEq/l of potassium are generally required to produce cardiovascular instability.

Midazolam

Midazolam belongs to the benzodiazepine family and frequently is used as a hypnotic in rapid sequence intubation. Like other members of its family, midazolam works on the GABA receptors. Based on dosing studies, the induction dose should be between 0.2–0.3 mg/kg intravenously [42, 43]. Sagarin et al. showed that midazolam is frequently underdosed and given at a range of 0.03–0.04 mg/kg [44].

Even with use of the correct dose, onset is slow (1.5–2.5 minutes) and sedation is not optimal. Midazolam also has negative hemodynamic effects as it causes reduction in systemic vascular resistance especially in the hypovolemic or hemodynamically unstable patient [42]. A study by Sivilotti et al. of various induction agents suggested that midazolam may be associated with suboptimal intubating conditions and increased difficulty of endotracheal intubation [45]. This makes midazolam a less attractive induction agent especially given that other more potent agents are available.

Propofol

Propofol is an alkyphenol sedative-hypnotic. It works on the GABA receptors and has gained popularity in the last decade. The rapid sequence induction dose is 2 mg/kg intravenously, with onset of hypnosis in 1 minute and duration of 5–10 minutes. Despite being an excellent induction agent in 'stable' patients, it is known to have direct depressant effects on blood pressure and myocardium. It also decreases cerebral perfusion. The manufacturer recommends that rapid bolus dosing be avoided. This precludes its use in a large proportion of emergency intubations because of the risk of hemodynamic instability [2, 42]. Propofol should be avoided in the hypotensive patient and the patient with known severe systolic ventricular dysfunction. It is a good choice in the hypertensive patient. The main advantage of propofol is that it is a category B drug in pregnancy, which makes it the induction agent of choice in that setting, in the absence of contraindications.

Conclusion

Rapid sequence intubation use by emergency physicians and intensivists has likely contributed to a marked increase in success rates for intubations compared to the pre-rapid sequence intubation era. Paralyzing agents are still likely under utilized in the ICU compared to the ED, mostly for concerns of failure to achieve intubation in a 'difficult to intubate' airway. This concern is likely over-represented. Rapid sequence intubation may also be beneficial in the pre-hospital setting, but general use for intubation of patients with respiratory distress in this setting is still subject to debate.

Physicians should always approach rapid sequence intubation in the systematic 7 P fashion described by Walls and Murphy [3]. Cricoid pressure remains entrenched in the culture despite the evidence that its usefulness may be a myth. Common practices, like pretreatment with atropine and use of defasciculating doses of non-depolarizing neuromuscular paralyzing agents, should likely be abandoned, in particular outside of the OR. Lidocaine use for pretreatment in the setting of increased ICP, and fentanyl where sympathetic responses should be blunted are recommended. The concern of increasing ICP with succinylcholine and the alternative use of long-acting non-depolarizing neuromuscular blockers is likely overexagerated. Finally, midazolam is a poor induction agent, propofol is useful in pregnancy, and etomidate seems to be a safe drug in most settings including septic shock.

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References

1. Taryle DA, Chandler JE, Good JT Jr, Potts DE, Sahn SA (1979) Emergency room intubations--complications and survival. Chest 75: 541 – 543
2. Hopson LR, Dornen SC (2004) Pharmacologic adjuncts to intubation. In: Roberts JR, Hedges, JR (ed) Clinical Procedures in Emergency Medicine, 4th edn. Saunders Elsevier, Philadelphia, pp 100 – 114
3. Walls R, Murphy (2008) Rapid sequence intubation. In: Walls RM (ed) Manual of Emergency Airway Management, 3rd edn. Lippincott Williams & Wilkins, Philadelphia, pp 24 – 35
4. Vrocher D, Hopson LR (2004) Basic airway management and decision-making. In: Roberts JR, Hedges, JR (ed) Clinical Procedures in Emergency Medicine, 4th edn. Saunders Elsevier, Philadelphia, pp 53 – 68
5. Field J, Hazinski MF, Gilmore D (2004) Handbook of Emergency Cardiovascular Care for Healthcare Providers. American Heart Association, Dallas
6. Fakhry SM, Scanlon JM, Robinson L, et al (2006) Prehospital rapid sequence intubation for head trauma: conditions for a successful program. J Trauma.60: 997 – 1001
7. Pearson S (2003) Comparison of intubation attempts and completion times before and after the initiation of a rapid sequence intubation protocol in an air medical transport program. Air Med J 22: 28 – 33
8. Davis DP, Hoyt DB, Ochs M, et al (2003) The effect of paramedic rapid sequence intubation on outcome in patients with severe traumatic brain injury. J Trauma 54: 444 – 453.
9. Caro D, Bush S (2008) Pretreatment agents. In: Walls RM (ed) Manual of Emergency Airway Management, 3rd edn. Lippincott Williams & Wilkins, Philadelphia, pp 222 – 233
10. King BD, Harris LC Jr, Greifenstein FE, Elder JD Jr, Dripps RD (1951) Reflex circulatory responses to direct laryngoscopy and tracheal intubation performed during general anesthesia. Anesthesiology 12: 556 – 566

11. Cottrell JE, Hartung J, Giffin JP, Shwiry, B (1983) Intracranial and hemodynamic changes after succinylcholine administration in cats. Anesth Analg 62: 1006 – 1009
12. Robinson J, Preston D, Shapiro B (2008) Proximal, distal, and generalized weakness. In: Bradley W, Daroff R, Fenichel G, Jankovic J (ed) Neurology in Clinical Practice, 5th edn. Butterworth Heinemann Elsevier, Philadelphia, pp 366 – 383
13. Schreiber JU, Lysakowski C, Fuchs-Buder T, Tramèr MR (2005) Prevention of succinylcholine-induced fasciculation and myalgia: a meta-analysis of randomized trials. Anesthesiology 103: 877 – 84.
14. Koenig KL (1992) Rapid-sequence intubation of head trauma patients: prevention of fasciculations with pancuronium versus minidose succinylcholine. Ann Emerg Med Aug; 21: 929 – 32
15. Yukioka H, Hayashi M, Terai T, Fujimori M (1993) Intravenous lidocaine as a suppressant of coughing during tracheal intubation in elderly patients. Anesth Analg 77: 309 – 312
16. Warner LO, Balch DR, Davidson PJ (1997) Is intravenous lidocaine an effective adjuvant for endotracheal intubation in children undergoing induction of anesthesia with halothane-nitrous oxide?. J Clin Anesth 9: 270 – 274
17. Robinson N, Clancy M (2001) In patients with head injury undergoing rapid sequence intubation, does pretreatment with intravenous lignocaine/lidocaine lead to an improved neurological outcome? A review of the literature. Emerg Med J 18: 453 – 457
18. Butler J, Jackson R (2002) Towards evidence based emergency medicine: best BETs from Manchester Royal Infirmary. Lignocaine premedication before rapid sequence induction in head injuries. Emerg Med J 19: 554
19. Brooks D, Anderson CM, Carter MA, et al (2001) Clinical practice guidelines for suctioning the airway of the intubated and nonintubated patient. Can Respir J 8: 163 – 181
20. Kelly MA, Finer NN (1984) Nasotracheal intubation in the neonate: physiologic responses and effects of atropine and pancuronium. J Pediatr 105: 303 – 309
21. Desalu I, Kushimo OT, Bode CO (2005) A comparative study of the hemodynamic effects of atropine and glycopyrolate at induction of anesthesia in children. West Afr J Med 24: 115 – 159
22. McAulife G, Bissonnette B, Boutin C (1995) Should the routine use of Atropine before succinylcholine in children be reconsidered?. Can J Anaesth 42: 724 – 729
23. McCauley CS, Boller LR (1988) Bradycardic responses to endotracheal suctioning. Crit Care Med 16: 1165 – 1166
24. Sørensen M, Engbaek J, Viby-Mogensen J, Guldager H, Molke Jensen F (1984) Bradycardia and cardiac asystole following a single injection of suxamethonium. Acta Anaesthesiol Scand 28: 232 – 235
25. Sellick BA (1961) Cricoid pressure to control regurgitation of stomach contents during induction of anesthesia. Lancet 2: 404 – 406
26. Butler J, Sen A (2005) Best evidence topic report. Cricoid pressure in emergency rapid sequence induction. Emerg Med J 22: 815 – 816
27. Allman KG (1995) The effect of cricoid pressure application on airway patency. J Clin Anesth 7: 197 – 199
28. Brimacombe JR, Berry AM (1997) Cricoid pressure. Can J Anaesth 44: 414 – 425
29. Smith KJ, Dobranowski J, Yip G, Dauphin A, Choi PT (2003) Cricoid pressure displaces the esophagus: an observational study using magnetic resonance imaging. Anesthesiology 99: 60 – 64
30. Bergen JM, Smith DC (1997) A review of etomidate for rapid sequence intubation in the emergency department. J Emerg Med 15: 221 – 230
31. Jabre P, Combes X, Lapostolle F, et al (2009) Etomidate versus ketamine for rapid sequence intubation in acutely ill patients: a multicentre randomised controlled trial. Lancet 374: 293 – 300
32. Cuthbertson BH, Sprung CL, Annane D, et al (2009) The effects of etomidate on adrenal responsiveness and mortality in patients with septic shock. Intensive Care Med 35: 1868 – 1876
33. Dmello D, Taylor S, O'brien J, Matuschak GM (2010) Outcomes of etomidate in severe sepsis and septic shock. Chest 138: 1327 – 1332
34. Ray DC, McKeown DW (2007) Effect of induction agent on vasopressor and steroid use, and outcome in patients with septic shock. Crit Care 11: R56

35. Halldin M, Wahlin A (1959) Effect of succinylcholine on the intraspinal fluid pressure. Acta Anaesthesiol Scand 3: 155 – 161
36. Minton MD, Grosslight K, Stirt JA, Bedford RF (1986) Increases in intracranial pressure from succinylcholine: prevention by prior nondepolarizing blockcade. Anesthesiology 65: 165 – 169
37. Kovarick WD, Mayberg TS, Lam AM, Mathisen TL, Winn HR (1994) Succinylcholine does not change intracranial pressure, cerebral blood flow velocity or the electroencephalogram in patients with neurologic injury. Anesth Analg 78: 469 – 473
38. McLeskey CH, Cullen BF, Kennedy RD, Galindo A (1974) Control of cerebral perfusion pressure during induction of anesthesia in high-risk neurosurgical patients. Anesth Analg 53: 985 – 992
39. Jeevendra Martyn JA, Richtsfeld M (2006) Succinylcholine-induced hyperkalemia in acquired pathological states: etiologic factors and molecular mechanisms. Anesthsiology 104: 158 – 169
40. Jeevendra Martyn JA, Fukushima Y, Chon JY, Yong HS (2006) Muscle relaxants in burns, trauma, and critical illness. Int Anesthesiol Clin 44: 123 – 143
41. Orebaugh SL (1999) Succinylcholine: adverse effects and alternatives in emergency medicine. Am J Emerg Med 17: 715 – 721.
42. Caro DA, Tyler KR (2008) Sedative induction agents. In: Walls RM (ed) Manual of Emergency Airway Management, 3rd edn. Lippincott Williams & Wilkins, Philadelphia, pp 235 – 245
43. Jensen S, Schou-Olsen A, Huttel MS (1982) Use of midazolam as an induction agent: comparison with thiopentone. Br J Anaesth 54: 605 – 607
44. Sagarin MJ, Barton ED, Sakles JC, et al (2003) Under dosing of midazolam in emergency endotracheal intubation. Acad Emerg Med 10: 329 – 338
45. Sivilotti ML, Ducharme J (1998) Randomized double-blind study on sedatives and hemodynamicsduring rapid sequence intubation in the emergency department: The SHRED study. Ann Emerg Med 31: 313 – 324

Research Priorities in Oral Care for Endotracheally-intubated Patients

S. Labeau and S. Blot

IV

Introduction

Oral health has long been recognized as an essential component of general health. Poor oral hygiene can negatively affect basic needs, such as swallowing, eating, drinking and communicating, and, thereby, the quality of life. Moreover, oropharyngeal colonization is associated with a variety of oral diseases as well as systemic conditions, including cardiovascular disease and stroke, chronic obstructive pulmonary disease (COPD), endocarditis, bacteremia, and a higher risk of preterm low birth-weight babies [1, 2]. In addition to the adverse clinical effects of poor oral hygiene, a substantial health-economic burden has been documented [3].

Healthy persons can maintain oral health independently, but critically ill patients in the intensive care unit (ICU) are generally unconscious and intubated. They are, therefore, dependent on the quality and frequency of care provided by healthcare professionals to prevent dental plaque formation and oral microbial growth. Maintaining adequate oral hygiene is clearly a key component of critical care. It is therefore encouraging to find that, in European ICUs, oral care is considered to be very important and a high priority in mechanically ventilated patients [4]. In contrast, in certain settings, cleaning the oral cavity is still believed to be primarily an intervention for patient comfort. Among the most important hindrances to the implementation of an adequate program for oral hygiene in the ICU is the lack of evidence-based recommendations [5]. Indeed, none of the existing research provides clear guidance concerning the various aspects of oral care. Therefore, well-designed randomized trials with adequate sample sizes are urgently needed [2, 6, 7].

Based on the results of a non-exhaustive review, this chapter presents an inventory of the topics within the field of oral care that –in our opinion– should be considered as research priorities.

Pathophysiology

Of all ICU patients, those who are intubated and mechanically ventilated are at particular risk of bad oral health. A number of physiological, pathological, mechanical, and immunological factors responsible for this increased susceptibility have been identified [2, 8].

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Alterations in Oral Microbial Ecology

The healthy oropharynx mainly consists of Gram-positive streptococci and dental microorganisms. Johanson et al. demonstrated that oropharyngeal colonization was rare in healthy volunteers and patients with moderate disease, while it was frequently observed in more severely ill patients [9]. Critical illness induces a decrease in patients' resistance to colonization, and thus an increase in vulnerability to colonization with exogenous microbes. The oral flora is known to alter into a predominance of Gram-negative organisms and *Staphylococcus aureus* within 48 hours of hospital admission [2]. Moreover, with increasing severity of illness and length of stay in the ICU, the degree of colonization with respiratory pathogens such as *S. aureus*, *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Acinetobacter baumannii* increases to more than 70 % [2].

Dental Plaque Formation

Dental plaque is a natural, hard-to-remove biofilm, built on tooth surfaces and compacted at gingival margins within 72 hours after cessation of an adequate oral hygiene regimen [10]. Bacteria constitute approximately 70 to 80 % of the solid plaque material, and 1 mm^3 of plaque contains at least 10^8 bacteria, including more than 300 different aerobic and anaerobic species [11]. The dental plaque of ICU patients can be colonized by potential respiratory pathogens [2].

Altered Salivary Production and Flow

Saliva plays a key role in preserving oral health by means of its antimicrobial, lubricating and buffering properties [2, 12]. In ICU patients, the threats to its production and distribution are numerous and include fever, diarrhea, extensive burn injury, and reduced or inadequate fluid intake [12].

Xerostomia can be provoked by stress and anxiety, by drug administration, and by medical devices –such as endotracheal tubes– that keep the patient's mouth continuously open [2]. Xerostomia may promote the development of mucositis, and the colonization of the oropharynx with Gram-negative bacteria [12]. Xerostomia also promotes the accumulation of dental plaque, and reduces the distribution of salivary immune factors in the oral cavity, including salivary immunoglobulin A (IgA) and lactoferrin [2]. Salivary IgA protects against respiratory pathogens, while lactoferrin has a bactericidal effect against numerous major pathogens, including *S. aureus*, *Pseudomonas aeruginosa* and *H. influenzae* [2]. Moreover, increased levels of proteases in the oral secretions of critically ill patients cause a depletion of fibronectin, a glycoprotein that interferes with binding of Gram-negative bacteria to epithelial cells and that acts as a reticuloendothelial mediated host defense system [13]. Because of this, receptors are exposed to the attachment of organisms such as *P. aeruginosa* to the buccal and pharyngeal epithelial cells [8].

Drug-induced Adverse Effects

As mentioned above, several drugs which are frequently administered to ICU patients are known to induce xerostomia, which has a detrimental effect on oral health [2]. These drugs include antihypertensives, anticholinergics, antihista-

mines, antipsychotics, anorectics, anticonvulsants, antineoplastics, sympathicomimetics, antidepressants, and diuretics [14]. Another potential drug-induced adverse effect is colonization of the oral cavity by opportunistic pathogens, which can be caused by the administration of antibiotics [15].

Effects of Orotracheal Intubation

Following endotracheal intubation, bacterial adherence to the mucosa is facilitated by a reduced mucosal IgA, damaged mucous membranes, an elevated airway pH, and an increase in protease production and in the numbers of airway receptors for bacteria because of acute illness and antimicrobial use [16]. An orotracheal tube *in situ*, combined with the administration of sedative drugs, also inhibits or hampers swallowing. This results in an accumulation of debris in the oral cavity, which provides an ideal environment for microorganisms to multiply exponentially. Moreover, oral intubation causes the mouth to be continuously open, thereby leading to xerostomia, inducing drying of the mucous membranes, accumulation of dental plaque and reduction of the distribution of salivary immune factors [2]. In contrast, oral intubation may cause hypersalivation by inducing a hyperactive gag reflex [17]. Finally, and importantly, the presence of an endotracheal tube can interfere with a thorough inspection of the oral cavity and limit access for oral care [15].

Complications of Poor Oral Health

Poor oral health in intubated patients may be associated with several complications. These may be limited to the oral cavity, but may also have a systemic impact.

Local Complications

In addition to caries, poor oral health may cause stomatitis, which is a painful inflammation of the mucous membranes of the mouth. Stomatitis increases the risk of bacterial translocation and may result in sepsis and subsequent multiple organ failure. Poor oral health may also induce gingivitis, i.e., inflammation of the gums in response to bacterial plaque on adjacent teeth [8]. Gingivitis induces a shift at the gingival surface from predominantly *Streptococcus* and *Actinomyces spp.* to aerobic Gram-negative bacilli. If dental plaque is allowed to further accumulate, subgingival inflammation may progress to periodontitis, which has been associated with numerous systemic diseases [1].

Systemic Complications

There is increasing evidence that periodontal disease may be associated with an increased risk of cardiovascular disease, premature low-birth-weight babies, and respiratory disease. Poor oral health has also been linked with poor glycemic control in diabetics, rheumatoid arthritis, and osteoporosis. Moreover, oral disease is recognized to be an important problem in medically or immunologically compromised patients suffering from a range of chronic conditions [1].

A major complication in mechanically ventilated patients is the development of ventilator-associated pneumonia (VAP), in which the colonization of the oro-

pharynx is deemed to play an important role [2, 16, 18]. Contaminated upper airway secretions may leak alongside the cuff of an endotracheal tube [2], thus increasing the risk of VAP. Additionally, endotracheal tubes interfere with the cough reflex, negatively impact the function of the mucociliary escalator, induce excessive secretion of mucus, and enable bacterial translocation from the oropharynx to the lower airways through a constantly open glottis [2].

Oral Care Practices

A plethora of practices and protocols for delivering oral care to intubated patients has been reported. The primary factor in good oral health is the routine control of dental plaque. Essentially, dental plaque can be removed mechanically or pharmacologically, or both strategies can be combined [2].

Mechanical Strategies

Commonly reported methods to clean the oral cavity mechanically include placing a foam swab in the oral cavity without agitation; placing lemon and glycerine swabs in the oral cavity; swabbing with mouthwash or water, swabbed fingers and/or forceps and gauze; brushing teeth with foamswabs; manual brushing with toothpaste; and –although very rarely– use of an electric toothbrush [2, 4]. While toothbrushes are suggested to be the devices of choice to clean the oral cavity mechanically, sponge toothettes and foam swabs are reported to be used more frequently than brushes in both European and American ICUs [4, 15, 19].

Pharmacological Strategies

In Europe, oral care practice primarily consists of mouthwashes, mainly with chlorhexidine gluconate [4]. In an American survey, in addition to chlorhexidine, use of other, less optimal and even dangerous solutions was reported: for example, hydrogen peroxide and sodium bicarbonate remove debris effectively, but may cause superficial burn injuries if not diluted carefully; lemon and glycerine swabs may stimulate the production of saliva initially, but are acidic, cause irritation and decalcification of the teeth, and rebound xerostomia [20]. More recently, the use of povidone-iodine to modulate oral colonization has also been suggested [21, 22].

Chlorhexidine

Chlorhexidine mouthwashes have been associated with a reduction in dental plaque [11], incidence of respiratory infections, including VAP [23], and nosocomial infections in general [23]. Chlorhexidine decontaminates the oropharynx effectively and, today, is the gold standard to which other antiplaque and gingivitis agents are compared. It adsorbs to tooth surfaces and disrupts cytoplasmic membranes of bacteria, thus killing both Gram-negative and Gram-positive microorganisms [24]. Moreover, after absorption, chlorhexidine is released over a long period of time, a property which is known as substantivity, explaining why chlorhexidine inhibits the formation of plaque in a clean mouth, but otherwise is of limited efficacy [24]. Logically, dental plaque needs to be physically removed for optimal chlorhexidine effectiveness [24].

The di-cationic structure of chlorhexidine gluconate is responsible for its antimicrobial properties, but at the same time for its most common adverse effect, extrinsic tooth staining [25]. In addition to this yellow-brown staining, taste alteration, calculus formation and mucosal desquamation have been reported with long-term use of chlorhexidine gluconate [26]. Chlorhexidine gluconate is inactivated by anionic dentifrice surfactants, so tooth brushing should precede its use or be performed 30 minutes after rinsing. Oral flora develops resistance after about six months' use, but baseline susceptibility is re-established after discontinuation [27].

Povidone-iodine

Povidone-iodine (polyvinylpyrrolidone-iodine complex) has a broad-spectrum antimicrobial activity, a low potential for developing resistance and adverse reactions, and wide availability. Its ease of use and low financial cost may constitute a valuable adjunct to current oral care practices. Generally, a 10 % aqueous solution is used [22], but its application as a 1 % concentration has also been reported [28].

Diluted povidone-iodine is able to kill periodontal pathogens *in vitro* in only 15 seconds of contact and bacteria and yeasts *in vivo* within 5 minutes of contact [21]. It has been shown to kill periodontal bacteria and to decrease bacteremia after oral surgery, but allergic sensitization is possible [21].

Combined Strategies

As stated above, dental plaque needs to be removed in order for chlorhexidine to be effective [24]. Generally, mouthwashes alone will not eliminate dental plaque formation, and the formation of a biofilm protects potentially deleterious bacteria against chemical agents. Oral care practices combining mechanical interventions, such as oropharyngeal suctioning and toothbrushing, with a pharmacological intervention, have been reported in intubated patients [2, 4, 29].

Research Priorities in Oral Care

The above findings from the literature clearly demonstrate a considerable variety in oral care practices worldwide for intubated patients receiving mechanically ventilation. This lack of consistency is, at least partially but quite importantly, due to the fact that evidence-based recommendations are lacking for almost all aspects of oral care. Research addressing the current multiple gaps in evidence-based knowledge is, therefore, pivotal. Below we list the aspects of oral care that, in our opinion, should be considered as priorities for future research.

Optimal Assessment of the Oral Cavity

Good oral care starts with an assessment of the patient's individual needs. Systemic oropharyngeal assessment may prevent more serious oropharyngeal infections. Treloar and Stechmiller developed a tool specifically for the oropharyngeal assessment of orally intubated patients, including the evaluation of salivary flow, plaque index, gingival index, lip color, tongue color, and mucosal color [30]. Their development study was, however, limited to the categorization of gingiva,

Table 1. The BRUSHED Assessment Model (derived from [17])

B	**Bleeding?** Gums, mucosa, coagulation status?
R	**Redness?** Gum, margins, tongue? Antibiotic stomatitis?
U	**Ulceration?** Size, shape, herpetic? Infection?
S	**Saliva?** Xerostomia, hypersalivation, characteristics?
H	**Halitosis?** Character? Acidotic? Infection?
E	**External factors?** Angular cheilitis? Endotracheal tapes?
D	**Debris?** Foreign particles? Visible plaque?

mucosa, and plaque, while the other categories of assessment were descriptive in nature [30, 31]. This limitation could present a challenge to the reliability of the tool [31]. A handy and user-friendly tool is the BRUSHED Assessment Model (**Table 1**) that prompts nurses to check for particular clinical signs during oral assessment by means of a simple mnemonic [17]. In critical care, however, no standard instrument has been accepted for use in the evaluation of the oral cavity in intubated patients [19].

It is important to be aware that other factors, in addition to oral intubation, have an impact on the oral mucosa. Research focusing on the identification or development and validation of a high-quality assessment tool is highly needed. Such a tool may sharpen healthcare professionals' awareness, and its use may result in methodical and careful cleaning of the oral cavity.

Optimal Method for Cleaning the Oral Cavity

Dental plaque needs to be physically removed to obtain optimal effectiveness from chemical agents [24], and it can be assumed that the best method to obtain and maintain oral health in intubated patients is a combined intervention, consisting of mechanical cleaning of the oral cavity, followed by application of a chemical agent. Additional research is however needed to turn this assumption into evidence.

Mechanical cleaning

It has been long and widely accepted that a toothbrush is the tool of choice for the most effective mechanical elimination of dental plaque [32–34]. In a modest study with only two participants, Pearson compared the ability of foam swabs and toothbrushes to remove plaque from the gingival crevice and from between teeth [33]. Three experiments were completed, each over a 6-day period, thus mimicking a timeframe in which plaque can accumulate. Foam swabs did not remove plaque from some sheltered areas and were not able to completely eliminate plaque from the sites under investigation. The toothbrush usually achieved complete removal of visible plaque from all sites [33]. Six years after the original study, the same group investigated whether the results could be generalized to a

wider population [34]. In a larger sample of 34 participants, a total number of 1632 plaque accumulation sites were studied. This replication trial confirmed the earlier finding that toothbrushes succeeded substantially better than foam swabs in removing plaque from the investigated sites [34].

Indeed, in spite of their popularity, the value of foam swabs and toothettes in removing plaque formation remains highly questionable [4, 33, 34]. In the meantime, toothbrushing is advised for almost all intubated patients, except those with severe ulceration or with profound clotting disturbances that may cause gingival hemorrhage [35]. It has been advocated that small-headed or pediatric toothbrushes are used in intubated patients because of their easy-to-handle smaller size [6]. Electric toothbrushes have been shown to improve the quality of oral care [36], and even special autoclavable electric toothbrushes with built-in suction devices are available [35]. Electric devices are nevertheless reported to be rarely used in the ICU [4]. Moreover, the benefit of their use in intubated patients remains largely unexplored [36]. A recent prospective, simple-blind, randomized trial of adult patients intubated for > 48 hours was undertaken to assess whether using a mechanical debridement system (electric tooth and tongue brushing) associated with standard oral care succeeded in reducing the incidence of VAP as compared to standard care with gauzes containing 0.12 % chlorhexidine digluconate [37]. Of 147 randomized patients, 74 were assigned to the toothbrush group. The control group and the intervention group had similar rates of suspected VAP (20.3 % vs. 24.7 %; p = 0.55). A scheduled interim analysis revealed that the incidence of microbiologically documented VAP was also similar in the two groups after adjustment for severity of illness and admission diagnosis (hazard ratio 0.84; 95 % confidence interval, 0.41 to 1.73). The groups appeared not to differ significantly in mortality, antibiotic-free days, duration of mechanical ventilation, or ICU length of stay. Following this interim analysis, the study was stopped prematurely. No adverse events were reported associated with electric toothbrushing. The authors concluded that the addition of electric toothbrushing to standard oral care with 0.12 % chlorhexidine digluconate seemed not to be effective for the prevention of VAP [37].

Well-designed clinical trials including adequate samples of critically ill intubated patients might help to determine whether toothbrushing is truly the best method to preserve oral health in this specific population. Specifically, further investigation into the relationship of mechanical oral care practices to bacteremia in mechanically ventilated patients is needed [38], as well as into the effectiveness, efficacy and safety of different types and sizes of toothbrushes.

Pharmacological cleaning

Pharmacological cleaning of the oral cavity is most often performed using chlorhexidine. The adverse effects of chlorhexidine as well as some contradictory study results concerning its effectiveness [11, 39] have led investigators to evaluate the effect of modulating oral colonization with povidone-iodine [22]. In a sample of patients with severe head trauma, researchers found that regular application of povidone-iodine as an oropharyngeal rinse significantly reduced the prevalence of VAP in comparison with standard care. Indeed, a 5-fold lower VAP prevalence was induced by the study protocol in comparison with application of saline or aspiration alone (8 % vs. 39 % and 42 %, respectively).

Despite this study's promising results, there is a lack of data about the potential danger of reactions to povidone-iodine, about its effectiveness against multi-

drug-resistant pathogens, and about the risk of promoting the development of albeit unlikely resistance. A future multicenter study focusing not only on effectiveness but also on other end-points, including adverse effects, effectiveness against multidrug resistant pathogens and the risk of promoting the development of resistance, is required before drawing more definite conclusions [21].

In the mean time, randomized controlled trials of oral decontamination demonstrated the effectiveness of the topical use of 0.12 % or 0.2 % chlorhexidine solution [23, 39 – 41], while a higher concentration of 2 % chlorhexidine solution was also suggested to be safe and effective [42]. However, it remains unclear which concentration is most beneficial, thereby offering another aspect of oral care for research to focus on.

In addition to its use in mouthwashes, chlorhexidne has been investigated as a 0.12 % dentifrice gel [43], 0.12 % and 0.2 % sprays [44], and in experimental toothbrushes with a slow-release system [45]. Compared to these applications, the mouthwash appeared to be significantly more effective [43 – 45]. Future research should focus on determining whether innovative and more practical methods for oral care that become available can improve the quality of oral care [4]. This is of particular importance because cleaning the oral cavity is considered as an unpleasant and difficult task [4]. The use of novel, effective equipment may help to modulate this negative perception.

Combined strategies

Combinations of mechanical and pharmacological interventions might have interactive effects that would enhance removal of dental plaque and microbial oral flora. Support for this notion is given by the physiological processes underlying the interventions [2]. Regrettably, studies addressing the essential need for mechanical cleaning prior to the application of a chemical agent are scarce.

Recently, Munro et al. examined the effects of mechanical (toothbrushing), pharmacological (topical oral chlorhexidine), and combination (toothbrushing plus chlorhexidine) oral care on the development of VAP in mechanically ventilated ICU patients [7]. Adult patients in three ICUs were enrolled in a randomized controlled clinical trial with a 2 x 2 factorial design. Thus, patients were assigned to 1 of 4 treatment groups: (1) 0.12 % chlorhexidine solution oral swab twice daily; (2) toothbrushing three times daily; (3) toothbrushing and chlorhexidine; and (4) control (standard care). Rather surprisingly, chlorhexidine was not shown to be beneficial in the total group. However, in the subgroup of patients who did not already have a Clinical Pulmonary Infection Score (CPIS) ≥ 6 on day 1, patients in the chlorhexidine group had significantly lower CPIS values on day 3, and pneumonia (CPIS ≥ 6) developed in significantly fewer patients by day 3. Toothbrushing appeared not to be associated with lower day 3 CPIS values or less pneumonia in this subset. The interaction of toothbrushing and chlorhexidine did not appear to be significant. The results of this study support the idea of a differential benefit of a reduction in the number of oral organisms based on level of pulmonary infection, with more benefit in patients without preexisting infection [7].

In contrast to these results, a reduced risk for VAP was reported in a study where oral care was performed using a 20-fold diluted povidone-iodine gargle in combination with manual toothbrushing every 8 hours [29]. This trial, however, was not randomized, but used a historical cohort of patients who had not received oral care as controls. The authors found that the incidence of VAP,

expressed as episodes of pneumonia per 1000 ventilator days, was significantly lower in the oral care group than in the non-oral care group (3.9 vs. 10.4 %). The relative risk of VAP in the oral care group compared to the controls was 0.37, with an attributable risk of –3.96 %.

Future research is required to fully understand the interactions between mechanical and chemical strategies for cleaning the oral cavity, and to determine the most beneficial combinations.

IV

Optimal Frequency of Oral Care

A considerable disparity exists in practice recommendations concerning the optimal frequency to provide oral care for intubated patients. It has been suggested that oral care should be provided based on an 'at risk' score, or anywhere between two and four hours, depending on the patient's condition [35]. Another protocol suggests brushing every two hours and oral moistening every two hours while the patient remains intubated [35]. Trieger [46] and Bopp and colleagues [47] recommend the use of a chlorhexidine 0.12 % mouth rinse every 12 hours. The optimal frequency of providing oral care is clearly another research priority.

Role of Oral Care in VAP

Numerous researchers have focused on the role of mechanical and chemical methods for oral care in the prevention of VAP [7, 11, 18, 40, 47, 48], with rather heterogeneous results. Often, the focus is on the impact of antiseptic-based oral care on VAP rates in ICU patients. Our group systematically reviewed the literature on this topic and conducted a subsequent meta-analysis [49]. Eleven trials totaling 1971 patients met the inclusion criteria, nine of which investigated the effects of oral care with chlorhexidine (1862 patients) and two with povidone-iodine (109 patients). The use of an antiseptic was associated with a significant reduction in the incidence of VAP (relative risk (RR) 0.63; 95 % CI 0.50 – 0.81; p = 0.0002). This finding was valid for both chlorhexidene (RR 0.68; 95 % CI 0.53 – 0.88; p = 0.004) and povidone-iodine (RR 0.38; 95 % CI 0.19 – 0.75; p = 0.005). Important differences in concentrations of the antiseptic used, frequency of oral care, study methodology, and diagnostic criteria for VAP were identified across the eleven studies included in the meta-analysis. Clinical heterogeneity was confirmed statistically and was moderate (I^2 = 43 %; p = 0.08) for the trials using chlorhexidine and high (I^2 = 66 %; p = 0.09) for those assessing povidone-iodine. Subgroup analyses revealed most beneficial effects with 0.12 % and 2 % concentrations of chlorhexidine and 10 % povidone-iodine, and in a population of cardiac surgery patients. In conclusion, this analysis suggests that oral decontamination with an antiseptic reduces the incidence of VAP significantly; chlorhexidine and povidone-iodine both showed this beneficial effect [49].

Future investigators will be challenged by the important issue of which oral care strategies can contribute to the prevention of VAP, meticulously taking into the account the numerous potential confounders that might bias their findings.

Conclusion

In the field of oral care for intubated patients, many research opportunities are available that could contribute to the acquisition of evidence-based insights into what should be recommended as optimal care. Well-designed multicenter trials including an adequate sample of intubated and mechanically ventilated critically ill adults are needed to: (1) identify or develop a validated standardized tool for the assessment of the oral cavity; (2) establish the optimal method –mechanical and/or pharmacological– to safely clean the oral cavity and preserve oral health; (3) determine the chemical product of choice and its optimal concentration; (4) establish the recommended frequency for providing oral care; and (5) further investigate the role of oral care in the prevention and development of VAP. Optimally, the results of these investigations should be bundled into a set of clear and unambiguous evidence-based recommendations. These guidelines could be a tremendous help for healthcare professionals in the ICU when providing oral care in daily practice, as well as for those involved in the decision-making process about which tools and products should be purchased for oral care. By achieving these goals, one more aspect of providing care to critically ill patients would no longer be based merely on belief and tradition, but on the reliable results of solid clinical trials. Finally, but importantly, in addition to the best techniques and products, the attitude and training of healthcare professionals will always remain pivotal for the successful implementation of an effective oral care protocol.

References

1. Seymour GJ, Ford PJ, Cullinan MP, Leishman S, Yamazaki K (2007) Relationship between periodontal infections and systemic disease. Clin Microbiol Infect 13: 3 – 10
2. Munro CL, Grap MJ (2004) Oral health and care in the intensive care unit: State of the science. Am J Crit Care 13: 25 – 33
3. Costello T, Coyne I (2008) Nurses' knowledge of mouth care practices. Br J Nurs 17: 264 – 268
4. Rello J, Koulenti D, Blot S, et al (2007) Oral care practices in intensive care units: A survey of 59 European ICUs. Intensive Care Med 33: 1066 – 1070
5. Cutler CJ, Davis N (2005) Improving oral care in patients receiving mechanical ventilation. Am J Crit Care 14: 389 – 394
6. Blot S, Vandijck D, Labeau S (2008) Oral care of intubated patients. Clin Pulm Med 15: 153 – 160
7. Munro CL, Grap MJ, Jones DJ, McClish DK, Sessler CN (2009) Chlorhexidine, toothbrushing, and preventing ventilator-associated pneumonia in critically ill adults. Am J Crit Care 18: 428 – 437
8. Berry AM, Davidson PM (2006) Beyond comfort: oral hygiene as a critical nursing activity in the intensive care unit. Intensive Crit Care Nurs 22: 318 – 328
9. Johanson WG, Pierce AK, Sanford JP (1969) Changing pharyngeal bacterial flora of hospitalized patients. Emergence of gram-negative bacilli. N Engl J Med 281: 1137 – 1140
10. Gilbert P, McBain A, Sreenivasan P (2007) Common therapeutic approaches for the control of oral biofilms: microbiological safety and efficacy. Clin Microbiol Infect 13: 17 – 24
11. Fourrier F, Dubois D, Pronnier P, et al (2005) Effect of gingival and dental plaque antiseptic decontamination on nosocomial infections acquired in the intensive care unit: A double-blind placebo-controlled multicenter study. Crit Care Med 33: 1728 – 1735
12. Dennesen P, van der Ven A, Vlasveld M, et al (2003) Inadequate salivary flow and poor oral mucosal status in intubated intensive care unit patients. Crit Care Med 31: 781 – 786
13. Brennan MT, Bahrani-Mougeot F, Fox PC, et al (2004) The role of oral microbial colonization in ventilator-associated pneumonia. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 98: 665 – 672

14. Barnett J (1991) A reassessment of oral healthcare. Prof Nurse 6: 703–704, 706–708
15. Jones H, Newton JT, Bower EJ (2004) A survey of the oral care practices of intensive care nurses. Intensive Crit Care Nurs 20: 69–76
16. Grap MJ, Munro CL, Elswick RK, Sessler CN, Ward KR (2004) Duration of action of a single, early oral application of chlorhexidine on oral microbial flora in mechanically ventilated patients: A pilot study. Heart Lung 33: 83–91
17. Hayes J, Jones C (1995) A collaborative approach to oral care during critical illness. Dent Health (London) 34: 6–10
18. Koeman M, van der Ven AJ, Hak E, et al (2006) Oral decontamination with chlorhexidine reduces the incidence of ventilator-associated pneumonia. Am J Respir Crit Care Med 173: 1348–1355
19. Feider L, Mitchell P, Bridges E (2010) Oral care practices for orally intubated critically ill adults. Am J Crit Care 19: 175–183
20. Grap MJ, Munro CL, Ashtiani B, Bryant S (2003) Oral care interventions in critical care: fre quency and documentation. Am J Crit Care 12: 113–118
21. Luna CM, Ríos FG (2006) Modulating the oral colonization with povidone-iodine antiseptic: A new approach for an old controversy. Crit Care Med 34: 1572–1573
22. Seguin P, Tanguy M, Laviolle B, Tirel O, Mallédant Y (2006) Effect of oropharyngeal decontamination by povidone-iodine on ventilator-associated pneumonia in patients with head trauma. Crit Care Med 34: 1514–1519
23. DeRiso AJ 2nd, Ladowski JS, Dillon TA, Justice JW, Peterson AC (1996) Chlorhexidine gluconate 0.12 % oral rinse reduces the incidence of total nosocomial respiratory infection and nonprophylactic systemic antibiotic use in patients undergoing heart surgery. Chest 109: 1556–1561
24. Wise M, Cole J, Williams D, Lewis M, Frost P (2008) Efficacy of oral chlorhexidine in critical care. Crit Care 12: 419
25. Moshrefi A (2002) Chlorhexidine. J West Soc Periodontol Periodontal Abstr 50: 5–9
26. McCoy LC, Wehler CJ, Rich SE, Garcia RI, Miller DR, Jones JA (2008) Adverse events associated with chlorhexidine use: results from the Department of Veterans Affairs Dental Diabetes Study. J Am Dent Assoc 139: 178–183
27. Choo A, Delac DM, Messer LB (2001) Oral hygiene measures and promotion: Review and considerations. Aust Dent J 46: 166–173
28. Chua JV, Dominguez EA, Sison CMC, Berba RP (2004) The efficacy of povidone-iodine oral rinse in preventing ventilator-associated pneumonia: a randomized, double-blind, placebo-controlled (VAPOR) Trial: Preliminary report. Philippine Journal of Microbiology and Infectious Diseases 33: 153–161
29. Mori H, Hirasawa H, Oda S, Shiga H, Matsuda K, Nakamura M (2006) Oral care reduces incidence of ventilator-associated pneumonia in ICU populations. Intensive Care Med 32: 230–236
30. Treloar DM, Stechmiller JK (1995) Use of a clinical assessment tool for orally intubated patients. Am J Crit Care 4: 355–360.
31. Barnason S, Graham J, Wild MC, et al (1998) Comparison of two endotracheal tube securement techniques on unplanned extubation, oral mucosa, and facial skin integrity. Heart Lung 27: 409–417
32. Nelsey L (1986) Mouthcare and the intubated patient: The aim of preventing infection. Intensive Care Nurs 1: 187–193
33. Pearson LS (1996) A comparison of the ability of foam swabs and toothbrushes to remove dental plaque: implications for nursing practice. J Adv Nurs 23: 62–69
34. Pearson LS, Hutton JL (2002) A controlled trial to compare the ability of foam swabs and toothbrushes to remove dental plaque. J Adv Nurs 39: 480–489
35. Abidia RF (2007) Oral care in the intensive care unit: a review. J Contemp Dent Pract 8: 76–82
36. Day J, Martin MD, Chin M (1998) Efficacy of a sonic toothbrush for plaque removal by caregivers in a special needs population. Spec Care Dent 18: 202–206
37. Pobo A, Lisboa T, Rodriguez A, et al (2009) A randomized trial of dental brushing for preventing ventilator-associated pneumonia. Chest 136: 433–439
38. Jones DJ, Munro CL (2008) Oral care and the risk of bloodstream infections in mechanically ventilated adults: A review. Intensive Crit Care Nurs 24: 152–161

39. MacNaughton PD, Bailey J, Donlin N, Branfield P, Williams A, Rowswell H (2004) A randomised controlled trial assessing the efficacy of oral chlorhexidine in ventilated patients. Intensive Care Med 30: S5-S18
40. Fourrier F, Cau-Pottier E, Boutigny H, Roussel-Delvallez M, Jourdain M, Chopin C (2000) Effects of dental plaque antiseptic decontamination on bacterial colonization and nosocomial infections in critically ill patients. Intensive Care Med 26: 1239 – 1247
41. Houston S, Hougland P, Anderson JJ, LaRocco M, Kennedy V, Gentry LO (2002) Effectiveness of 0.12 % chlorhexidine gluconate oral rinse in reducing prevalence of nosocomial pneumonia in patients undergoing heart surgery. Am J Crit Care 11: 567 – 570
42. Tantipong H, Morkchareonpong C, Jaiyindee S, Thamlikitkul V (2008) Randomized controlled trial and meta-analysis of oral decontamination with 2 % chlorhexidine solution for the prevention of ventilator-associated pneumonia. Infect Control Hosp Epidemiol 29: 131 – 136
43. Slot DE, Lindeboom R, Rosema NAM, Timmerman MF, van der Weijden GA (2007) The effect of 0.12 % chlorhexidine dentifrice gel on plaque accumulation: a 3-day non-brushing model. Int J Dent Hyg 5: 45 – 52
44. Stoeken JE, Versteeg PA, Rosema NAM, Timmerman MF, van der Velden U, van der Weijden GA (2007) Inhibition of "de novo" plaque formation with 0.12 % chlorhexidine spray compared to 0.2 % spray and 0.2 % chlorhexidine mouthwash. J Periodontol 78: 899 – 904
45. Van Strydonck DAC, Timmerman MF, Van der Velden U, Van der Weijden F (2008) Clinical efficacy of a chlorhexidine-delivering toothbrush. J Clin Periodontol 35: 584 – 590
46. Trieger N (2004) Oral care in the intensive care unit. Am J Crit Care 13: 24
47. Bopp M, Darby M, Loftin KC, Broscious S (2006) Effects of daily oral care with 0.12 % chlorhexidine gluconate and a standard oral care protocol on the development of nosocomial pneumonia in intubated patients: a pilot study. J Dent Hyg 80: 1 – 13
48. Munro CL, Grap MJ, Elswick RK Jr, McKinney J, Sessler CN, Hummel RS, III (2006) Oral health status and development of ventilator-associated pneumonia: a descriptive study. Am J Crit Care 15: 453 – 460
49. Van de Vyver K, Labeau S, Brusselaers N, Vogelaers D, Blot S (2010) Impact of antiseptic based oral care on rates of ventilator-associated pneumonia in intensive care unit patients: a meta-analysis. Clin Microbiol Infect 16: S112 (abst)

V Ventilator Issues

Pros and Cons of Assisted Mechanical Ventilation in Acute Lung Injury

M. Gama de Abreu, P.R.M. Rocco, and P. Pelosi

Introduction

Protective ventilation with low tidal volume (V_T) has become the standard of care in patients with acute lung injury/acute respiratory distress syndrome (ALI/ARDS) to prevent ventilator-associated lung injury (VALI) [1]. While tight control of V_T is more easily achieved with controlled ventilation, assisted ventilatory modes are available, and their performance and suitability for use in ALI/ARDS differs according to specific criteria. In the present chapter, we discuss the effects and applications of various assisted ventilation modes on different aspects of ALI/ARDS.

Modes of Assisted Ventilation

The major advantages and disadvantages of the most commonly used, promising or innovative modes of ventilator are summarized in **Table 1**. These modes are:

a) Volume assist-control ventilation
In volume assist-control ventilation a fixed V_T is delivered in time-cycled manner (independently from the patient) in response to inspiratory activity. Two limitations of this method are stacked breaths and a mismatch between the needed and the delivered V_T [2], which can be improved by proper setting of peak inspiratory flow [3].

Retrospective analyses of the ARMA trial [1] showed that low V_T during volume assist-control ventilation was not associated with increased need for sedation [4] or neuromuscular blocking agents (NMBAs) [5]. The combination of NMBAs and volume assist-control ventilation seems to be associated with improved oxygenation [6] and decreased lung inflammation [7] in ARDS. In ARDS patients with $PaO_2/FiO_2 < 120$ mmHg, the use of NMBAs in the first 48 hours of volume assist-control ventilation decreased mortality [8]. Nevertheless, the possibility of stacked breaths or patient/ventilator asynchrony in volume assist-control ventilation, resulting from mechanisms that have not been elucidated yet, suggests that this ventilation mode should be avoided in the first 48 hours of severe ARDS.

b) Pressure assist-control ventilation
As with volume assist-control ventilation, pressure assist-control ventilation can be triggered by both the patient's inspiratory effort and time cycling. However, in

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Table 1. Major advantages and disadvantages of the most commonly used, promising and innovative modes of assisted mechanical ventilation in acute lung injury/acute respiratory distress syndrome

Mode	VACV	PACV	PSV	BiPAP/APRV + SB	PAV/PPS	ASV	NAVA	Noisy PSV
Advantages	1) tight control of V_T settings 2) allows controlled ventilation 3) best clinically investigated mode	1) tight control of inspiratory Paw 2) allows controlled ventilation 3) decelerating flow profile 4) improves synchrony	1) tight control of inspiratory Paw 2) large clinical experience 3) improves lung function and inflammation	1) tight control of inspiratory Paw 2) allows non-supported breaths 3) improves lung function	1) adapts to the patient's demand 2) improves synchrony 3) improves comfort 4) increases variability of the respiratory pattern	1) control of inspiratory Paw 2) allows smooth transition from controlled to assisted ventilation 3) growing clinical experience	1) best synchrony 2) adapts to the patient's demand 3) increases variability of the respiratory pattern 4) reduces lung function and inflammation in experimental models	1) allows to increase the variability of the respiratory pattern independent of patient's own variability 2) decreases work of breathing 3) improves lung function and inflammation in experimental models
Disadvantages	1) potential for asynchrony 2) potential for stacked breaths 3) does not adapt to the patient's demand 4) may worsen lung function and inflammation in severe ARDS	1) no tight control of V_T 2) impact on lung function and inflammation not well known 3) does not adapt to the patient's demand	1) no tight control of V_T 2) only for assisted ventilation 3) does not adapt to the patient's demand	1) no tight control of V_T 2) increases work of breathing 3) potential for asynchrony	1) no tight control of V_T 2) only for assisted ventilation 3) potential for runaway	1) no tight control of V_T 2) physician has no control of relevant settings	1) no tight control of V_T (as part of the concept) 2) requires placement of an esophageal catheter and its proper position 3) only for assisted ventilation	1) no tight control of V_T (as part of the concept) 2) does not adapt to the patient's demand 3) no clinical data available

VACV: volume assist-control ventilation; PACV: pressure assist-control ventilation; PSV: pressure support ventilation; BiPAP/APRV+SB: biphasic intermittent positive airway pressure/airway pressure release ventilation with non-supported spontaneous breathing; PAV/PPS: proportional assist ventilation/proportional pressure support; ASV: adaptive support ventilation; NAVA: neurally-adjusted ventilatory assist; Noisy PSV: noisy pressure support ventilation; Paw: airway pressure

pressure assist-control ventilation, inspiratory flow is delivered at a variable rate and with a decelerating pattern. In addition, the resulting V_T depends strongly on the mechanical properties of the respiratory system and inspiratory effort. Thus, during pressure assist-control ventilation there is even less guarantee that V_T will be within the protective range. On the other hand, patient/ventilator synchrony during pressure assist-control ventilation may be improved and work of breathing reduced as compared to volume assist-control ventilation [9].

c) Pressure support ventilation

Pressure support ventilation (PSV) is the most common mode of assisted mechanical ventilation [10]. During PSV, each breath is supported by the same level of pressure at the airway (Paw). Pressure support can be triggered by either Paw or flow during inspiration. Cycling-off typically occurs at 25 % of peak flow. Patient-ventilator synchrony is improved with PSV, reducing the work of breathing and preventing fatigue of respiratory muscles. On the other hand, PSV depends on sufficient ventilatory drive and preserved mechanics of the respiratory system. As a consequence, V_T may exceed the limits of protective ventilation. In addition, typical cyclic-off settings of PSV are associated with proportionally shorter inspiration times, resulting in decreased mean Paw and possibly also in lung derecruitment. This limitation can be overcome by adjustments of cycling-off, pressure rise time, and positive end-expiratory pressure (PEEP).

d) Biphasic positive airway pressure/airway pressure release ventilation + supported/non-supported spontaneous breathing

In contrast to the previous modes, biphasic intermittent positive airway pressure and airway pressure release ventilation (BiPAP/APRV) allows free non-supported spontaneous breathing (SB) at two continuous positive airway pressure (CPAP) levels. Cycling between CPAP levels at pre-defined rates guarantees minimal alveolar ventilation. Between-cycle V_T depends on the mechanical properties of the respiratory system, cycling times and driving pressure itself (difference between CPAP levels), whereas V_T during spontaneous breathing depends on patient effort.

A major advantage of BiPAP/APRV+SB is a high mean Paw, which may be useful to stabilize alveoli in ALI/ARDS. Furthermore, inspiratory muscle activity non-supported by a positive Paw may promote lung recruitment, whereas intrathoracic pressures may decrease during free spontaneous breaths, facilitating venous return and improving cardiac filling [11]. Conversely, since inspiratory effort can occur at any moment during cycling, spontaneous breathing during the change from lower to higher CPAP may increase V_T above the protective range. Moreover, it is currently not known how much spontaneous breathing activity should be used during BiPAP/APRV+SB. Although in clinical studies spontaneous breathing was responsible for 10 – 20 % of total minute ventilation, animal studies have reported values as high as 60 %. Thus, the most suitable settings for BiPAP/APRV+SB in patients with ALI/ARDS remain to be determined.

e) Proportional assist ventilation/proportional pressure support

Proportional assist ventilation/proportional pressure support (PAV/PPS) generates positive pressure throughout inspiration in proportion to patient-generated flow and volume – in other words, the ventilator is able to adapt to changes in the patient's ventilatory demand. Despite this advantage, PAV/PPS is rarely used. This

is due in part to the need for online measurements of elastance and resistance of the respiratory system to optimize the settings of flow and volume assist components. More recently, a modification of PAV (PAV+) has been proposed to overcome this limitation. In PAV+, the mechanical properties of the respiratory system are assessed automatically during periodic occlusions of the mechanical ventilator at end-inspiration, when inspiratory muscle activity declines to zero [12].

Although patient/ventilator synchrony seems to be improved in PAV, V_T may be outside the protective range, even in the absence of runaway. The reduction in flow and volume assistance that could theoretically resolve this limitation would probably increase the work of breathing.

V

f) Adaptive support ventilation

Adaptive support ventilation (ASV) is a closed loop mode that adapts respiratory rates and V_T based on the Otis least work of breathing formula. After defining the desired minute ventilation, the ventilator iteratively adjusts the respiratory rate and V_T based on estimation of expiratory resistance and compliance of the respiratory system, at the lowest possible Paw. One particular advantage of ASV is that it can be used for both controlled and assisted ventilation (dual-mode), with smooth transition to the weaning period. If the spontaneous respiratory rate is not high enough during weaning, mandatory cycles are generated.

Although different respiratory rates and V_T are possible during ASV, a 'safety window' limits V_T ranges to avoid non-protective ventilation in ALI/ARDS. In a physical lung model with varying mechanical properties, ASV successfully avoided peak Paw > 28 cmH_2O compared to conventional protective ventilation [13]. However, V_T generated by ASV for the ideal body weight (IBW) seems to be slightly higher than 8 ml/kg during an open lung approach in patients with ALI [14]. These findings suggest that in patients with ALI/ARDS and fairly preserved respiratory system mechanics, ASV could lead to V_T higher than 6 ml/kg.

g) Neurally-adjusted ventilatory assist

In this innovative approach, the mechanical ventilator is not triggered or cycled-off by Paw or inspiratory flow. Neurally-adjusted ventilatory assist (NAVA) uses the electrical activity of the diaphragm (EAdi) as an indicator of respiratory drive to guide ventilatory support. This seems to be advantageous in terms of patient-ventilator synchrony.

Theoretically, V_T during NAVA could exceed the protective range, since volumes are solely driven by inspiratory drive and a gain factor is used to convert electrical diaphragmatic activity into pressure support. Nevertheless, relatively low V_T has been reported during NAVA [15]. These findings suggest that central respiratory drive and electrical diaphragmatic activity both adapt to prevent high V_T in ALI/ARDS. However, V_T during NAVA is not always determined by diaphragmatic activity – it may also be influenced by airway flow. Thus, if intercostal muscle movement precedes diaphragmatic electrical activity, NAVA applies a fixed pressure support to the airways, working as PSV.

h) Noisy pressure support ventilation

The respiratory system may benefit from breath-by-breath variations in Paw [16]. In contrast to controlled mechanical ventilation, most of the assisted ventilation modes support such variability.

Noisy PSV has an advantage over other assisted ventilation modes such as PAV and NAVA. During PSV, breath-by-breath differences in inspiratory effort and inspiratory time may generate oscillations in V_T and respiratory rate, but these are mostly reduced when compared to normal spontaneous breathing [17]. In contrast, PAV [17] and NAVA [18] may result in higher variabillity of the respiratory pattern than PSV. However, the variability of the respiratory pattern depends on the intrinsic variability of the patient, and is therefore influenced by sedation and disease. Noisy PSV is able to overcome such limitations by allowing pressure support to vary breath by breath as triggered by the patient, even if the respiratory center and muscles are not able to generate enough variability [19].

V_T values in noisy PSV can reach below or above the recommended limits, depending on the intrinsic inspiratory drive, mechanical properties of the respiratory system, and the level of variability chosen.

Effects on Gas Exchange

Most of the assisted ventilation modes described in this chapter have been reported to improve oxygenation compared to controlled mechanical ventilation in experimental ALI/ARDS. Our group [19] found that PSV improved oxygenation and reduced intrapulmonary shunt compared to controlled ventilation in a model of ALI/ARDS. In contrast, clinical studies have reported conflicting results concerning the effects of PSV on gas exchange. Cereda et al. [20] found that controlled ventilation and PSV led to comparable PaO_2 in patients with ALI. Yoshida et al. [21] documented improved oxygenation when patients with ARDS were switched from controlled ventilation to PSV. Differences in the severity or phase of respiratory failure may explain these conflicting findings.

The beneficial effects of BiPAP/APRV+SB on PaO_2 and intrapulmonary shunt have been well documented in oleic acid-induced respiratory failure [22]. Furthermore, BiPAP/APRV+SB seems to improve gas exchange more than PSV [23]. Our group observed similar improvements in oxygenation during BiPAP/APRV+SB compared to controlled ventilation, but not PSV, in other models of ALI/ARDS [19]. Clinical trials confirm that BiPAP/APRV+SB improves oxygenation compared to controlled ventilation [23, 24]. One recent study suggests that this mode results in even higher PaO_2 and lower intrapulmonary shunt than PSV in ARDS [21].

In a mixed population of patients with respiratory failure resulting from obstructive as well as restrictive lung disease, PAV was not superior to PSV in terms of gas exchange [25]. It should be noted that studies on the effects of PAV and ASV on gas exchange in ALI/ARDS are lacking.

In a rodent model of ALI/ARDS, NAVA resulted in improved oxygenation compared to controlled ventilation [26]. However, V_T values were not matched, resulting in increased lung injury in the controlled ventilation group. To our knowledge, there are no clinical studies comparing the effects of NAVA and controlled ventilation on gas exchange in ALI/ARDS.

An experimental pilot study from our group suggested that noisy PSV might improve oxygenation and reduce intrapulmonary shunt compared to controlled ventilation in ALI/ARDS induced by saline lung lavage [19]. However, V_T differed between the groups. Furthermore, oxygenation during noisy PSV was higher than during PSV and BiPAP/APRV+SB. Interestingly, the level of variability seems to play an important role in noisy PSV. Maximal improvement in PaO_2 is achieved

when the resulting coefficient of variation of V_T is between 20–30 %, i.e., similar to spontaneous breathing in healthy subjects [27]. However, there are no clinical data on noisy PSV in ALI/ARDS.

Effects on the Regional Distribution of Lung Aeration

Spontaneous breathing not supported by pressure is able to increase lung gas volumes during mechanical ventilation with BiPAP/APRV in experimental lung injury [28]. In oleic acid-induced ALI/ARDS, the amount of non-aerated (-100 to 0 Hounsfield Units, HU) and poorly aerated (-500 to -100 HU) lung tissue in the most caudal lung zones decreases during BiPAP/APRV+SB, suggesting that diaphragmatic muscle activity is an effective means for reversing atelectasis in those areas. Such alveolar recruitment seems to be associated with a more even distribution of aeration and less hyperinflated (-1000 to -900 HU) lung tissue [28]. In addition, BiPAP/APRV+SB is more effective for increasing lung aeration at end-expiration compared to PSV [29]. Recently, a clinical study has confirmed that BiPAP/APRV+SB and PSV both increase lung aeration in patients with ALI/ARDS in relation to controlled ventilation [21].

The potential of BiPAP/APRV+SB to reduce cyclic changes in lung aeration is illustrated in **Figure 1**. In addition to the potential of BiPAP/APRV+SB for lung

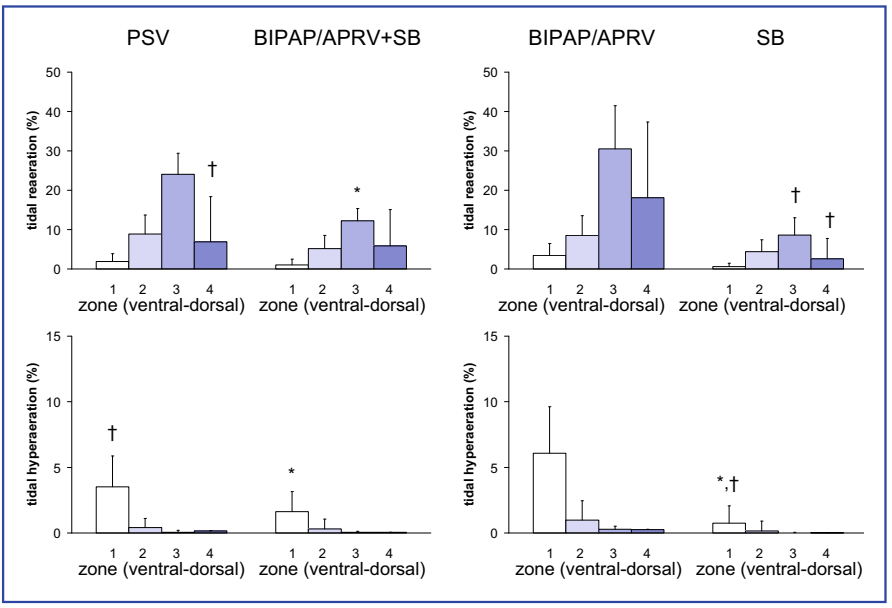

Fig. 1. Tidal reaeration and hyperaeration during pressure support ventilation (PSV), biphasic positive pressure ventilation/airway pressure release ventilation+ spontaneous breaths (BIPAP/APRV+SB), controlled (BIPAP/APRV) and spontaneous (SB) breath cycles in experimental acute lung injury. Calculations were performed for different lung zones from ventral to dorsal (1-ventral, 2-mid-ventral, 3-mid-dorsal and 4-dorsal) at lung base using dynamic computed tomography. Bars and vertical lines represent means and standard deviations, respectively. *, $p < 0.05$ *vs.* PSV; †, $p < 0.05$ vs. BIPAP/APRV (controlled ventilation). Adapted from [29] with permission.

recruitment, lower V_T during spontaneous breaths seem to be an important co-determinant of reduced tidal reaeration and hyperaeration in dynamic computed tomography (CT) scans in this mode.

Effects on the Regional Distribution of Lung Ventilation

In assisted ventilation, changes in the regional distribution of ventilation normally follow changes in aeration. Using dynamic CT scanning, our group did not detect a ventilation shift to more caudal lung regions during PSV compared to controlled ventilation [29] in experimental lung injury. Accordingly, in patients with ALI/ARDS, PSV did not improve ventilation/perfusion matching as compared to pressure controlled ventilation [23]. Using the technique of vibration response imaging, Dellinger et al. [30] were able to show that pressure support of spontaneous breathing was not associated with increased acoustic energy in more caudal lung regions as compared to pressure control ventilation.

A shift of ventilation during BiPAP/APRV+SB from non-dependent towards dependent lung zones has been reported in pigs with ALI/ARDS [28, 31]. Using the MIGET technique, an improvement in global ventilation/perfusion matching was detected during BiPAP/APRV+SB compared to controlled ventilation in patients with ALI/ARDS in the supine position [23], suggesting that ventilation was redistributed to dorsal areas. However, using dynamic CT analysis, we were not able to show that BIPAP/APRV+SB shifted the distribution of ventilation compared to PSV in experimental ALI/ARDS [29].

Effects on Regional Distribution of Lung Perfusion

It is a common belief that improved oxygenation following assisted ventilation reflects lung recruitment with increased perfusion of dependent regions.

In experimental models of ALI/ARDS, assisted ventilation with BiPAP/APRV+SB seems to result in increased perfusion of dependent lung zones compared to controlled ventilation [31]. Nevertheless, local ventilation/perfusion matching was not significantly increased in dorsal areas during BiPAP/APRV+SB compared to controlled ventilation [31], suggesting that oxygenation is strongly dependent on regional aeration.

In fact, recent works from our group have shown that increased oxygenation during PSV and noisy PSV compared to controlled ventilation is mediated by a shift of perfusion from dependent towards non-dependent lung zones [19, 32]. Accordingly, reduced regional aeration and alveolar derecruitment were observed in those areas (**Fig. 2**). Possibly, when hypoxic pulmonary vasoconstriction is preserved, a lower mean airway and transpulmonary pressure during PSV and noisy PSV may further contribute to the redistribution of perfusion by decreasing capillary impedance of better-aerated, non-dependent zones. Such a mechanism was likely involved in the improvement in oxygenation observed in patients with ALI/ARDS during PSV compared to controlled ventilation [21].

It seems that assisted ventilation has the potential to recruit the lungs if enough transpulmonary pressure is generated in dependent lung zones, and also to divert perfusion towards better aerated lung areas if recruitment does not occur.

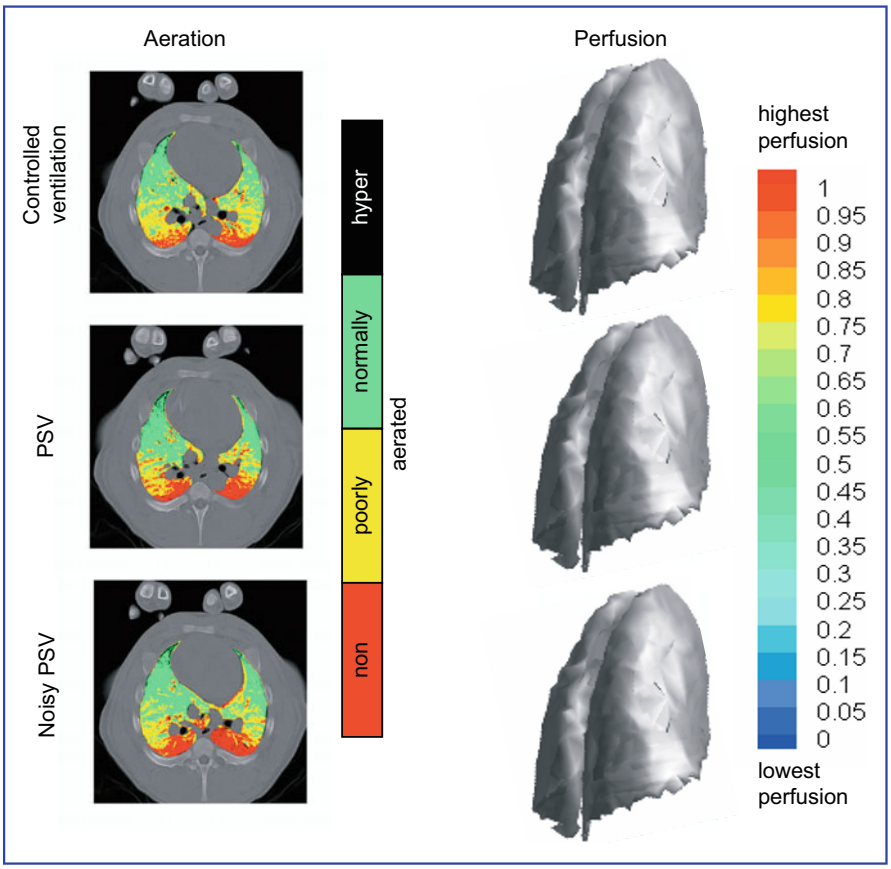

Fig. 2. Color maps of aeration on computed tomography (CT) scans of chest at hilum (left column) and of regional perfusion in whole lungs (right column) in a pig with acute lung injury induced by saline lavage. Measurements were performed during controlled ventilation as well as assisted pressure support ventilation (PSV) and noisy PSV in the same animal. The lung surface extracted from CT analysis is shown to facilitate the visualization of the spatial distribution of perfusion in the lungs. Arterial oxygenation improved during PSV and noisy PSV compared to controlled ventilation due to redistribution of perfusion towards better aerated regions rather than increased lung aeration. Adapted from [19] with permission.

Ventilator-associated Lung Injury

Mechanical ventilation may initiate or exacerbate lung injury as a result of stress and/or strain [33], opening and closing of collapsed peripheral airways and/or atelectatic lung regions, mainly located in dependent lung regions, or redistribution of pulmonary perfusion [34]. These mechanisms involve physical disruption of the lung and promote cell and inflammatory-mediator-induced injury. Inflammatory-mediator induced injury is particularly relevant because of possible systemic sequels such as multiple system organ failure, the primary cause of death in ALI/ARDS.

Assisted mechanical ventilation has been suggested to minimize the development of VALI by increasing lung volume and reducing atelectasis, leading to

improvement in lung elastance, with consequent reduction in transpulmonary pressure and in the amount of opening and closing of peripheral airways and atelectasis. Moreover, pleural pressures are redistributed. On the other hand, spontaneous breathing during assisted mechanical ventilation may exacerbate lung injury by increasing patient-ventilator asynchrony and rapid shallow breathing, and inducing further atelectasis and tidal recruitment–derecruitment [35]. Additionally, negative pleural pressures may increase intrathoracic blood volume, worsening pulmonary edema and lung damage [36].

Transpulmonary pressure is the difference between the pressure inside the alveoli (Palv) and pleural pressure (Ppl). Ppl plays a relevant role, since it influences factors that promote VALI, as mentioned above. However, there are major differences between the effects of Palv and Ppl in controlled and assisted mechanical ventilation (**Fig. 3**). During controlled mechanical ventilation, Ppl depends on V_T and lung elastance. The resulting Palv depends on V_T and the elastances of the lung and chest wall. In case of normal or quasi normal chest wall elastance, Ppl is easily predictable from Palv and V_T delivered. Increasing V_T increases Ppl and Palv accordingly. In cases of altered chest wall elastance, for the same delivered V_T, Palv may be substantially higher for unchanged Ppl. However, even in this case, if Palv is maintained within usually recommended safe limits (28 to 30 cmH_2O), the consequent Ppl might be lower, but not higher, than expected.

In contrast, during assisted mechanical ventilation, Palv does not necessarily reflect Ppl, since the degree of activation of respiratory muscles and consequent reduction in Ppl must be taken into account. In other words, even with constant Palv, the increase in inspiratory effort and Ppl, determines higher transpulmonary pressure. This has some clinical implications: a) Direct evaluation can be made based on the estimation of inspiratory effort by means of the P0.1, muscular pressure (for example, during PAV), or measurement of diaphragmatic activity (during NAVA); b) since Paw, which roughly represents Palv, does not provide any useful and reliable information about the real transpulmonary pressure, it should be carefully interpreted in the setting of minimally injurious ventilatory parame-

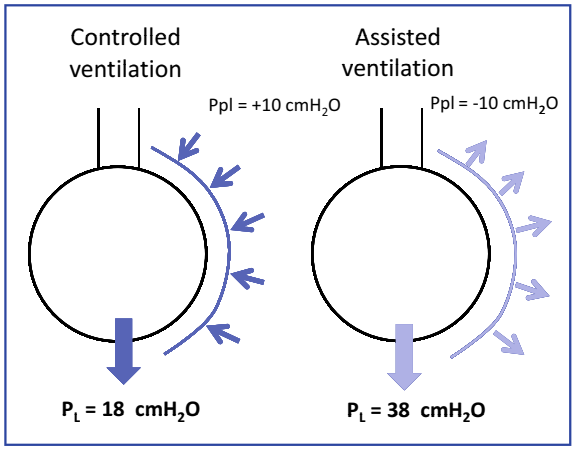

Fig. 3. Schematic representation of possible pressures applied to two alveoli during controlled (left alveolus) and assisted (right alveolus) mechanical ventilation. The pressure applied to the visceral pleura corresponds to the distending force of the lung per unit area. This is the transpulmonary pressure (P_L), which is the difference between the pressure inside the alveoli (Palv) and pleural pressure (Ppl). For the situation presented, readings of airway pressure (≈ Palv) are near the protective value of 28 cmH_2O during both controlled and assisted ventilation. However, P_L is only 18 cmH_2O during controlled ventilation, and as high as 38 cmH_2O during assisted ventilation.

ters. When assisted mechanical ventilation is associated with minimal inspiratory effort, Palv becomes a more reliable indicator of the real transpulmonary pressure; c) since ineffective breathing and higher transpulmonary pressure may occur during assisted mechanical ventilation, they should be carefully monitored.

Few experimental studies have evaluated the effects of assisted mechanical ventilation on VALI. Saddy et al. [37] compared the effects of different assisted ventilation modes (pressure assist-control ventilation with inspiratory:expiratory ratio [I:E] = 1:2 and 1:1, and Bi-Vent, a variant of BiPAP that allows spontaneous breaths assisted by pressure support in both the lower and the higher Paw levels) with pressure control ventilation on lung histology, arterial blood gases, inflammatory and fibrogenic mediators in experimental ALI in rats. Interestingly, the tidal volume delivered and the inspiratory effort were higher during assisted mechanical ventilation modes. However, inspiratory effort estimated by P0.1 was lower with Bi-Vent and PSV, and higher during assisted-pressure control modes. The main findings were that assisted ventilation modes had more beneficial effects on respiratory function and reduced lung injury compared to PSV. Among assisted ventilation modes, Bi-Vent and PSV had better functional results with less lung damage and expression of inflammatory mediators. This study raised interesting questions for assisted mechanical ventilation: a) V_T, within certain limits, and increased transpulmonary pressure may not be specific determinants of VALI; b) higher inspiratory effort during assisted mechanical ventilation could increase injury, and the 'safe' level of inspiratory effort should be determined in the near future; c) P0.1 could be useful to optimize assisted ventilation by achieving optimal recruitment with minimal stress and strain; d) modalities of assisted ventilation that favor lower I:E ratio may lead to less hyperinflation. Interestingly, Bi-Vent and PSV were associated with lower hyperinflation compared to pressure assist-control ventilation 1:1, which could be due to a better animal-ventilator interaction that reduced respiratory drive with consequent decrease in the inspiratory transpulmonary pressure.

In line with these data, Gama de Abreu et al. [29], showed that reduced tidal re-aeration and hyperaeration during BiPAP/APRV+SB compared to PSV did not result from a decrease in non-aerated areas at end-expiration or different distribution of ventilation, but rather from lower mean V_T. This suggests that the ratio between spontaneous and controlled breaths plays a pivotal role in reducing tidal re-aeration and hyperaeration during BIPAP/APRV+SB.

Different factors may promote reduced lung injury during assisted ventilation: a) recruitment of dependent atelectatic lung regions, reducing opening and closing during tidal breath, thus limiting shear stress forces; b) more homogeneous distribution of regional transpulmonary pressures; c) variability of breathing pattern; d) redistribution of perfusion towards non-atelectatic injured areas [19]; and e) improved lymphatic drainage.

In another experimental study, Brander et al. [26] found that NAVA was as effective as protective ventilation in preventing VALI, attenuating excessive systemic and remote organ inflammation, and preserving cardiac and kidney function in rabbits. However, in that study, the V_T delivered by NAVA was substantially lower that that delivered during a protective ventilation strategy (3 vs. 6 ml/kg).

Our group has recently shown that in saline lung lavage, protective ventilation with PSV and noisy PSV was associated with reduced histological lung damage and reduction in interleukin (IL)-6 in the lung tissue as compared to protective

controlled mechanical ventilation [38]. However, other authors found that BiPAP/APRV+SB did not improve hemodynamic and respiratory function, causing greater histopathologic damage to the lungs in a model of intra-abdominal hypertension [39]. In contrast with most experimental findings, Forel et al. [7] showed that NMBAs reduced pulmonary and systemic inflammation in patients with ARDS ventilated with a lung-protective strategy in volume assist-control ventilation. More recently, the same group reported a decrease in mortality in severe ARDS (PaO_2/FiO_2 < 120 mmHg) with the use of NMBAs [8].

Taken together, these observations suggest that the type of assisted mechanical ventilation and the amount of inspiratory effort play a relevant role in VALI, especially in more severe ARDS patients. In patients with abdominal compartment syndrome, assisted mechanical ventilations should be used cautiously or avoided.

Patient-ventilator Asynchrony

Patient-ventilator asynchrony refers to the uncoupling between the mechanically delivered breath and the patient's respiratory effort. It is common during assisted mechanical ventilation and may affect the morbidity of critically ill patients. Close inspection of pressure, volume and flow waveforms – displayed by modern ventilators – may help the physician to recognize and act appropriately to minimize patient-ventilator asynchrony.

A large prospective study reported that one-fourth of critically ill patients exhibited a high incidence of asynchrony during assisted ventilation. Such a high incidence was associated with prolonged duration of mechanical ventilation. Patients with frequent ineffective triggering may receive excessive levels of ventilatory support [35]. It has been shown that in patients with ARDS and increased breathing effort receiving small V_Ts, pressure-targeted compared to volume assist controlled ventilation may provide more comfort by decreasing respiratory drive during the triggering phase [40].

During PSV, markedly reducing the level of support or inspiratory duration to reach a V_T of about 6 ml/kg eliminated ineffective triggering in two-thirds of critically ill patients with weaning difficulties and a high percentage of ineffective efforts without inducing excessive work of breathing or modifying patient respiratory rate [41]. Furthermore, different studies have shown that optimization of pressure rise time and/or inspiratory/expiratory triggering is mandatory to avoid patient ventilator asynchronies in patients with ALI [42].

Sigh during Assisted Mechanical Ventilation

Assisted mechanical ventilation, especially pressure limited modalities, might promote progressive derecruitment when mean airway pressure is not optimized. For this reason, periodic hyperinflations (sighs) might be useful to prevent progressive reduction in lung volume and atelectasis. Sighs have been shown to improve recruitment and gas-exchange in ALI/ARDS patients during controlled mechanical ventilation [43]. Sighs during PSV in patients with early ARDS have been proposed to improve gas exchange and lung volume and decrease the respiratory drive [44]. In a paraquat-induced ALI model, Steimback et al. [45] showed that a reduction in sigh frequency of up to 10 sighs per hour had a protective

effect on lung and distal organs. No clinical data are currently available about the effects of sighs during assisted ventilation in ALI/ARDS.

Ventilator-induced Diaphragmatic Dysfunction

Controlled mechanical ventilation is an important cause of diaphragmatic weakness, associated with a syndrome known as ventilator-induced diaphragmatic dysfunction [46]. Clinical studies report that the duration of mechanical ventilation is associated with a decline in diaphragmatic force. It is unclear whether this relation is causal or influenced by other confounders [47]. Animal studies have demonstrated that ventilator-induced diaphragmatic dysfunction is minimized with the use of partial support modes of mechanical ventilation [48, 49]. A recent study found that healthy piglets ventilated for 72 h with adaptive support ventilation (ASV) presented greater phrenic nerve-stimulated diaphragmatic strength and fewer histological signs of atrophy compared to those ventilated with controlled mechanical ventilation [50]. Therefore, it seems important to allow as much diaphragmatic activity as possible. However, further studies are required to ascertain the optimal level of diaphragmatic effort and to determine whether the specific method of promoting diaphragmatic effort during mechanical ventilation (e.g., spontaneous breathing trials, assist-control, pressure-support, newer modes such as NAVA, etc.) has any impact on the risk of ventilator-induced diaphragmatic dysfunction. In addition, persistent oxidative stress [49] and substantial residual deficit of diaphragmatic force have been associated with partial support modes of mechanical ventilation or intermittent periods of spontaneous breathing, even in the absence of atrophy [48]. These findings suggest that other measures designed to target the specific cellular pathways involved in muscle injury may be required in order to prevent or reverse ventilator-induced diaphragmatic dysfunction.

Conclusion

The use of assisted mechanical ventilation in ALI/ARDS improves oxygenation, decreases the need for sedation and vasoactive drugs, and preserves the force of contraction and structure of respiratory muscles. Assisted ventilation modes that allow no or less supported spontaneous breathing require increased muscle respiratory activity and are more likely to recruit the lungs compared to modes that support individual breaths. In experimental ALI/ARDS, breath supported ventilation improves oxygenation by redistribution of perfusion to better aerated lung zones, rather than recruitment.

Even though assisted ventilation has been shown not to affect or decrease VALI in animal models of ALI/ARDS, recent evidence suggests that in the first 48 hours of severe ARDS ($PaO_2/FiO_2 < 120$ mmHg) the use of controlled ventilation combined with NMBAs helps to preserve lung function and reduce mortality, when compared to a ventilatory strategy in which the patient triggers the mechanical ventilator to get a predefined fixed V_T. Thus, spontaneous breathing activity should be avoided in such patients during ventilation with volume assist-control ventilation in the early phase of severe ARDS. Whether such restriction also applies to other forms of assisted ventilation that allow better patient-ventilator synchrony and how these modes compare to each other is still unclear.

References

1. The Acute Respiratory Distress Syndrome Network (2000) Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med 342: 1301 – 1308
2. Kallet RH, Campbell AR, Dicker RA Katz JA, Mackersie RC (2006) Effects of tidal volume on work of breathing during lung-protective ventilation in patients with acute lung injury and acute respiratory distress syndrome. Crit Care Med 34: 8 – 14
3. Chiumello D, Pelosi P, Calvi E, Bigatello LM, Gattinoni L (2002) Different modes of assisted ventilation in patients with acute respiratory failure. Eur Respir J 20: 925 – 933
4. Kahn JM, Andersson L, Karir V, Polissar NL, Neff MJ, Rubenfeld GD (2005) Low tidal volume ventilation does not increase sedation use in patients with acute lung injury. Crit Care Med 33: 766 – 771
5. Cheng IW, Eisner MD, Thompson BT, Ware LB, Matthay MA (2005) Acute effects of tidal volume strategy on hemodynamics, fluid balance, and sedation in acute lung injury. Crit Care Med 33: 63 – 70
6. Gainnier M, Roch A, Forel JM, et al (2004) Effect of neuromuscular blocking agents on gas exchange in patients presenting with acute respiratory distress syndrome. Crit Care Med 32: 113 – 119
7. Forel JM, Roch A, Marin V, et al (2006) Neuromuscular blocking agents decrease inflammatory response in patients presenting with acute respiratory distress syndrome. Crit Care Med 34: 2749 – 2757
8. Papazian L, Forel JM, Gacouin A, et al (2010) Neuromuscular blockers in early acute respiratory distress syndrome. N Engl J Med 363: 1107 – 1116
9. Kallet RH, Campbell AR, Alonso JA, Morabito DJ, Mackersie RC (2000) The effects of pressure control versus volume control assisted ventilation on patient work of breathing in acute lung injury and acute respiratory distress syndrome. Respir Care 45: 1085 – 1096
10. Esteban A, Ferguson ND, Meade MO, et al (2008) Evolution of mechanical ventilation in response to clinical research. Am J Respir Crit Care Med 177: 170 – 177
11. Varelmann D, Muders T, Zinserling J, et al (2008) Cardiorespiratory effects of spontaneous breathing in two different models of experimental lung injury: a randomized controlled trial. Crit Care 12: R135
12. Younes M, Webster K, Kun J, Roberts D, Masiowski B (2001) A method for measuring passive elastance during proportional assist ventilation. Am J Respir Crit Care Med 164: 50 – 60
13. Sulemanji D, Marchese A, Garbarini P, Wysocki M, Kacmarek RM (2009) Adaptive support ventilation: an appropriate mechanical ventilation strategy for acute respiratory distress syndrome? Anesthesiology 111: 863 – 870
14. Dongelmans DA, Veelo DP, Binnekade JM, et al (2010) Adaptive support ventilation with protocolized de-escalation and escalation does not accelerate tracheal extubation of patients after nonfast-track cardiothoracic surgery. Anesth Analg 111: 961 – 967
15. Colombo D, Cammarota G, Bergamaschi V, De Lucia M, Corte FD, Navalesi P (2008) Physiologic response to varying levels of pressure support and neurally adjusted ventilatory assist in patients with acute respiratory failure. Intensive Care Med 34: 2010 – 2018
16. Suki B, Alencar AM, Sujeer MK et al (1998) Life-support system benefits from noise. Nature 393: 127 – 128
17. Varelmann D, Wrigge H, Zinserling J, Muders T, Hering R, Putensen C (2005) Proportional assist versus pressure support ventilation in patients with acute respiratory failure: cardiorespiratory responses to artificially increased ventilatory demand. Crit Care Med 33: 1968 – 1975
18. Schmidt M, Demoule A, Cracco C, et al (2010) Neurally adjusted ventilatory assist increases respiratory variability and complexity in acute respiratory failure. Anesthesiology 112: 670 – 681
19. Gama de Abreu M, Spieth P, Pelosi P, et al (2008) Noisy pressure support ventilation: a pilot study on a new assisted ventilation mode in experimental lung injury. Crit Care Med 36: 818 – 827
20. Cereda M, Foti G, Marcora B, et al (2000) Pressure support ventilation in patients with acute lung injury. Crit Care Med 28: 1269 – 1275

21. Yoshida T, Rinka H, Kaji, A et al (2009) The impact of spontaneous ventilation on distribution of lung aeration in patients with acute respiratory distress syndrome: airway pressure release ventilation versus pressure support ventilation. Anesth Analg 109: 1892 – 1900
22. Wrigge H, Zinserling J, Neumann P, et al (2003) Spontaneous breathing improves lung aeration in oleic acid-induced lung injury. Anesthesiology 99: 376 – 384
23. Putensen C, Mutz N, Putensen-Himmer G, Zinserling J (1999) Spontaneous breathing during ventilatory support improves ventilation-perfusion distributions in patients with acute respiratory distress syndrome. Am J Respir Crit Care Med 159: 1241 – 1248
24. Putensen C, Zech S, Wrigge H, et al (2001) Long-term effects of spontaneous breathing during ventilatory support in patients with acute lung injury. Am J Respir Crit Care Med 164: 43 – 49
25. Kondili E, Xirouchaki N, Vaporidi K, Klimathianaki M, Georgopoulos D (2006) Short-term cardiorespiratory effects of proportional assist and pressure-support ventilation in patients with acute lung injury/acute respiratory distress syndrome. Anesthesiology 105: 703 – 708
26. Brander L, Sinderby C, Lecomte F, et al (2009) Neurally adjusted ventilatory assist decreases ventilator-induced lung injury and non-pulmonary organ dysfunction in rabbits with acute lung injury. Intensive Care Med 35: 1979 – 1989
27. Spieth P, Carvalho AR, Güldner A, et al (2009) Effects of different levels of pressure support variability in experimental lung injury. Anesthesiology 110: 342 – 350
28. Wrigge H, Zinserling J, Neumann P, et al (2005) Spontaneous breathing with airway pressure release ventilation favors ventilation in dependent lung regions and counters cyclic alveolar collapse in oleic-acid-induced lung injury: a randomized controlled computed tomography trial. Crit Care 9: R780-R789
29. Gama de Abreu M, Cuevas M, Spieth PM, et al (2010) Regional lung aeration and ventilation during pressure support and biphasic positive airway pressure ventilation in experimental lung injury. Crit Care 14: R34
30. Dellinger RP, Jean S, Cinel I, et al (2007) Regional distribution of acoustic-based lung vibration as a function of mechanical ventilation mode. Crit Care 11: R26
31. Neumann P, Wrigge H, Zinserling J, et al (2005) Spontaneous breathing affects the spatial ventilation and perfusion distribution during mechanical ventilatory support. Crit Care Med 33: 1090 – 1095
32. Carvalho AR, Spieth PM, Pelosi P, et al (2009) Pressure support ventilation and biphasic positive airway pressure improve oxygenation by redistribution of pulmonary blood flow. Anesth Analg 109: 856 – 865
33. Gattinoni L, Carlesso E, Cadringher P, Valenza F, Vagginelli F, Chiumello D (2003) Physical and biological triggers of ventilator-induced lung injury and its prevention. Eur Respir J Suppl 47: 15s-25s
34. Hotchkiss JR, Jr., Blanch L, Naveira A, et al (2001) Relative roles of vascular and airspace pressures in ventilator-induced lung injury. Crit Care Med 29: 1593 – 1598
35. Thille AW, Rodriguez P, Cabello B, Lellouche F, Brochard L (2006) Patient-ventilator asynchrony during assisted mechanical ventilation. Intensive Care Med 32: 1515 – 1522
36. Kallet RH, Alonso JA, Luce JM, Matthay MA (1999) Exacerbation of acute pulmonary edema during assisted mechanical ventilation using a low-tidal volume, lung-protective ventilator strategy. Chest 116: 1826 – 1832
37. Saddy F, Oliveira GP, Garcia CS, et al (2009) Assisted ventilation modes reduce the expression of lung inflammatory and fibrogenic mediators in a model of mild acute lung injury. Intensive Care Med 36: 1417 – 1426
38. Gama de Abreu M, Spieth PM, Carvalho AR, et al (2010) Pressure support ventilation improves oxygenation with less lung injury and is further improved by random variation of pressure support. Am J Respir Crit Care Med 181: A4073 (abst)
39. Henzler D, Hochhausen N, Bensberg R, et al (2010) Effects of preserved spontaneous breathing activity during mechanical ventilation in experimental intra-abdominal hypertension. Intensive Care Med 36: 1427 – 1435
40. Yang LY, Huang YC, Macintyre NR (2007) Patient-ventilator synchrony during pressure-targeted versus flow-targeted small tidal volume assisted ventilation. J Crit Care 22: 252 – 257

41. Thille AW, Cabello B, Galia F, Lyazidi A, Brochard L (2008) Reduction of patient-ventilator asynchrony by reducing tidal volume during pressure-support ventilation. Intensive Care Med 34: 1477 – 1486
42. Chiumello D, Pelosi P, Taccone P, Slutsky A, Gattinoni L (2003) Effect of different inspiratory rise time and cycling off criteria during pressure support ventilation in patients recovering from acute lung injury. Crit Care Med 31: 2604 – 2610
43. Pelosi P, Cadringher P, Bottino N, et al (1999) Sigh in Acute Respiratory Distress Syndrome. Am J Respir Crit Care Med 159: 872 – 880
44. Patroniti N, Foti G, Cortinovis B, et al (2002) Sigh improves gas exchange and lung volume in patients with acute respiratory distress syndrome undergoing pressure support ventilation. Anesthesiology 96: 788 – 794
45. Steimback PW, Oliveira GP, Rzezinksi AF, et al (2009) Effects of frequency and inspiratory plateau pressure during recruitment manoeuvres on lung and distal organs in acute lung injury. Intensive Care Med 35: 1120 – 1128
46. Levine S, Nguyen T, Taylor N, et al (2008) Rapid disuse atrophy of diaphragm fibers in mechanically ventilated humans. N Engl J Med 358: 1327 – 1335
47. Hermans G, Agten A, Testelmans D, Decramer M, Gayan-Ramirez G (2010) Increased duration of mechanical ventilation is associated with decreased diaphragmatic force: a prospective observational study. Crit Care 14: R127
48. Sassoon CS, Zhu E, Caiozzo VJ (2004) Assist-control mechanical ventilation attenuates ventilator-induced diaphragmatic dysfunction. Am J Respir Crit Care Med 170: 626 – 632
49. Futier E, Constantin JM, Combaret L, et al (2008) Pressure support ventilation attenuates ventilator-induced protein modifications in the diaphragm. Crit Care 12: R116
50. Jung B, Constantin JM, Rossel N, et al (2010) Adaptive support ventilation prevents ventilator-induced diaphragmatic dysfunction in piglet: an in vivo and in vitro study. Anesthesiology 112: 1435 – 1443

Can 'Permissive' Hypercapnia Modulate the Severity of Sepsis-induced ALI/ARDS?

G. Curley, M. Hayes, and J.G. Laffey

V

Introduction

Ventilatory strategies that reduce lung stretch by reducing tidal and minute ventilation, which results in a 'permissive' hypercapnic acidosis, improve outcome in patients with acute lung injury/acute respiratory distress syndrome (ALI/ARDS) [1, 2]. Reassuringly, evidence from clinical studies attests to the safety and lack of detrimental effects of hypercapnic acidosis [2]. Of particular importance, a secondary analysis of data from the ARDSnet tidal volume study [1] demonstrated that the presence of hypercapnic acidosis at the time of randomization was associated with improved patient survival in patients who received high tidal volume ventilation [3]. These findings have resulted in a shift in paradigms regarding hypercapnia – from avoidance to tolerance – with hypercapnia increasingly permitted in order to realize the benefits of low lung stretch. Consequently, low tidal and minute volume ventilation and the accompanying 'permissive' hypercapnia are now the standard of care for patients with ALI/ARDS, and are increasingly used in the ventilatory management of a diverse range of diseases leading to acute severe respiratory failure, including asthma and chronic obstructive pulmonary disease.

The inflammatory response plays a central role in the pathogenesis of injury and in the repair process in ALI/ARDS [4]. Inflammation is a highly conserved process in evolution, which is essential for survival. It functions to resolve the injurious process, facilitate repair, and return the host to a state of homeostasis. The ideal inflammatory process is rapid, causes focused destruction of pathogens, yet is specific and ultimately self-limiting [5]. In contrast, when the inflammatory response is dysregulated or persistent, this can lead to excessive host damage, and contribute to the pathogenesis of lung and systemic organ injury, leading to multiple organ failure and death. The potential for hypercapnia and/or its associated acidosis to potently inhibit the immune response is increasingly recognized [6, 7]. Where the host immune response is a major contributor to injury, such as in non-septic ALI/ARDS, these effects would be expected to result in potential benefit. This has been demonstrated clearly in relevant pre-clinical ALI/ARDS models, where hypercapnic acidosis has been demonstrated to attenuate ALI induced by free radicals [8], pulmonary [9] and systemic ischemia-reperfusion [10], pulmonary endotoxin instillation [11], and excessive lung stretch [12]. The protective effects of hypercapnic acidosis in these models appear due, at least in part, to its anti-inflammatory effects.

The effects of hypercapnia in sepsis-induced lung injury, where a robust immune response to microbial infection is central to bacterial clearance and

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recovery, is less clear. Of concern, severe sepsis-induced organ failure, whether pulmonary or systemic in origin, is the leading cause of death in critically ill adults and children [13]. Sepsis-induced ARDS is associated with the highest mortality rates. Evidence suggests that approximately 40 % of patients with severe sepsis develop ARDS [13]. Furthermore, infection frequently complicates critical illness due to other causes, with an infection prevalence of over 44 % reported in this population [14]. These issues underline the importance of understanding the effects of hypercapnia on the immune response, and the implications of these effects in the setting of sepsis.

Hypercapnia and the Innate Immune Response

Function of the Innate Immune Response

The immune system can be viewed as having two interconnected branches, namely the innate and adaptive immune responses [5]. The innate immune system is an ancient, highly conserved response, being present in some form in all metazoan organisms. This response is activated by components of the wall of invading microorganisms, such as lipopolysaccharide (LPS) or peptidoglycan, following the binding of these pathogen-associated molecular patterns to pattern recognition receptors, such as the Toll-like receptors (TLRs) on tissue macrophages. The innate immune response is also activated by endogenous 'danger' signals, such as mitochondrial components [15], providing an elegant explanation for why non-septic insults can also lead to organ injury and dysfunction. An inflammatory cascade is then initiated, involving cytokine signaling activation of phagocytes that kill bacteria, as is activation of the (later) adaptive immune response.

Activation of the Innate Immune Response

Hypercapnic acidosis has been demonstrated to inhibit multiple components of the host innate immune responses. Activation of the innate immune response initiates a conserved signaling cascade that culminates in the activation of transcription factors, such as nuclear factor kappa-B (NF-κB) [5]. These transcription factors drive the expression of multiple genes that activate and regulate the pro-inflammatory and repair processes. Increasing evidence suggests that hypercapnic acidosis directly inhibits the activation of NF-κB [16]. Intriguingly, this effect of hypercapnic acidosis may be a property of the CO_2 rather than its associated acidosis [17–19]. If confirmed, this finding suggests the presence of a molecular CO_2 sensor in mammalian cells. This mechanism of action of hypercapnic acidosis has been demonstrated to underlie some of the anti-inflammatory effects of hypercapnia [16], and to be a key mechanism by which hypercapnia – whether buffered or not – reduces pulmonary epithelial wound healing [18].

Coordination of the Innate Immune Response

Hypercapnic acidosis also interferes with coordination of the innate immune response by reducing cytokine signaling between immune effector cells. Hypercapnic acidosis reduces neutrophil [20] and macrophage [21] production of pro-inflammatory cytokines such as tumor necrosis factor (TNF)-α, interleukin (IL)-

1β, IL-8 and IL-6. Hypercapnic acidosis reduced endotoxin stimulated macrophage release of TNFα and IL-1β *in vitro* [21]. Peritoneal macrophages incubated under hypercapnic conditions demonstrated a prolonged reduction in endotoxin-stimulated TNF-α and IL-1β release [22]. In contrast, a recent study reported rapid onset and rapid reversibility of IL-6 inhibition by hypercapnia in mature macrophage stimulated with LPS [19]. The mechanism underlying hypercapnic acidosis-mediated inhibition of cytokine and chemokine production appears to be mediated at least in part *via* inhibition of activation of NF-κB.

The Cellular Innate Immune Response

Neutrophils and macrophages are important effectors of the innate immune response in the setting of bacterial infection. Neutrophils rapidly migrate from the bloodstream to areas of infection, and rapidly phagocytose invading microorganisms. Tissue macrophages and their blood borne monocyte counterparts are activated by bacterial products such as endotoxin, and coordinate the activation of the adaptive immune response in the setting of infection by presenting foreign antigen to lymphocytes and secreting chemokines. Both monocytes and macrophages phagocytose and kill pathogens by similar mechanisms but at a slower rate than neutrophils.

Hypercapnic acidosis may impact on the cellular immune response *via* both direct and indirect mechanisms. Hypercapnic acidosis inhibits neutrophil expression of the chemokines, selectins and intercellular adhesion molecules [16, 20], which facilitate neutrophil binding to the endothelium and migration out of the vascular system. The potential for hypercapnic acidosis to inhibit neutrophil chemotaxis and migration to the site of injury has been confirmed *in vivo*, where hypercapnic acidosis inhibits pulmonary neutrophil infiltration in response to endotoxin instillation [11]. Hypercapnic acidosis directly impairs neutrophil phagocytosis *in vitro* [23]. This inhibitory effect appears to be a function of the acidosis *per se*, with buffering restoring neutrophil phagocytosis [24]. Hypercapnic acidosis also inhibits phagocytosis of opsonized polystyrene beads by human alveolar macrophages, although the levels of CO_2 utilized to demonstrate this effect were well beyond the range encountered clinically [19].

Neutrophils and macrophages kill ingested bacteria by producing free radicals such as superoxide, hydrogen peroxide, and hypochlorous acid, and releasing these into the phagosome. This is a pH-dependent process, with free radical production decreased at low pH [25]. Hypercapnic acidosis inhibits the generation of oxidants such as superoxide by unstimulated neutrophils and by neutrophils stimulated with opsonized *Escherichia coli* or with phorbol esters [20]. In contrast, hypocapnic alkalosis stimulates neutrophil oxidant generation [20]. Inhibition of the intracellular pH changes with acetazolamide attenuated these effects. More recently, hypercapnic acidosis has been demonstrated to reduce oxidative reactions in the endotoxin injured lung by a mechanism involving inhibition of myeloperoxidase-dependent oxidation [26]. The potential for hypercapnic acidosis to reduce free radical formation, while beneficial where host oxidative injury is a major component of the injury process, may be disadvantageous in sepsis, where free radicals are necessary to cause bacterial injury and death.

Neutrophil apoptosis following phagocytic activity generally occurs within 48 hours of release into the circulation. Conversely, neutrophil death via necrosis causes release of intracellular contents, including harmful enzymes, which can

cause tissue destruction. Neutrophils appear to have an increased probability of dying by necrosis following intracellular acidification during phagocytosis [27]. Hypercapnic acidosis may, therefore, increase the probability of neutrophil cell death occurring via necrosis rather than apoptosis.

Hypercapnia and the Adaptive Immune Response

The adaptive immune system is activated by the innate response following activation of pattern recognition receptors that detect molecular signatures from microbial pathogens. Specific major histocompatibility complex molecules on T and B lymphocytes also bind microbial components. These activation events lead to the generation of T and B lymphocyte-mediated immune responses over a period of several days.

Much of the focus to date regarding the effects of hypercapnic acidosis on immune response to injury and/or infection has been on the innate immune response. Less is known about the effects of hypercapnic acidosis on adaptive or acquired immunity. However, important clues as to the potential for hypercapnic acidosis to modulate the adaptive response come from the cancer literature. The tumor microenvironment is characterized by poor vascularization, resulting in tissue hypoxia and acidosis. In a situation analogous to sepsis, acidosis in this setting may hamper the host immune response to tumor cells, potentially leading to increased tumor growth and spread. The cytotoxic activity of human lymphokine activated killer cells and natural killer cells is diminished at acidic pH [28]. Metabolic acidosis reduces lysis of various tumor cell lines by cytotoxic T-lymphocytes [29]. In contrast, the motility of IL-2-stimulated lymphocytes appears to be stimulated in the presence of an acidified extracellular matrix and severe extracellular acidosis (pH 6.5) also appears to enhance the antigen presenting capacity of dendritic cells [30]. The net effect of these contrasting actions of metabolic acidosis on the adaptive immune response is unclear. However, the demonstration that hypercapnic acidosis enhanced systemic tumor spread in a murine model [31] raises clear concerns regarding the potential for hypercapnic acidosis to suppress cell-mediated immunity.

Hypercapnia and Acidosis Modulate Bacterial Proliferation

Carbon dioxide has broadly similar effects within the various families of microorganisms, but the sensitivity to CO_2 varies across the families, e.g., yeasts are quite resistant to the inhibitory effects of CO_2, Gram-positive organisms are somewhat less resistant, and Gram-negative organisms are the most vulnerable [32]. Optimal anaerobic *E. coli* growth occurs at a CO_2 tension (PCO_2) of 0.05 atmospheres, which is similar to the PCO_2 in the gut. The aerobic growth rate of *E. coli* was not inhibited by a PCO_2 of 0.2 atmospheres but was inhibited at partial pressures above 0.6 atmospheres [33]. It is important to remember that these levels are extremely high in the context of human physiology.

Of concern, however, is the demonstration by Pugin et al. that more clinically relevant degrees of metabolic acidosis can directly enhance bacterial proliferation *in vitro* [34]. Cultured lung epithelial cells exposed to cyclic stretch similar to that seen with mechanical ventilation produced a lactic acidosis that markedly

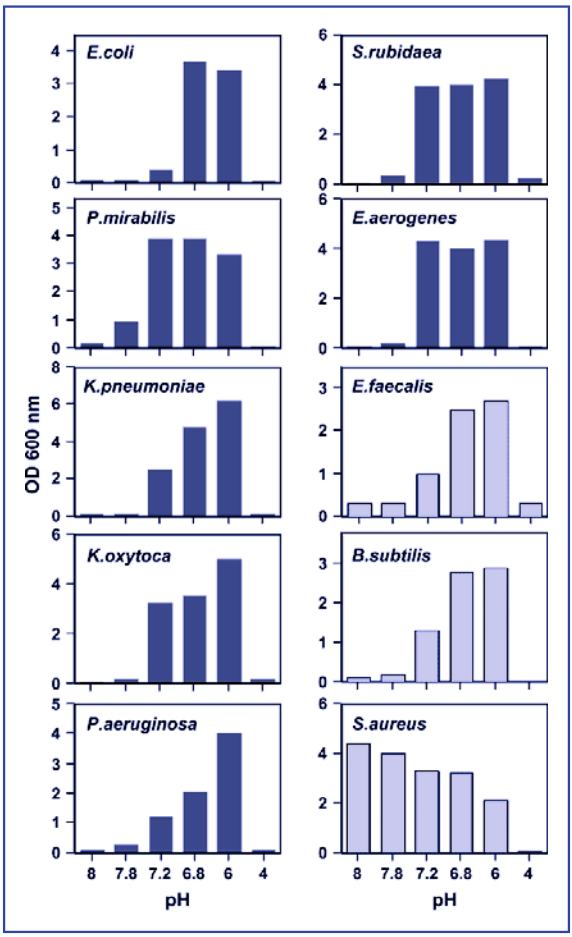

Fig. 1. Bacterial pathogens proliferate more rapidly in the setting of metabolic acidosis. All bacterial strains tested, except for a methicillin-resistant *S. aureus,* had a marked growth advantage at moderately acidic pH levels (7.2–7.6) relevant to the clinical setting. Gram-negative bacteria are represented by dark blue bars while Gram-positive bacteria are represented by light blue bars. From [34] with permission

enhanced the growth of *E. coli* [34]. This was a direct effect of hydrogen ions, as direct acidification of the culture medium to a pH of 7.2 with hydrochloric acid enhanced *E. coli* growth. In contrast, alkalinizing the pH of conditioned media from stretched lung cells abolished the enhancement of *E. coli* growth. A range of Gram-positive and Gram-negative bacteria (including *E. coli, Proteus mirabilis, Serratia rubidaea, Klebsiella pneumoniae, Enterococcus faecalis*, and *Pseudomonas aeruginosa*) isolated from patients with ventilator-associated pneumonia (VAP), grew better in acidified media (**Fig. 1**). Interestingly, this effect was not seen with a methicillin resistant *Staphylococcus aureus* (MRSA) strain, which appeared to grow best at an alkaline pH [34].

The effects of hypercapnic acidosis on bacterial proliferation at levels encountered in the context of permissive hypercapnia are unclear. The net effect is likely to be a combination of the effects of the acidosis and of the hypercapnia. Nevertheless, the demonstration that clinically relevant levels of metabolic acidosis enhance bacterial growth is of concern.

Implications for Hypercapnia in Sepsis

Immunocompetence is essential to an effective host response to microbial infection. Hypercapnia and/or acidosis may modulate the interaction between host and bacterial pathogen *via* several mechanisms, resulting in a broad based suppression of the inflammatory response.

Hypercapnia, Acidosis and the Host Response

The initial host response to invading pathogens is dominated by neutrophil activation, migration to the infective site, and phagocytosis and killing of bacteria. Compartmentalized release of neutrophil proteolytic enzymes and myeloperoxidase-dependent oxygen radicals results in effective pathogen destruction. However, excessive release of these potent mediators into the extracellular space results in damage to host tissue and worsening ALI. Consistent with this is the finding that recovery of neutrophil count in neutropenic patients worsens the severity of ALI [35]. Hypercapnic acidosis may reduce the potential for damage to host tissue during the response to infection, by reducing lung neutrophil recruitment [10], adherence [16], intracellular pH regulation [12], oxidant generation [8], and phagocytosis [23]. These mechanisms are considered to underlie some of the protective effects of hypercapnic acidosis in non-sepsis induced ALI [7]. However, these effects of hypercapnic acidosis may be detrimental in sepsis, given the central role of neutrophil mediated phagocytosis of microbial pathogens and activation of the cytokine cascade to the host response to infection. In this context, defects in neutrophil function are associated with increased sepsis severity and worse outcome [36].

Early Versus Late Bacterial Infection

The effects of this hypercapnic acidosis-induced immune modulation may vary depending upon the stage of the infective process. The anti-inflammatory properties of hypercapnic acidosis may reduce the intensity of the initial host response to infection, thus attenuating tissue damage (**Fig. 2**). However, the mechanisms whereby bacteria mediate tissue injury are complex and not limited to the contribution from an excessive host response. In late or prolonged pneumonia, in which tissue injury from direct bacterial spread and invasion makes a significant contribution, hypercapnic acidosis might impair bactericidal host responses. In the absence of effective antibiotic therapy, this may lead to enhanced bacterial spread and replication leading to more severe tissue destruction and lung and systemic organ injury (**Fig. 2**).

Impact on Repair Following Injury

Hypercapnic acidosis has been demonstrated to retard the repair process following lung cell and tissue injury. Hypercapnia slowed resealing of stretch-induced cell membrane injuries [37] and inhibited the repair of pulmonary epithelial wounds [18] by a mechanism involving inhibition of the NF-κB pathway. These findings raise the potential that hypercapnic acidosis could lead to increased bacterial translocation through defects in the pulmonary epithelium, while also delaying the recovery process following a septic insult.

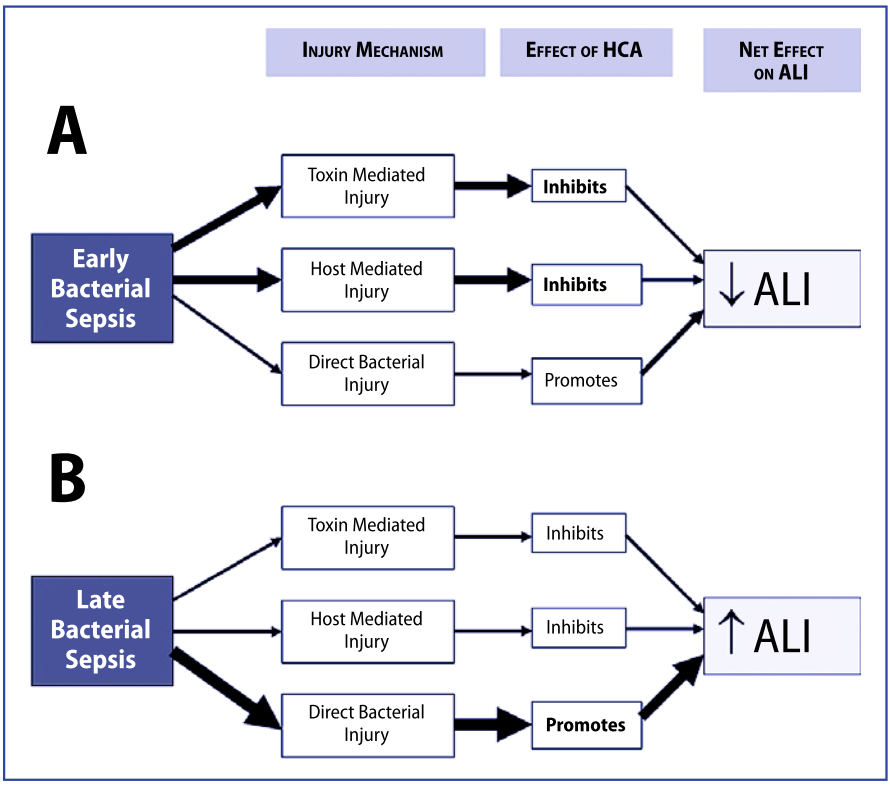

Fig. 2. Potential mechanisms underlying the effects of hypercapnic acidosis in sepsis. **Panel A** represents early sepsis, in which hypercapnic acidosis may reduce the host inflammatory response and decrease the contribution of bacterial toxin mediated injury to tissue injury and damage. This might result in an overall decrease in lung injury. **Panel B** represents late or prolonged bacterial sepsis, where a hypercapnic acidosis-mediated decrease in the host response to bacterial infection might result in unopposed bacterial proliferation, thereby increasing direct bacterial tissue invasion and injury, and worsening lung injury. ALI: acute lung injury; HCA: hypercapnic acidosis.

Recent studies in relevant preclinical models have significantly advanced our understanding of the effects of hypercapnic acidosis in both pulmonary and systemic sepsis-induced ALI/ARDS. These studies reveal the importance of severity, site, and stage of the infective process, the need for antibiotic therapy, and the utility of buffering the hypercapnic acidosis in this setting.

Hypercapnia in Pulmonary Sepsis

Early Lung Infection

The effect of hypercapnic acidosis on pneumonia-induced ALI appears to depend on the stage and severity of the infection. In an acute severe bacterial pneumonia-induced lung injury, hypercapnic acidosis improved physiological indices of injury [38]. Intriguingly, these protective effects were mediated by a mechanism independent of neutrophil function. In contrast, hypercapnic acidosis did not

alter the magnitude of lung injury in a less severe acute bacterial pneumonia [39]. Importantly these *in vivo* studies showed no increase in bacterial count in animals exposed to hypercapnic acidosis, a reassuring finding given concerns regarding retardation of the host bactericidal response and potential bacterial proliferation.

In the clinical setting, many critically ill patients will have established infection at the time of presentation. Thus animal models of established bacterial pneumonia, in which hypercapnic acidosis was introduced several hours following induction of infection with *E. coli*, more closely resemble the clinical setting. In an established pneumonia model, hypercapnic acidosis induced after the development of a significant pneumonia-induced lung injury reduced physiological indices of lung injury [40]. Of importance, these protective effects of hypercapnic acidosis were enhanced in the presence of appropriate antibiotic therapy [40]. Again, reassuringly, lung bacterial loads were similar in the hypercapnic acidosis and normocapnia groups [40].

Prolonged Lung Infection

In an animal model of prolonged untreated pneumonia, sustained hypercapnic acidosis *worsened* histological and physiological indices of lung injury, including compliance, arterial oxygenation, alveolar wall swelling and neutrophil infiltration [23]. Of particular concern to the clinical setting, hypercapnic acidosis was associated with a higher lung bacterial count. The mechanism underlying this effect appeared to be inhibition of neutrophil function, as evidenced by impaired phagocytotic ability in neutrophils isolated from hypercapnic rats [23]. Of importance to the clinical context, the use of appropriate antibiotic therapy abolished these deleterious effects of hypercapnia, reducing lung damage and lung bacterial load to levels comparable to those seen with normocapnia.

These findings have been confirmed and considerably expanded in a recent study of hypercapnia in the fruit fly [41]. Helenius et al., in a series of elegant *in vivo* studies, found that prolonged hypercapnia decreased expression of specific anti-microbial peptides in *Drosophilia melanogaster* [41]. Hypercapnia decreased bacterial resistance in adult flies exposed to pathogens as evidenced by increased bacterial loads and increased mortality in flies inoculated with *E. faecalis, A. tumefaciens*, or *S. aureus* [41]. The previously demonstrated suppressive effects of hypercapnic acidosis on the NF-κB pathway appeared to underlie the decreased resistance to infection [41]. These findings raise significant concerns regarding the safety of hypercapnia in the setting of prolonged pneumonia, particularly in the absence of effective antibiotic therapy.

Hypercapnia in Systemic Sepsis

A growing body of evidence attests to a beneficial role of hypercapnia in the setting of systemic sepsis. Improvements in hemodynamic parameters and lung injury have been demonstrated in evolving, established, and prolonged systemic sepsis in animal models. This is in contrast to the detrimental effects of hypercapnic acidosis seen in prolonged pulmonary sepsis, suggesting that the effects of hypercapnic acidosis depend not only on the stage of the infective process, but also on the site of the primary infection.

Early Systemic Sepsis

Hypercapnic acidosis reduces the severity of early septic shock and lung injury induced by systemic sepsis. In a rodent model of peritoneal sepsis induced by cecal ligation and puncture, hypercapnic acidosis slowed the development of hypotension, preserved central venous oxygen saturation, and attenuated the rise in serum lactate compared to control conditions, in the first 3 hours post injury [42]. The severity of early lung injury was reduced as evidenced by a decrease in the alveolar-arterial oxygen gradient, and reduced lung permeability, compared to normocapnia. Alveolar neutrophil concentration was reduced by hypercapnic acidosis but IL-6 and TNF-α were unchanged [42]. Of importance, there were no differences in bacterial loads in the lung, blood, or peritoneum in the hypercapnia group.

Prolonged Systemic Sepsis

Using an ovine model of fecal peritonitis, Wang et al compared the effects of hypercapnic acidosis with those of dobutamine [43]. Over an 18-hour study period, hypercapnic acidosis resulted in improved hemodynamics of a magnitude comparable to that of dobutamine. Compared with normocapnia, both hypercapnic acidosis and dobutamine raised cardiac index and systemic oxygen delivery and reduced lactate levels. In addition, hypercapnic acidosis attenuated indices of lung injury, including lung edema, alveolar-arterial oxygen partial pressure difference and shunt fraction. Hypercapnic acidosis did not decrease survival time compared to normocapnia in this setting [43]. In a more prolonged systemic sepsis model, Costello et al. demonstrated that sustained hypercapnic acidosis reduced histological indices of lung injury compared with normocapnia in rodents following cecal ligation and puncture [42]. Reassuringly there was no evidence of an increased bacterial load in the lung, blood, or peritoneum of animals exposed to hypercapnia.

Intraperitoneal Hypercapnia

Direct intra-abdominal administration of CO_2 – by means of a pneumoperitoneum – reduces the severity of abdominal sepsis-induced lung and systemic organ injury. Insufflation of CO_2 into the peritoneal cavity prior to laparotomy for endotoxin contamination increased animal survival [44]. Most recently, CO_2 pneumoperitoneum has been demonstrated to increase survival in mice with polymicrobial peritonitis induced by cecal ligation and puncture (**Fig. 3**) [31]. These protective effects of intraperitoneal carbon dioxide insufflation appear be due to the immunomodulatory effects of hypercapnic acidosis, which include an IL-10 mediated downregulation of TNF-α [44]. Importantly, these effects appear to be mediated by the localized peritoneal acidosis, rather than by any systemic effect.

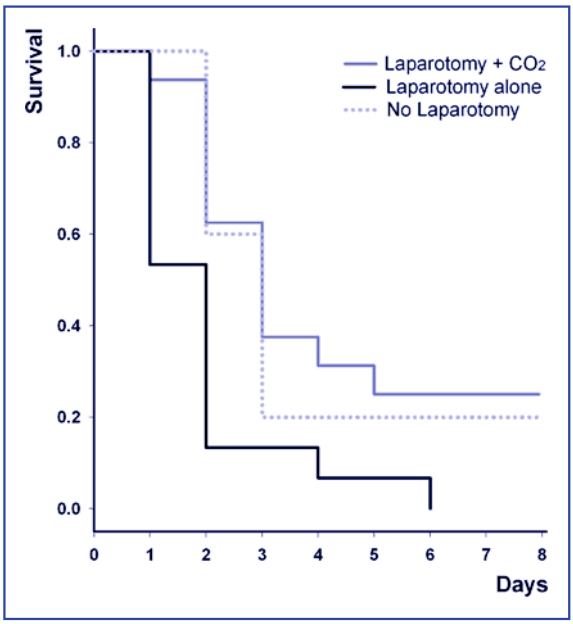

Fig. 3. Insufflation of CO_2 into the peritoneal cavity improves survival following cecal ligation and puncture-induced systemic sepsis. Animals were first subjected to cecal ligation and puncture. Four hours later, animals underwent a laparotomy and induction of a CO_2 pneumoperitoneum (laparotomy + CO_2), laparotomy alone, or no laparotomy; survival was determined over the following 8 days. Modified from [31] with permission.

V

Buffering Hypercapnic Acidosis in Sepsis

The immunomodulatory effects of hypercapnic acidosis in sepsis may occur as a function of either hypercapnia or acidosis. As discussed, evidence suggests that hypercapnic acidosis exerts certain effects via its associated acidosis [24], while other effects appear be a function of the hypercapnia *per se* [17]. Buffered hypercapnia, i.e., hypercapnia in the presence of normal pH, may be seen in ALI/ARDS patients as a renal compensatory measure, or as a result of the administration of bicarbonate, a common clinical practice in the ICU, and one that was permitted in the ARDSnet tidal volume study [1]. Aside from well established concerns regarding the use of sodium bicarbonate, there is evidence from animal models of lung and systemic sepsis that the anti-inflammatory and protective effects of hypercapnic acidosis are lost with buffering. This has significant implications in clinical scenarios where the buffering of hypercapnia resulting from protective ventilator strategies is considered.

Pulmonary Sepsis

In rodent models of acute pneumonia induced by intratracheal *E. coli* and by endotoxin, buffered hypercapnia worsened lung injury [24]. Compared with normocapnic controls, buffered hypercapnia increased multiple indices of lung injury including arterial oxygenation, lung compliance, pro-inflammatory pulmonary cytokine concentrations, and measurements of structural lung damage. In these experiments, buffered hypercapnia was established in the animals by exposure to hypercapnic conditions until renal buffering to normal pH had occurred, thus avoiding the confounding effects of exogenous acid or alkali administration.

This contrasts with the protective effects of hypercapnic acidosis in similar models [11, 38]. Of note, buffered hypercapnia did not reduce the phagocytic capacity of neutrophils, and did not increase lung bacterial load in these studies [24].

Systemic Sepsis

In a study designed to assess the contribution of acidosis *versus* hypercapnia to the effects of hypercapnic acidosis on the lung and hemodynamic profile in systemic sepsis, Higgins et al. exposed rats to environmental hypercapnia until renal buffering had restored pH to the normal range [45]. Both buffered hypercapnia and hypercapnic acidosis reduced the severity of early shock and attenuated the increase in serum lactate compared with normocapnia. In contrast, buffered hypercapnia did not attenuate physiologic or histologic indices of lung injury in these studies [45]. Reassuringly, there was no evidence to suggest that buffered hypercapnia worsened the degree of lung injury compared to normocapnia, and buffered hypercapnia did not increase the bacterial load in the lungs or the bloodstream [45].

Hypercapnia and Sepsis: Where are we Now?

The generally beneficial effects of hypercapnic acidosis in the setting of experimental non-septic inflammatory injury contrast with a more complex spectrum of effects in the setting of live bacterial infection. Hypercapnia and/or acidosis exert diverse – and potentially conflicting – effects on the innate and adaptive immune responses. Overall, hypercapnic acidosis appears to suppress the immune response, although the net effect of its multiple actions appears to vary depending on the site of infection and also on whether the acidosis produced by the hypercapnia is buffered or not. Hypercapnic acidosis appears to protect the lung from injury induced by evolving or more established lung and systemic bacterial sepsis in relevant pre-clinical models. In contrast, the effects of hypercapnic acidosis in prolonged untreated bacterial sepsis appear to differ depending on the source of the infection, with the immunosuppressive effects of hypercapnic acidosis worsening lung injury in the setting of prolonged pneumonia. This deleterious effect is abrogated by effective antibiotic therapy. In contrast, hypercapnic acidosis reduced lung damage caused by prolonged systemic sepsis, again highlighting the potential importance of the source of infection. Finally, buffering of the acidosis induced by hypercapnia does not confer significant benefit in the setting of lung or systemic sepsis, and may actually worsen lung injury in the setting of pneumonia.

Taken together, recent experimental findings in relevant pre-clinical models provide some reassurance regarding the safety of hypercapnia in sepsis, particularly in early pneumonia, and in the setting of abdominal sepsis. However, in the setting of prolonged pneumonia, the immunosuppressive effects of hypercapnia remain a concern. While the use of ventilation strategies resulting in hypercapnia is clearly justified in patient with ALI/ARDS, care is warranted in the setting of sepsis. The finding that deleterious effects of hypercapnia in the setting of prolonged pneumonia are abrogated by appropriate antibiotic therapy is of importance.

Clinicians should carefully consider the use of early empiric antibiotic therapy in hypercapnic ALI/ARDS patients in whom sepsis is suspected or confirmed.

However, concerns persist, particularly where antibiotic cover may be suboptimal, or the bacteria are more resistant to antibiotic therapy. The findings that hypercapnia may increase septic lung injury in the setting of prolonged pneumonia is also of relevance to other patient groups, such as patients with infective exacerbations of chronic obstructive airways disease.

Conclusion

Hypercapnia is an integral component of protective lung ventilatory strategies in patients with severe respiratory failure. The potential for hypercapnia to modulate the immune response, and the mechanisms underlying these effects are increasingly well understood. The findings that hypercapnic acidosis is protective in systemic sepsis, and in the earlier phases of pneumonia-induced sepsis, provide reassurance regarding the safety of hypercapnia in the clinical setting. However, the potential for hypercapnic acidosis to worsen injury in the setting of prolonged lung sepsis must be recognized. Additional studies are needed to further elucidate the mechanisms underlying the effects of hypercapnia and acidosis in the setting of sepsis-induced lung injury.

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References

1. The ARDS Network (2000) Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med 342: 1301 – 1308
2. Hickling KG, Walsh J, Henderson S, Jackson R (1994) Low mortality rate in adult respiratory distress syndrome using low-volume, pressure-limited ventilation with permissive hypercapnia: a prospective study. Crit Care Med 22: 1568 – 1578
3. Kregenow DA, Rubenfeld GD, Hudson LD, Swenson ER (2006) Hypercapnic acidosis and mortality in acute lung injury. Crit Care Med 34: 1 – 7
4. Ware LB, Matthay MA (2000) The acute respiratory distress syndrome. N Engl J Med 342: 1334 – 1349
5. Barton GM (2008) A calculated response: control of inflammation by the innate immune system. J Clin Invest 118: 413 – 420
6. Laffey JG, Kavanagh BP (1999) Carbon dioxide and the critically ill--too little of a good thing? Lancet 354: 1283 – 1286
7. Laffey JG, O'Croinin D, McLoughlin P, Kavanagh BP (2004) Permissive hypercapnia--role in protective lung ventilatory strategies. Intensive Care Med 30: 347 – 356
8. Shibata K, Cregg N, Engelberts D, Takeuchi A, Fedorko L, Kavanagh BP (1998) Hypercapnic acidosis may attenuate acute lung injury by inhibition of endogenous xanthine oxidase. Am J Respir Crit Care Med 158: 1578 – 1584
9. Laffey JG, Jankov RP, Engelberts D, et al (2003) Effects of therapeutic hypercapnia on mesenteric ischemia-reperfusion injury. Am J Respir Crit Care Med 168: 1383 – 1390
10. Laffey JG, Tanaka M, Engelberts D, et al (2000) Therapeutic hypercapnia reduces pulmonary and systemic injury following in vivo lung reperfusion. Am J Respir Crit Care Med 162: 2287 – 2294
11. Laffey JG, Honan D, Hopkins N, Hyvelin JM, Boylan JF, McLoughlin P (2004) Hypercapnic acidosis attenuates endotoxin-induced acute lung injury. Am J Respir Crit Care Med 169: 46 – 56

12. Sinclair SE, Kregenow DA, Lamm WJ, Starr IR, Chi EY, Hlastala MP (2002) Hypercapnic acidosis is protective in an in vivo model of ventilator-induced lung injury. Am J Respir Crit Care Med 166: 403 – 408
13. Hudson LD, Milberg JA, Anardi D, Maunder RJ (1995) Clinical risks for development of the acute respiratory distress syndrome. Am J Respir Crit Care Med 51: 293 – 301
14. Vincent JL, Bihari DJ, Suter PM, et al (1995) The prevalence of nosocomial infection in intensive care units in Europe. Results of the European Prevalence of Infection in Intensive Care (EPIC) Study. EPIC International Advisory Committee. JAMA 274: 639 – 644
15. Zhang Q, Raoof M, Chen Y, et al (2010) Circulating mitochondrial DAMPs cause inflammatory responses to injury. Nature 464: 104 – 107
16. Takeshita K, Suzuki Y, Nishio K,et al (2003) Hypercapnic acidosis attenuates endotoxin-induced nuclear factor-kappa B activation. Am J Respir Cell Mol Biol 29: 124 – 132
17. Cummins EP, Oliver KM, Lenihan CR, et al (2010) NF-kB links CO2 sensing to innate immunity and inflammation in mammalian cells. J Immunol 185: 4439 – 44
18. O'Toole D, Hassett P, Contreras M, et al (2009) Hypercapnic acidosis attenuates pulmonary epithelial wound repair by an NF-kappaB dependent mechanism. Thorax 64: 976 – 982
19. Wang N, Gates KL, Trejo H,et al (2010) Elevated CO2 selectively inhibits interleukin-6 and tumor necrosis factor expression and decreases phagocytosis in the macrophage. Faseb J 24: 2178 – 2190
20. Coakley RJ, Taggart C, Greene C, McElvaney NG, O'Neill SJ (2002) Ambient pCO2 modulates intracellular pH, intracellular oxidant generation, and interleukin-8 secretion in human neutrophils. J Leukoc Biol 71: 603 – 610
21. West MA, Baker J, Bellingham J (1996) Kinetics of decreased LPS-stimulated cytokine release by macrophages exposed to CO2. J Surg Res 63: 269 – 274
22. Gupta A, Watson DI (2001): Effect of laparoscopy on immune function. Br J Surg 88: 1296 – 1306
23. O'Croinin DF, Nichol AD, Hopkins N, et al (2008) Sustained hypercapnic acidosis during pulmonary infection increases bacterial load and worsens lung injury. Crit Care Med 36: 2128 – 2135
24. Nichol AD, O'Cronin DF, Howell K, et al (2009) Infection-induced lung injury is worsened after renal buffering of hypercapnic acidosis. Crit Care Med 37: 2953 – 2961
25. Swallow CJ, Grinstein S, Sudsbury RA, Rotstein OD (1993) Relative roles of Na+/H+ exchange and vacuolar-type H+ ATPases in regulating cytoplasmic pH and function in murine peritoneal macrophages. J Cell Physiol 157: 453 – 460
26. Nichol AD, O'Cronin DF, Naughton F, Hopkins N, Boylan J, McLoughlin P (2010) Hypercapnic acidosis reduces oxidative reactions in endotoxin-induced lung injury. Anesthesiology 113: 116 – 125
27. Coakley RJ, Taggart C, McElvaney NG, O'Neill SJ (2002) Cytosolic pH and the inflammatory microenvironment modulate cell death in human neutrophils after phagocytosis. Blood 100: 3383 – 3391
28. Severin T, Muller B, Giese G, et al (1994) pH-dependent LAK cell cytotoxicity. Tumour Biol 15: 304 – 310
29. Redegeld F, Filippini A, Sitkovsky M (1991) Comparative studies of the cytotoxic T lymphocyte-mediated cytotoxicity and of extracellular ATP-induced cell lysis. Different requirements in extracellular Mg2+ and pH. J Immunol 147: 3638 – 3645
30. Vermeulen M, Giordano M, Trevani AS, et al (2004) Acidosis improves uptake of antigens and MHC class I-restricted presentation by dendritic cells. J Immunol 172: 3196 – 3204
31. Metzelder M, Kuebler JF, Shimotakahara A, Chang DH, Vieten G, Ure B (2008) CO2 pneumoperitoneum increases survival in mice with polymicrobial peritonitis. Eur J Pediatr Surg 18: 171 – 175
32. Dixon NM, Kell DB (1989) The inhibition by CO2 of the growth and metabolism of microorganisms. J Appl Bacteriol 67: 109 – 136
33. Mori H, Kobayashi T, Shimizu S (1983) Effect of carbon dioxide on growth of microorganisms in fed-batch cultures. J Ferment Technol 61: 211 – 213
34. Pugin J, Dunn-Siegrist I, Dufour J, Tissieres P, Charles PE, Comte R (2008) Cyclic stretch of human lung cells induces an acidification and promotes bacterial growth. Am J Respir Cell Mol Biol 38: 362 – 370

35. Azoulay E, Darmon M, Delclaux C, et al (2002) Deterioration of previous acute lung injury during neutropenia recovery. Crit Care Med 30: 781 – 786
36. Alves-Filho JC, de Freitas A, Spiller F, Souto FO, Cunha FQ (2008): The role of neutrophils in severe sepsis. Shock 30 (Suppl 1): 3 – 9
37. Doerr CH, Gajic O, Berrios JC, et al (2005) Hypercapnic acidosis impairs plasma membrane wound resealing in ventilator-injured lungs. Am J Respir Crit Care Med 171: 1371 – 1377
38. Ni Chonghaile M, Higgins BD, Costello JF, Laffey JG (2008) Hypercapnic acidosis attenuates severe acute bacterial pneumonia-induced lung injury by a neutrophil-independent mechanism. Crit Care Med 36: 3135 – 3144
39. O'Croinin DF, Hopkins NO, Moore MM, Boylan JF, McLoughlin P, Laffey JG (2005) Hypercapnic acidosis does not modulate the severity of bacterial pneumonia-induced lung injury. Crit Care Med 33: 2606 – 2612
40. Chonghaile MN, Higgins BD, Costello J, Laffey JG (2008) Hypercapnic acidosis attenuates lung injury induced by established bacterial pneumonia. Anesthesiology 109: 837 – 848
41. Helenius IT, Krupinski T, Turnbull DW, et al (2009) Elevated CO2 suppresses specific Drosophila innate immune responses and resistance to bacterial infection. Proceedings of the National Academy of Sciences of the United States of America 106: 18710 – 18715
42. Costello J, Higgins B, Contreras M, et al (2009) Hypercapnic acidosis attenuates shock and lung injury in early and prolonged systemic sepsis. Crit Care Med 37: 2412 – 2420
43. Wang Z, Su F, Bruhn A, Yang X, Vincent JL (2008) Acute hypercapnia improves indices of tissue oxygenation more than dobutamine in septic shock. Am J Respir Crit Care Med 177: 178 – 183
44. Fuentes JM, Hanly EJ, Aurora AR, et al (2006) CO2 abdominal insufflation pretreatment increases survival after a lipopolysaccharide-contaminated laparotomy. J Gastrointest Surg 10: 32 – 38
45. Higgins BD, Costello J, Contreras M, Hassett P, D OT, Laffey JG (2009): Differential Effects of Buffered Hypercapnia versus Hypercapnic Acidosis on Shock and Lung Injury Induced by Systemic Sepsis. Anesthesiology 111: 1317 – 1326

NAVA: Why, When, Who?

C. Sinderby and J. Beck

V

Introduction

This chapter is written in an attempt to document some of the reasons behind the development of the ventilatory mode known as neurally-adjusted ventilatory assist (NAVA).

Why NAVA?

In patients with acute respiratory failure, the function of a mechanical ventilator is to support or substitute the task of the respiratory muscles and to maintain adequate ventilation through the removal of CO_2 and delivery of O_2. Although a life-saving intervention, mechanical ventilation is known to have unwanted side-effects that may be deleterious to the patient. Ventilator-induced lung injury (VILI), for example, has been suggested to occur with ventilation at high tidal volumes (for reviews see [1, 2]), and has been associated with increased mortality [3]. Ventilator-induced diaphragmatic dysfunction – characterized by a rapidly developing weakness and atrophy of the diaphragm – is caused in part by ventilator-induced diaphragmatic inactivity (for review see [4–6]. Ventilator associated pneumonia (VAP), a nosocomial lung infection associated with mechanical ventilation, in particular with the use of endotracheal tubes, increases morbidity and mortality, and its risk is related to exposure, i.e., time on mechanical ventilation [7]. It should be noted that age and increased time on mechanical ventilation are also predictors for increased morbidity and mortality [8]. From an economical perspective, a recent study in the United States showed an estimated national cost of $27 billion for mechanical ventilation, that is 12 % of all hospital costs [9]. Hence, there are also strong economical incentives to limit the adverse effects of mechanical ventilation.

It has been demonstrated that mechanical ventilation with reduced tidal volumes decreases mortality [3]. Active breathing on ventilatory assist has experimentally been shown to prevent ventilator-induced diaphragmatic dysfunction [10]. Protocols in patients promoting more active breathing by either reducing/removing sedation [11–13] or using spontaneous breathing trials [14, 15] have been found to shorten time on mechanical ventilation. A combined intervention – "wake up and breathe" – has been shown to further reduce the time on mechanical ventilation [16]. In fact, avoiding the use of sedatives completely has been found to be possible in a selected group of acute respiratory failure patients and was associated with shorter duration of mechanical ventilation [17].

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Restricted use of sedatives, however, necessitates that the mechanical ventilator is adequate for delivering assist to an actively breathing patient.

A common tale of mechanical ventilation is that of a "patient fighting the ventilator". It has been known for a long time that pneumatically controlled ventilators (i.e., those that trigger assist via pressure, flow, and/or volume) frequently fail to deliver assist in time with the patient's inspiratory effort (for example [18–21]). Such triggering and cycling asynchrony is most likely to occur during situations of low respiratory drive, e.g., during excessive assist delivery [21] or high sedation [22]. In addition, leaks either in the respiratory circuit or in the patient-ventilator interface significantly impair the function of pneumatic triggering and cycling [23]. The latter is also a major limiting factor to the successful administration of mechanical ventilation with non-invasive interfaces.

In terms of the prevalence of poor timing between the ventilator's assist delivery and the patient's breathing effort, it has been reported that about 25 % of mechanically ventilated (intubated) patients show more than 10 % error in the accuracy of delivering assist in relation to the patient's breathing [24–26]. The portion of patients with more than 10 % error in the accuracy of timely delivery of assist increases to 43 % in patients ventilated with non-invasive interfaces [27]. This is likely the tip of the iceberg, since it is quite challenging to detect patient triggering/cycling asynchrony based on airway pressure, flow, and volume tracings. **Figure 1** shows an example of an adult patient where 10 % of the inspiratory efforts do not trigger the ventilator in pressure support mode. Note that the remainder of the breaths is actually triggered close to the peak of the diaphrag-

Fig. 1. Tracings obtained from a patient breathing on pressure support ventilation. Note that about 10 % of the neural efforts are not effective to trigger the ventilator. The upper panel shows an overlay waveform of the diaphragmatic electrical activity – EAdi (grey line) and the pressure delivered by the ventilator – Pvent (yellow line). The small red highlighted portions of the Pvent waveform indicate pneumatic triggering of the ventilator's assist. The lower panel indicates the flow (green line). Note also that all triggered/assisted breaths are actually initiated at the peak/end of the neural (EAdi) inspiratory effort. Hence, if delivered at all, the assist generates inspiratory flow when the inspiratory muscles are relaxing, i.e., during neural expiration.

matic electrical activity and hence the assist – although triggered – is actually delivered when the patient is neurally expiring. Further, be aware that the asynchrony of delivering assist during neural exhalation is not easily detectable from the airway pressure and flow tracings (**Fig. 1**). Due to inadequate monitoring, severe inaccuracies of mechanical ventilators controlled by pneumatic signals (flow, volume, pressure) may pass unnoticed. In other words, for a vital sign as simple as respiratory rate, the ventilator display of this parameter reflects the *ventilator's rate* of breath delivery, and may not relate at all to the patient's breathing rate. In fact, in certain patients the error between the patient's neural respiratory rate and the pneumatically triggered ventilator's assist rate may range from being twice that reported by the ventilator to complete respiratory arrest [28]. Thus the scientifically reported shortcomings of pneumatic trigger systems cannot be effortlessly detected at the bedside.

It has been shown that patients with severely impaired timing between ventilator assist delivery and breathing efforts remain on mechanical ventilation significantly longer [24–26, 29]. However, it is not clear whether the asynchrony in itself is the direct cause for the prolonged time on mechanical ventilation. It could be speculated that the asynchrony induces discomfort and agony, which in turn leads to increased sedation and increased assist levels, and this may be the link to increased duration of mechanical ventilation. A related tale to that of "the patient fighting the ventilator" is the one that says that sedation is applied to "restore synchrony". In fact, deeper sedation results in more ineffective triggering of mechanical ventilation [22]. Since deeper sedation likely reduces respiratory drive, a further consequence of deeper sedation is that the patient likely needs increased levels of assist and even mandatory ventilation, which in turn may impair the trigger and cycling asynchrony. In the end, the "restored synchrony" may represent a therapy-induced hypopnea or apnea rather than a restoration of the patient's ability to receive ventilatory assist timely to inspiratory efforts.

Animal studies have repeatedly shown that inactivity of the diaphragm is deleterious to its function (for review see [6]). Several studies in human patients with acute respiratory failure have revealed that mechanical ventilation is associated with extreme weakness of the diaphragm [30–32], which can develop within the first days of mechanical ventilation [32]. In agreement with these studies, diaphragmatic inactivity in mechanically ventilated humans has been demonstrated to atrophy the diaphragm causing an approximate 50 % reduction in muscle fiber diameter after 18 to 69 hours [33]. Comorbidities and medications are also known to impair muscle function [34, 35] and may speed its progress.

In the spirit of the above reported limitations to pneumatic triggering and cycling of ventilatory assist, NAVA was developed in the 1990s. The purpose of NAVA was to overcome the reported problems of patient-ventilator asynchrony both with regards to its detection and its correction [36]. The advantage of NAVA over conventional modes of mechanical ventilation was the introduction of transesophageal measurements of diaphragmatic electrical activity (EAdi) using a consensus approved technology to limit errors of its measurement and allowing EAdi to reliably monitor and control ventilatory assist [37]. NAVA uses the EAdi to trigger assist when a breath is initiated and terminates the assist when the EAdi decreases, hence, NAVA does not depend on measurement of the patient's airway pressure, flow or volume, and maintains assist in synchrony with inspiratory efforts [21, 25, 38–44] (**Table 1**). Since the neural regulation of breathing is strongly integrated to that of the upper airways, NAVA gains an advantage during

Table 1. Summary of recent human physiological trials using neurally-adjusted ventilatory assist (NAVA)

Authors (year)	Ref	Subjects (n)	Intervention	Major findings
Studies in adults				
Sinderby (2007)	[51]	Healthy (10)	NAVA with increasing levels	Down-regulation of EAdi to prevent over assist during TLC maneuvers
Moerer (2008)	[38]	Healthy (7)	Neural vs. flow trigger with helmet interface	Improved synchrony and comfort with neural trigger
Colombo (2008)	[25]	Mixed ICU (14)	NAVA vs. PSV with increasing assist	NAVA improved synchrony, averted the risk of over-assist
Schmidt (2010)	[52]	Mainly ALI (12)	NAVA vs. PSV with increasing assist	NAVA increased breathing pattern variability
Brander (2009)	[50]	Mixed ICU (15)	NAVA with increasing levels	Down-regulation of EAdi to detect an optimal NAVA level
Spahija (2010)	[21]	Mainly COPD (14)	Increasing NAVA Increasing PSV	Improved synchrony with NAVA, maintained blood gases
Terzi (2010)	[39]	ARDS (11)	Increasing NAVA Increasing PSV	Improved synchrony with NAVA, prevention of over assist with NAVA
Wu (2009)	[40]	ARDS (18)	Increasing NAVA Increasing PSV	Improved synchrony with NAVA
Passath (2010)	[59]	Mixed ICU (20)	Increasing PEEP during NAVA	At an adequate NAVA level, monitoring V_T per EAdi allows optimal PEEP adjustment
Karagiannidis (2010)	[56]	Critically ill on ECMO (6)	NAVA during different ECMO settings	NAVA followed the ventilator response to changes in ECMO
Coisel (2010)	[53]	Post-operative (12)	NAVA vs. PSV for 24 h	Respiratory parameter variability and oxygenation increased during NAVA
Studies in Children				
Beck (2009)	[41]	Premature infants ready for extubation (7)	NAVA vs. PSV, PSV+VG, NAVA NIV	NAVA improved synchrony. Synchrony with NAVA NIV was not affected by leak.
Zhu (2010)	[43]	Cardiac surgery (15)	Prone vs. supine NAVA vs. PSV	Improved synchrony
Breatnach (2010)	[44]	Mainly cardiac patients (16)	NAVA vs. PSV	NAVA improved synchrony, showed lower peak airway pressures, and was well tolerated
Bengtsson (2010)	[60]	Post-op (21)	NAVA vs. PSV	NAVA is safe, peak airway pressures decreased over time during NAVA
Zhu (2009)	[42]	Post-op (21)	NAVA vs. PSV	Improved synchrony, better oxygenation

EAdi: electrical activity of the diaphragm; ECMO: extracorporeal membrane oxygenation; NIV: non-invasive ventilation; PEEP: positive end-expiratory pressure; PSV: pressure-support ventilation; TLC: total lung capacity; VG: volume guarantee; V_T: tidal volume

non-invasive positive pressure ventilation by strictly obeying neural output. This for example means that assist cannot be delivered during swallowing since inspiration (and thus EAdi) is inhibited, which suggests a lesser risk of gastric insufflations. For safety and comfort, NAVA was designed to combine the EAdi triggering and cycling with pneumatic triggering and cycling.

Inspired by proportional assist ventilation (PAV) using pneumatic signals to modulate assist in proportion to effort using the principles of the equation of motion [45], NAVA delivers assist in proportion to EAdi during the neural inspiration, i.e., between EAdi triggering and cycling [36, 46]. This allows NAVA to deliver assist both in time with EAdi [e.g., 21, 25, 41] and restrict excessive dosage [21, 25, 47–51], and allows for more natural variability in breathing pattern [52, 53]. In terms of appropriate dosage, NAVA can take advantage of vagally mediated lung protective reflexes as, e.g., the Hering Breuer reflex [47, 48, 51, 54, 55]. Inherent to a neurally controlled proportional assist system, NAVA obeys metabolic demands; e.g., ventilatory response to decreased sweep gas flow on extracorporeal membrane oxygenation (ECMO) in patients on NAVA was found to be rapid, and immediately regulated $PaCO_2$ tightly towards a physiological pH value [56]. Experimentally, NAVA has also been demonstrated to be a potentially lung protective mode of ventilation [57].

In other words, NAVA acts as an accessory respiratory muscle that is very closely integrated with the sensory-motor control system that regulates ventilation and delivers assist with better synchrony to patient breathing effort than a pneumatically triggered and cycled ventilatory assist system. By improving the synchrony between the patient's neural efforts and the breath delivery by the ventilator, monitoring of patient respiratory rate may be more reliable in NAVA. In addition, monitoring the presence of the EAdi waveform ensures a patient is spontaneously breathing and takes the guessing game out of "is my patient breathing?"

NAVA: When and Who?

This section is based on the assumptions that

- spontaneous breathing is encouraged and that assist and sedation levels during ventilatory assist should not be excessive
- undetected patient-ventilator asynchrony due to poor ventilator settings or ventilator failure is unwanted
- the time on mechanical ventilation should be reduced to a minimum

Most mechanically ventilated patients remain on mechanical ventilation for a relatively short period of time, i.e., < 4 days; however, as many as 40 % of patients are projected (in the US) to remain > 4 days on mechanical ventilation [9]. Of particular interest is that patients who remain more than 4 days on mechanical ventilation can be identified as those with severe trigger/cycling asynchrony during the first 24 hours of mechanical ventilation [26]; this group of patient contributes to about 25 % of mechanically ventilated patients [24, 26]. As discussed above, respiratory muscles deteriorate rapidly and show extreme weakness already after a few days on mechanical ventilation. Hence, the earliest possible intervention is crucial to ensure that mechanical ventilation is adequately applied (for review of this topic see [5, 58]).

Essentially, neural (EAdi) monitoring and NAVA can be tried on any patient who is expected to be actively breathing while on ventilatory assist. Preference could however be recommended for patients:

- suffering patient-ventilator asynchrony – "fighting the ventilator"
- expected to remain on ventilation for several days
- who failed a spontaneous breathing trial.

As the EAdi expresses the neural respiratory drive to the diaphragm, it adds a window for bedside evaluation of how the assist is impacting on the patient regardless of the ventilator mode used. Application of neural monitoring is helpful to evaluate the response to delivered assist and to aid in correcting problems of excessive assist and sedation leading to an overly depressed respiratory drive. EAdi monitoring allows detection of poorly timed assist delivery and can be used to guide corrective adjustments in any ventilator mode. Moreover, diagnostic and prognostic information, such as intermittent or permanent absence of EAdi (e.g., central apneas, diaphragm paralysis), abnormal breathing patterns (e.g., Cheyne-Stokes) can be derived with the supplement of EAdi monitoring. Using EAdi in combination with tidal volume has been demonstrated as a monitoring tool to optimize positive end-expiratory pressure (PEEP) settings from the perspective of neuro-ventilatory efficiency [59].

Regardless of the mode of ventilatory assist, neural monitoring can be used to ensure that EAdi:

- is reduced with increasing assist – this confirms that respiratory muscles are unloading
- is always present – this minimizes the risk of excessive assist/sedation
- is synchronized to assist delivery – to allow appropriate timing of assist to patient inspiration.

If these goals are achieved at all times, this strategy should meet the current recommendations for shortening time on mechanical ventilation [4–6, 35, 58].

Implementation of NAVA reduces faults of pneumatically triggered/cycled modes in that it supports ventilation and unloads respiratory muscles, while promoting active breathing with synchronized assist. Thus, NAVA should be considered an alternative to any mode of ventilatory assist and has today been estimated to have been used in more than 20,000 patients of all ages using both invasive and non-invasive interfaces. Similar to all modes of ventilatory assist, one has to ensure that also during NAVA, ventilation, applied pressures, tidal volumes, respiratory rate and blood gases remain within tolerable limits. In addition, NAVA is by design 'self weaning' in that it reduces assist as the neural drive decreases with improved respiratory function [44, 47, 60].

Conclusion

The adverse effects of mechanical ventilation increase morbidity and mortality, prolong the duration of ventilation, and burden the economy. The majority of mechanical ventilators are today based on pneumatic sensors/controllers to detect breaths. This technology is limited in its accuracy of delivering assist in response to the patient's breathing effort. As a consequence, the metrics presented for respiratory rate, a cornerstone in setting the assist and determining weaning, can-

not be considered trustworthy. In fact, one in every four mechanically ventilated patients suffer severe trigger/cycling asynchrony, a syndrome associated with excessive assist levels and prolonged duration of mechanical ventilation. Moreover, correct monitoring and quantification of the patient's breathing effort is not readily obtained with pneumatic sensor-based systems. This increases the risk of unwanted respiratory muscle inactivity due to excessive sedation and/or assist, a syndrome resulting in rapid wasting of the diaphragm.

NAVA was developed to overcome these shortcomings of mechanical ventilation. NAVA offers online monitoring and quantification of respiratory drive, improves patient-ventilator synchrony, prevents excessive assist-induced diaphragm inactivation. Early monitoring of EAdi (neural drive) and application of NAVA is an option for improvement of ventilatory assist in patients who: i) suffer patient-ventilator asynchrony ("fight the ventilator"); ii) are expected to remain on mechanical ventilation for several days; and/or iii) have failed a spontaneous breathing trial.

References

1. Ricard JD, Dreyfuss D, Saumon G (2002) Ventilator-induced lung injury. Curr Opin Crit Care 8: 12 – 20
2. Moloney ED, Griffiths MJ (2004) Protective ventilation of patients with acute respiratory distress syndrome. Br J Anaesth 92: 261 – 270
3. The Acute Respiratory Distress Syndrome Network (2000) Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med 342: 1301 – 1308
4. Griffiths RD, Hall JB (2010) Intensive care unit-acquired weakness. Crit Care Med 38: 779 – 787
5. Tobin MJ, Laghi F, Jubran A (2010) Narrative review: ventilator-induced respiratory muscle weakness. Ann Intern Med 153: 240 – 245
6. Vassilakopoulos T (2008) Ventilator-induced diaphragm dysfunction: the clinical relevance of animal models. Intensive Care Med 34: 7 – 16
7. Joseph NM, Sistla S, Dutta TK, Badhe AS, Parija SC (2010) Ventilator-associated pneumonia: A review. Eur J Intern Med 21: 360 – 368
8. Feng Y, Amoateng-Adjepong Y, Kaufman D, Gheorghe C, Manthous CA (2009) Age, duration of mechanical ventilation, and outcomes of patients who are critically ill. Chest 136: 759 – 764
9. Wunsch H, Linde-Zwirble WT, Angus DC, Hartman ME, Milbrandt EB, Kahn JM. (2010) The epidemiology of mechanical ventilation use in the United States. Crit Care Med 38: 1947 – 1953
10. Sassoon CS, Zhu E, Caiozzo VJ. (2004) Assist-control mechanical ventilation attenuates ventilator-induced diaphragmatic dysfunction. Am J Respir Crit Care Med 170: 626 – 632
11. Kress JP, Pohlman AS, O'Connor MF, Hall JB (2000) Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. N Engl J Med 342: 1471 – 1477
12. Treggiari MM, Romand JA, Yanez ND, et al (2009) Randomized trial of light versus deep sedation on mental health after critical illness. Crit Care Med 37: 2527 – 2534
13. Hall JB, Schweickert W, Kress JP (2009) Role of analgesics, sedatives, neuromuscular blockers, and delirium. Crit Care Med 37 (10 Suppl): S416 – 421
14. Esteban A, Frutos F, Tobin MJ, et al (1995) A comparison of four methods of weaning patients from mechanical ventilation. Spanish Lung Failure Collaborative Group. N Engl J Med 332: 345 – 350
15. Ely EW, Baker AM, Dunagan DP, et al (1996) Effect on the duration of mechanical ventilation of identifying patients capable of breathing spontaneously. N Engl J Med 335: 1864 – 1869

16. Girard TD, Kress JP, Fuchs BD, et al (2008) Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (Awakening and Breathing Controlled trial): a randomised controlled trial. Lancet 371: 126 – 134
17. Strøm T, Martinussen T, Toft P (2010) A protocol of no sedation for critically ill patients receiving mechanical ventilation: a randomised trial. Lancet 375: 475 – 480
18. Gianoulli E, Webster K, Roberts D, Younes M (1999) Response of ventilator-dependent patients to different levels of pressure support and proportional assist. Am J Respir Crit Care Med 159: 1716 – 1725
19. Aslanian P, El Atrous S, Isabey D, et al (1998) Effects of flow triggering on breathing effort during partial ventilatory support. Am J Respir Crit Care Med 157: 135 – 143
20. Leung P, Jubran A, Tobin MJ (1997) Comparison of assisted ventilator modes on triggering, patient effort, and dyspnea. Am J Respir Crit Care Med 155: 1940 – 1948
21. Spahija J, de Marchie M, Albert M, et al (2010) Patient-ventilator interaction during pressure support ventilation and neurally adjusted ventilatory assist. Crit Care Med 38: 518 – 526
22. de Wit M, Pedram S, Best AM, Epstein SK (2009) Observational study of patient-ventilator asynchrony and relationship to sedation level. J Crit Care 24: 74 – 80
23. Calderini E, Confalonieri M, Puccio PG, et al (1999) Patient-ventilator asynchrony during noninvasive ventilation: the role of expiratory trigger. Intensive Care Med 25: 662 – 667
24. Thille AW, Rodriguez P, Cabello B, Lellouche F, Brochard L (2006) Patient-ventilator asynchrony during assisted mechanical ventilation. Intensive Care Med 32: 1515 – 1522.
25. Colombo D, Cammarota G, Bergamaschi V, De Lucia M, Corte FD, Navalesi P (2008) Physiologic response to varying levels of pressure support and neurally adjusted ventilatory assist in patients with acute respiratory failure. Intensive Care Med 34: 2010 – 2018
26. de Wit M, Miller KB, Green DA, Ostman HE, Gennings C, Epstein SK (2009) Ineffective triggering predicts increased duration of mechanical ventilation. Crit Care Med 37: 2740 – 2745
27. Vignaux L, Vargas F, Roeseler J, et al (2009) Patient-ventilator asynchrony during noninvasive ventilation for acute respiratory failure: a multicenter study. Intensive Care Med 35: 840 – 846
28. Sinderby C, Brander L, Beck J (2009) Bedside monitoring of diaphragm electrical activity during mechanical ventilation. In: Vincent JL (ed) Yearbook of Intensive Care Medicine. Springer Verlag, Germany, pp 385 – 393
29. Chao DC, Scheinhorn DJ, Stearn-Hassenpflug M (1997) Patient-ventilator trigger asynchrony in prolonged mechanical ventilation. Chest 112: 1592 – 1599
30. Laghi F, Cattapan SE, Jubran A, et al (2003) Is weaning failure caused by low-frequency fatigue of the diaphragm? Am J Respir Crit Care Med 167: 120 – 127
31. Watson AC, Hughes PD, Louise Harris M, et al (2001) Measurement of twitch transdiaphragmatic, esophageal, and endotracheal tube pressure with bilateral anterolateral magnetic phrenic nerve stimulation in patients in the intensive care unit. Crit Care Med 29: 1325 – 1331
32. Hermans G, Agten A, Testelmans D, Decramer M, Gayan-Ramirez G (2010) Increased duration of mechanical ventilation is associated with decreased diaphragmatic force: a prospective observational study. Crit Care 14: R127
33. Levine S, Nguyen T, Taylor N, et al (2008) Rapid disuse atrophy of diaphragm fibers in mechanically ventilated humans. N Engl J Med 358: 1327 – 1335
34. Callahan LA, Supinski GS (2010) Diaphragm weakness and mechanical ventilation – what's the critical issue? Crit Care 14: 187
35. Sassoon CSh, Caiozzo VJ. (2009) Bench-to-bedside review: Diaphragm muscle function in disuse and acute high-dose corticosteroid treatment. Crit Care 13: 221
36. Sinderby C, Navalesi P, Beck J, et al (1999) Neural control of mechanical ventilation in respiratory failure. Nat Med 5: 1433 – 1436
37. Aldrich T, Sinderby C, McKenzie D, Estenne M, Gandevia S (2002) Electrophysiologic techniques for the assessment of respiratory muscle function. In: the ATS/ERS Statement on Respiratory Muscle Testing. Am J Respir Crit Care Med 166: 548 – 558
38. Moerer O, Beck J, Brander L, et al (2008) Subject-ventilator synchrony during neural versus pneumatically triggered non-invasive helmet ventilation. Intensive Care Med 34: 1615 – 1623

39. Terzi N, Pelieu I, Guittet L, et al (2010) Neurally adjusted ventilatory assist in patients recovering spontaneous breathing after acute respiratory distress syndrome: physiological evaluation. Crit Care Med 38: 1830 – 1837
40. Wu XY, Huang YZ, Yang Y, Liu SQ, Liu HG, Qiu HB (2009) Effects of neurally adjusted ventilatory assist on patient-ventilator synchrony in patients with acute respiratory distress syndrome. Zhonghua Jie He He Hu Xi Za Zhi 32: 508 – 512
41. Beck J, Reilly M, Grasselli G, et al (2009) Patient-ventilator interaction during neurally adjusted ventilatory assist in low birth weight infants. Pediatr Res 65: 663 – 668
42. Zhu LM, Shi ZY, Ji G, et al (2009) Application of neurally adjusted ventilatory assist in infants who underwent cardiac surgery for congenital heart disease]. Zhongguo Dang Dai Er Ke Za Zhi 11: 433 – 436
43. Zhu LM, Xu ZM, Ji G, et al (2010) Effect of prone or spine position on mechanically ventilated neonates after cardiac surgery with acute lung injury. Zhonghua Yi Xue Za Zhi 90: 1260 – 1263
44. Breatnach C, Conlon NP, Stack M, Healy M, O'Hare BP (2010) A prospective crossover comparison of neurally adjusted ventilatory assist and pressure-support ventilation in a pediatric and neonatal intensive care unit population. Pediatr Crit Care Med 11: 7 – 11
45. Younes M (1992) Proportional assist ventilation, a new approach to ventilatory support. Theory. Am Rev Respir Dis 145: 114 – 120
46. Sinderby C, Beck J (2008) Proportional assist ventilation and neurally adjusted ventilatory assist--better approaches to patient ventilator synchrony? Clin Chest Med 29: 329 – 342
47. Allo JC, Beck JC, Brander L, Brunet F, Slutsky AS, Sinderby CA (2006) Influence of neurally adjusted ventilatory assist and positive end-expiratory pressure on breathing pattern in rabbits with acute lung injury. Crit Care Med 34: 2997 – 3004
48. Lecomte F, Brander L, Jalde F, et al (2009) Physiological response to increasing levels of neurally adjusted ventilatory assist (NAVA). Respir Physiol Neurobiol 166: 117 – 124
49. Beck J, Campoccia F, Allo JC, Brander L, Brunet F, Slutsky AS, Sinderby C (2007) Improved synchrony and respiratory unloading by neurally adjusted ventilatory assist (NAVA) in lung-injured rabbits. Pediatr Res 61: 289 – 294
50. Brander L, Leong-Poi H, Beck J, et al (2009) Titration and implementation of neurally adjusted ventilatory assist in critically ill patients. Chest 135: 695 – 703
51. Sinderby C, Beck J, Spahija J, et al (2007) Inspiratory muscle unloading by neurally adjusted ventilatory assist during maximal inspiratory efforts in healthy subjects. Chest 131: 711 – 717
52. Schmidt M, Demoule A, Cracco C, et al (2010) Neurally adjusted ventilatory assist increases respiratory variability and complexity in acute respiratory failure. Anesthesiology 112: 670 – 681
53. Coisel Y, Chanques G, Jung B, et al (2010) Neurally adjusted ventilatory assist in critically ill postoperative patients: A crossover randomized study. Anesthesiology 113: 925 – 935
54. Loring SH, Malhotra A (2007) Inspiratory efforts during mechanical ventilation: is there risk of barotrauma? Chest 131: 646 – 648
55. Leiter JC, Manning HL (2010) The Hering-Breuer reflex, feedback control, and mechanical ventilation: the promise of neurally adjusted ventilatory assist. Crit Care Med 38: 1915 – 1916
56. Karagiannidis C, Lubnow M, Philipp A, et al (2010) Autoregulation of ventilation with neurally adjusted ventilatory assist on extracorporeal lung support. Intensive Care Med 36: 2038 – 2044
57. Brander L, Sinderby C, Lecomte F, et al (2009) Neurally adjusted ventilatory assist decreases ventilator-induced lung injury and non-pulmonary organ dysfunction in rabbits with acute lung injury. Intensive Care Med 35: 1979 – 1789
58. Brochard L, Thille AW (2009) What is the proper approach to liberating the weak from mechanical ventilation? Crit Care Med 37 (10 Suppl): S410 – 415
59. Passath C, Takala J, Tuchscherer D, Jakob SM, Sinderby C, Brander L (2010) Physiologic response to changing positive end-expiratory pressure during neurally adjusted ventilatory assist in sedated, critically ill adults. Chest 138: 578 – 587
60. Bengtsson JA, Edberg KE (2010) Neurally adjusted ventilatory assist in children: an observational study. Pediatr Crit Care Med 11: 253 – 257

Therapeutic Aerosols in Mechanically Ventilated Patients

S. Ruickbie, A. Hall, and J. Ball

Introduction

- An aerosol is a suspension of solid or liquid particles in a gas.
- A nebulizer is a device that can convert a liquid into aerosol droplets suitable for patient inhalation.

Aerosols have been used medicinally for thousands of years [1]. The inherent appeal of therapeutic aerosols is two fold: First, the delivery of pulmonary pharmaceuticals direct to the tracheo-bronchial and/or alveolar epithelium, and second, the rapid delivery of drugs to the systemic circulation. The latter, exploits the easily accessible, large absorptive surface area and minimal diffusion distance to the circulation that the respiratory tract provides, together with avoidance of first pass entero-hepatic metabolism.

However, aerosols lack reliable and titratable dose delivery. This, coupled with the ready availability of intravenous access has largely relegated aerosolized therapy, in the mechanically ventilated intensive care unit (ICU) patient, to the empirical use of bronchodilators.

In this chapter, we will examine whether newer aerosol producing technologies and recently published *in vitro* and *in vivo* testing allow us to reconsider the reliability of this method of drug delivery. We will also consider the efficacy of a range of aerosolized drugs that are commonly and less commonly used in mechanically ventilated ICU patients.

Basic Aerosol Physics

The ability of particles to remain suspended in a gas can be predicted from their size, shape and density, and the density and viscosity of the gas – known as Stokes law [2]. The properties of an aerosol are commonly expressed by two variables, the mass median aerosol diameter (MMAD), a measure of the average particle size, and the geometric standard deviation (GSD), a measure of the distribution or heterogeneity of particle sizes. Both can be calculated from the cumulative particle size distribution curve [3].

Reliable estimates of likely deposition site within the respiratory tree/ventilator circuit can be made based upon particle size (**Table 1**). In order to assess the efficiency of an aerosol generator, it is necessary to determine both the distribution of particle sizes and the rate at which they are produced.

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Table 1. Probable site of aerosol deposition related to particle size

Particle size (μm)	Site of deposition in respiratory tract
> 5	Deposition in upper airways/ventilator circuit
2 – 6	Tracheobronchial deposition
0.5 – 3	Alveolar deposition
< 0.5	Stay suspended in gas and are exhaled

Methods of Aerosol Generation

Pressurized Metered Dose Inhalers (MDIs)

These devices contain a pressurized mixture of propellants, surfactants, preservatives, flavoring agents, and active drug, the latter comprising approximately 1 % of the total contents [4]. As the mixture is released, the propellant evaporates. The extent to which evaporation occurs is dependent on the ambient temperature and the physical properties of the mixture. The design of the release system must be specifically optimized for each mixture. Patient device synchrony is difficult to achieve yet essential to the effective delivery of active ingredient. This can be largely overcome by deploying the drug dose into a holding chamber or spacer. A variety of such chambers that interface with mechanical ventilator circuits have been developed [4]. However, the reliable delivery of an aerosol via these devices still requires a complex number of steps [4]. Given the comparative simplicity of nebulizers and the limited number of available drugs, pressurized MDI use in mechanically ventilated patients is employed in only a minority of ICUs.

Dry Powder Inhalers (DPIs)

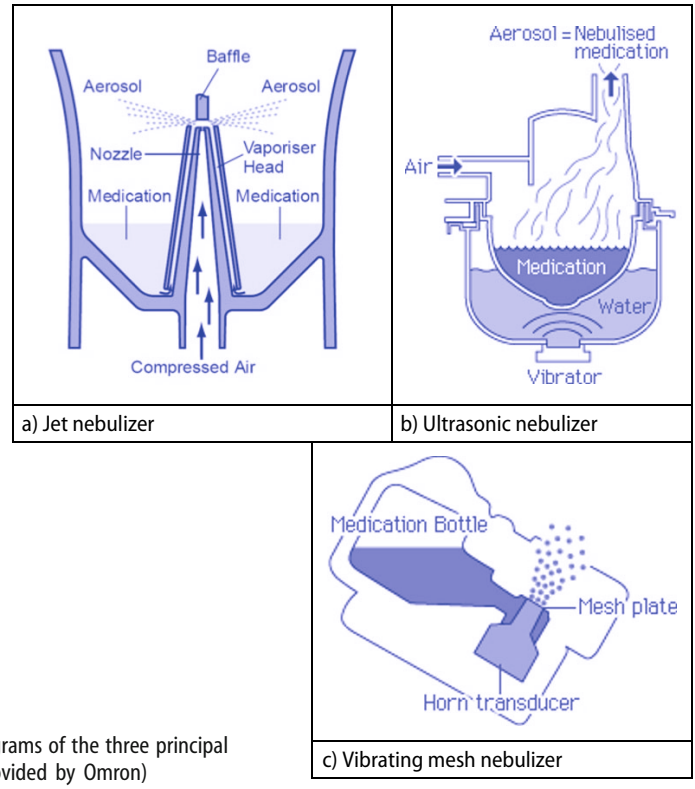
These devices produce reliable aerosols by placing a fixed volume of loosely aggregated, or carrier particle bound, micronized powder at the end of a shaped tube. As gas is drawn through the tube on inspiration, the power aerosolizes either passively or due to an active dispersion mechanism. Unlike pressurized MDIs, no patient device synchronization is required. However, the aerosolization process tends to produce a comparatively higher percentage of charged particles which results in a higher proportion of early/upper airway particle deposition [5]. Although interface devices that integrate DPIs into mechanical ventilator circuits have been developed [4], none are currently in widespread use.

Nebulizers

There are three principal designs of nebulizer: Jet, ultrasonic and vibrating mesh (**Fig. 1**). There are over 35 designs of jet nebulizer, at least 7 ultrasonic, and 6 vibrating mesh systems available. The performance of these devices varies widely. Reay and colleagues have published a detailed review of comparative performance [3].

Jet nebulizers

These devices direct a gas inflow at 5 – 10 l/min through a liquid reservoir chamber. The gas is accelerated through a narrow orifice above the liquid, overlying which there is a baffle. The resulting high speed jet creates a negative pressure gradient which draws the drug solution into an aerosol. The size of the generated



a) Jet nebulizer

b) Ultrasonic nebulizer

c) Vibrating mesh nebulizer

Fig. 1. Schematic diagrams of the three principal nebulizer designs (provided by Omron)

particles varies considerably; however, all but the smallest impact on the chamber walls or outflow and return to the reservoir. In a mechanical ventilator circuit, the resulting aerosol is carried into the stream of gas emanating from the ventilator at some point proximal to the patient.

Jet nebulizers cool and tend to concentrate solutions. They also inflict significant sheer stresses that can degrade larger molecules/complex microstructures such as proteins and liposomes.

Ultrasonic nebulizers

These devices are based on a high frequency vibrating piezoelectric crystal. The crystal emits ultrasonic vibrations, classically at ~3 MHz, which are transmitted via one of various designs to a liquid reservoir. The transmitted energy disrupts the liquid's surface tension causing cavitation and aerosolization. As a rule, the higher the frequency, the smaller the particle generated.

Ultrasonic nebulizers heat solutions, the effect being proportional to the frequency and, hence, the smaller the particles generated the more marked the effect.

Vibrating mesh nebulizers

These devices are also based on a high frequency vibrating piezoelectric crystal. The crystal is used to vibrate a precision engineered micron mesh at very high frequency. A micro pump delivers a small volume of liquid from a reservoir onto

the vibrating mesh resulting in a precise aerosol. These devices neither cool nor heat the solution. Nor do they inflict significant sheer stresses and they are consequently recommended for use with complex microstructures and large molecules.

Comparison of the Different Types of Nebulizer

There are no outcome studies comparing different types of nebulizer in mechanically ventilated patients. Jet nebulizers are simple and cheap in comparison to ultrasonic or vibrating mesh devices and hence are by far the commonest technology employed. Given the heterogeneity of the performance of different designs of jet nebulizer [3], let alone the different technologies, it seems unlikely that any comparative outcome studies are feasible. The most important real world disadvantage of jet nebulizers is the need to entrain an additional 5–10 l/min of gas into the ventilator circuit, which inevitably affects tidal volume and potentially the dynamic compliance of the patient's ventilatory profile. Other potentially meaningful differences, such as time to complete therapy and percentage of therapy delivered to the desired target site, are more dependent on the ventilator circuit and settings than the aerosol generator.

Issues of Aerosol Delivery in Mechanically Ventilated Patients

Delivering aerosolized particles from a generator to the distal airways/alveoli of a mechanically ventilated patient is challenging. Numerous factors will affect the proportion of drug successfully delivered and these are outlined in **Table 2**.

Many of these factors are interdependent, in particular, the rate of aerosol production, the bias flow, the inspiratory flow profile, the respiratory rate, the tidal volume, and the use of continuous or inspiratory synchronized generation. In short, how you set the ventilator and the patient's airflow physiology/pathophysiology determines delivery.

Optimal ventilator settings for peripheral drug deposition are as follows:

- A low bias flow [6] – facilitates carrier gas-aerosol mixing
- A higher tidal volume – should ensure a wider distribution
- A long, slow, continuous inspiratory profile – minimizes turbulent flow, thereby reducing proximal particle impaction
- A long end inspiratory pause – to maximize particle impaction/drop out in the peripheries
- A small amount of positive end-expiratory pressure (PEEP).

In the authors' experience, ventilator settings are never changed/optimized during nebulization.

Only two of the circuit factors are easily amenable to manipulation. Humidification is achieved either using a heater humidifier typically with a heated wire, at least in the inspiratory limb, or a heat and moisture exchanger (HME) typically coupled with a filter. There is no evidence to suggest either method is superior to the other [7]. Cost and individual unit preference tend to dictate the choice. Whereas the performance of heater humidifiers is fairly uniform, the performance characteristics of HMEs vary considerably [8]. As a rule, when aerosols are exposed to gas saturated with water vapor, the particles become hydrated and

Table 2. Factors that affect the delivery of aerosols to the distal airways/alveoli in mechanically ventilated patients

Ventilator	• Bias flow • Tidal volume • Respiratory rate • Inspiratory profile – time, flow rate • End inspiratory pause • Positive end expiratory pressure (PEEP) • Gas composition
Circuit	• Method, location and efficiency of humidification • Presence of any restrictions distal to the aerosol generator, e.g., pneumotachograph • Temperature/temperature gradient • Geometry of entire circuit – especially endotracheal/tracheostomy tube • Position of the nebulizer (or pMDI) within the circuit.
Nebulizer	• MMAD and GSD produced • Rate of production – ml/min • Continuous verses inspiratory synchronization
Drug solution	• Physical properties – density, viscosity, drug (& additive) concentration, drug (& additive) solubility • Oxidation potential
Patient	• Proximal airway geometry • Degree and pattern of ventilatory heterogeneity – especially position of convection diffusion front • Airway and/or parenchymal pathology • Ventilation perfusion matching • Spontaneous respiratory efforts and ventilatory synchrony

pMDI: pressurized metered dose inhaler: MMAD: mass median aerosol diameter; GSD: geometric standard deviation

increase in size resulting in a reduction in peripheral delivery [9]. Conversely, aerosols exposed to dry gas become dehydrated. This can result in crystallization of the drug/additives and may reduce effective delivery [8]. The significance of this effect depends upon exposure time and thus the position of the nebulizer within the circuit [6, 9]. The results of *in vitro* experiments suggest that a dry carrier gas is superior to a saturated one and that the optimal position is ~15 cm before the Y-piece. However, if an HME is used, the nebulizer has to be placed distal to the HME and hence typically between the HME and the catheter mount that connects to the endotracheal tube. As with ventilator settings, the effects of position and humidification are not widely appreciated and seldom acted upon.

Although the optimal nebulizer remains to be defined, the synchronization of aerosol production with inspiration is now a common feature of modern ventilators and dramatically increases the delivery of drug.

There has been extensive *in vitro* testing reported of aerosol delivery systems in mechanical ventilator circuits. However, such research is often difficult to extrapolate to the clinical arena. There has been very limited *in vivo* testing, the methodologies employed are often questionable, and the assessment of bioequivalence flawed [10].

In summary, there remains considerable ignorance regarding aerosol delivery in mechanically ventilated patients and evidence of a failure to convert what we do know into everyday clinical practice.

Aerosolized Drugs

Bronchodilators

The most commonly prescribed drug for nebulization in mechanically ventilated patients is racemic salbutamol (albuterol). This β_2-agonist has a proven place in the management of acute and chronic asthma and chronic obstructive pulmonary disease (COPD). In addition to its bronchodilator action, racemic salbutamol has been reported to enhance alveolar fluid clearance in experimental settings and a few small trials [11] and may promote mucociliary clearance [12]. It is often prescribed in mechanically ventilated patients in the absence of proven or even suspected reversible small airways obstruction, even though no clinical trial has demonstrated that it, or any other bronchodilator, has any beneficial effect in such patients [13]. Indeed, two large international multicenter trials in acute lung injury patients were both abandoned at interim analysis due to lack of efficacy [13, 14]. It is also noteworthy that there is conflicting evidence regarding racemic salbutamol toxicity [15] and a well documented propensity for this drug to cause lactic acidemia [16]. There is also circumstantial evidence of harm in acute decompensated cardiac failure [17]. There are few published data on the use of alternative β_2-agonists in mechanically ventilated patients.

The second most commonly prescribed drug for nebulization in mechanically ventilated patients is the anticholinergic bronchodilator, ipratropium bromide. As with salbutamol, it is commonly prescribed in ventilated patients despite no clinical trial to demonstrate its efficacy.

Magnesium sulphate is widely used and recommended as an adjunctive bronchodilator in the setting of life-threatening acute severe asthma [18, 19]. It is usually given intravenously but may be equally efficacious when nebulized [20].

In patients with acute severe asthma, who fail conservative therapy and require intubation and mechanical ventilation there is no proven rescue therapy. As mentioned above, there is at least circumstantial evidence that racemic salbutamol may be toxic in high doses [16] and contributes to, or even is responsible for, such treatment failure. Although somewhat outmoded, nebulized epinephrine may be of value in such patients [21]. There is also both a biological and pharmacological rationale, and limited trial evidence, to suggest a useful role for nebulized lidocaine [22, 23].

In summary, although bronchodilators have an established role in the management of acute and chronic asthma and COPD, there is a distinct lack of evidence of efficacy for empirical bronchodilator therapy in mechanically ventilated patients without these conditions.

Corticosteroids

Like bronchodilators, aerosolized corticosteroids have an established role in chronic asthma and COPD. In acute exacerbations, systemic steroid therapy is added and the role of adjunctive inhaled therapy is unclear [24]. It is noteworthy that corticosteroids have a marked effect on the physiological downregula-

tion of β_2 receptors. So important is this role that all major guidelines recommend corticosteroid use in all patients requiring chronic β_2-agonist therapy. Thus, if empirical nebulized salbutamol is used, or indeed trialed, active consideration should be given to the co-administration of nebulized or systemic corticosteroid therapy. However, there are currently no clear indications for nebulized corticosteroids.

Mucolytic Agents

The main constituents of normal respiratory tract secretions are gel-forming mucin glycoproteins that form large oligomeric structures. Sputum, or pathological respiratory mucus, contains additional components, specifically deoxyribonucleic acid (DNA), principally from necrotizing neutrophils, together with F-actin. As a consequence of these additions, sputum tends to have a much higher viscosity than mucus [25]. This increased viscosity favors cough clearance but hinders mucociliary clearance [26]. As intubated, mechanically ventilated patients have a diminished cough and mucociliary clearance, therapy to reduce sputum viscosity has obvious therapeutic potential.

N–acetylcysteine (NAC), either nebulized or oral, is perhaps the best known and most widely recommend mucolytic. This is surprising as there is no evidence to support its efficacy in any pathological condition [25, 27]. In contrast, there is good evidence to support the efficacy of nebulized hypertonic saline (3 – 14 %) [25, 28]. Of note, there is also no evidence to support the use of nebulized 0.9 % (isotonic) saline. An emerging alternative/adjunctive therapy is nebulized mannitol [29, 30].

Patients with cystic fibrosis produce very small quantities of mucin glycoproteins and their high sputum viscosity is predominantly due to highly polymerized DNA. These polymers are effectively broken down by nebulized phosphorylated glycosylated recombinant human deoxyribonuclease 1 (rhDNase). There is obvious appeal for rhDNase in all mechanically ventilated patients with thick mucopurulent secretions. To date, there have been two trials of this approach, both in pediatric patients, and both of which suggest that this is a promising therapy [31, 32].

Pulmonary Vasodilators

Mechanically ventilated patients with acute lung injury, together with a number of other conditions, may develop acute or acute on chronic pulmonary hypertension. This tends to manifest as refractory hypoxemia and acute right heart failure. Nebulized prostacyclin [33 – 35] and sildenafil [36] have both been described and show significant promise. Combination, rather than monotherapy, may be advantageous [37]. Formal trials are ongoing.

Nebulized Antimicrobial Therapy

Ventilator associated pneumonia (VAP) is a serious complication of mechanical ventilation. As with all nosocomial infections, the incidence can be minimized by adherence to common sense infection control guidelines [38]. VAP is a syndrome that evolves through a series of stages starting with inoculation (via aspiration) and colonization of the respiratory tract. This progresses to ventilator associated

tracheobronchitis (VAT) and finally consolidation/pneumonia [39]. The role of aerosolized antibiotic therapy in the prevention and treatment of both VAT and VAP has begun to be investigated but many unanswered questions remain.

The appeal of nebulized antimicrobial therapy is the dramatically enhanced delivery of drug direct to the site of colonization/infection. Experimental studies have demonstrated concentrations in blind tracheal aspirates that are 20 – 100x the *in vitro* minimum inhibitory concentration (MIC) of the target organisms – which is 10 – 50x that typically achieved by systemic therapy. There are concerns, however, regarding the reliability and variability of drug delivery, especially to consolidated lung. Penetration of drug into dense aggregates of sputum or areas of consolidation may be very limited giving rise to sub-MIC concentrations and predisposing to the emergence of resistant strains [40]. However, systemic antibiotic administration suffers from the same limitations. This has led to a small number of studies investigating the enhanced efficacy of using adjunctive nebulized antimicrobials to systemic therapy which show promising results [41]. Such an approach may be particularly valuable with recurrent, multiresistant and/or polymicrobial VAT/VAP. Although definitive trials of aerosolized antimicrobials in ventilated patients are lacking, there is certainly sufficient positive evidence and the absence of increased emergence of resistance to justify them. Primary prophylaxis of VAT/VAP should probably be confined to mucolytics while trials in colonized patients, as well as those with VAT and VAP, should be undertaken.

Additional advantages of aerosolized antimicrobials include a reduction in systemic toxicity and unaltered gastro-intestinal flora. It should be noted that only tobramycin and colistin are manufactured in formulations specifically designed for inhalation. Using intravenous preparations exposes the respiratory tract to preservatives, hypertonic and irritant solutions that can provoke bronchospasm, although in the authors' experience in mechanically ventilated patients this has never been a problem.

Heparin, Antithrombin, Activated Protein C and Sodium Bicarbonate

Inhalation of smoke and toxic chemicals can result in diffuse airway damage and, in particular, local hemorrhage and fibrin based airway casts [42]. There are plausible arguments for using a combination of unfractionated heparin with adjunctive antithrombin, or activated protein C to break up such casts and facilitate removal. There are a small number of published studies that support such an approach. Nebulized sodium bicarbonate may have a role in the reactive airways dysfunction syndrome seen following exposure to chlorine gas [43].

Conclusion

Aerosolized therapy in ventilated patients has an intuitive appeal, the realization of which continues to be frustrated by the variability and unreliability of drug delivery. Newer technologies, especially vibrating mesh nebulizers, together with pro-active ventilator management can largely overcome these problems. However, this is poorly appreciated and rarely practiced. The unfounded use of empirical nebulized bronchodilators and NAC continues, whereas hypertonic mucolytics and perhaps antimicrobials remain under investigated and probably under utilized.

References

1. Rubin BK (2010) Air and soul: the science and application of aerosol therapy. Respir Care 55: 911 – 921
2. Crowder TM, Rosati JA, Schroeter JD, Hickey AJ, Martonen TB (2002) Fundamental effects of particle morphology on lung delivery: Predictions of Stokes' law and the particular relevance to dry powder inhaler formulation and development. Pharmaceutical Res 19: 239 – 245
3. Reay CA, Bousfield DR, Colechin ES, Menes JA, Sims AJ (2009) Buyers' guide: Nebulizers. NHS Purchasing and Supply Agency Centre for Evidence-based Purchasing, London
4. Dhand R (2005) Inhalation therapy with metered-dose inhalers and dry powder inhalers in mechanically ventilated patients. Respir Care 50: 1331 – 1334
5. Ali M, Mazumder MK, Martonen TB (2009) Measurements of electrodynamic effects on the deposition of MDI and DPI aerosols in a replica cast of human oral-pharyngeal-laryngeal airways. J Aerosol Med Pulm Drug Deliv 22: 35 – 44
6. Ari A, Atalay OT, Harwood R, Sheard MM, Aljamhan EA, Fink JB (2010) Influence of nebulizer type, position, and bias flow on aerosol drug delivery in simulated pediatric and adult lung models during mechanical ventilation. Respir Care 55: 845 – 851
7. Kelly M, Gillies D, Todd David A, Lockwood C (2010) Heated humidification versus heat and moisture exchangers for ventilated adults and children. Cochrane Database Syst Rev CD004711
8. Demers RR, (2001) Bacterial/viral filtration. Chest 120: 1377 – 1389
9. Ari A, Areabi H, Fink JB (2010) Evaluation of aerosol generator devices at 3 locations in humidified and non-humidified circuits during adult mechanical ventilation. Respir Care 55: 837 – 844
10. Arieta AG (2010) Bioequivalence assessment of inhalation products: Interchangeability, study design and statistical methods. Pulm Pharmacol Ther 23: 156 – 158
11. Mutlu GM, Factor P (2008) Alveolar epithelial 2-adrenergic receptors. Am J Respir Cell Mol Biol 38: 127 – 134
12. Restrepo RD (2007) Inhaled adrenergics and anticholinergics in obstructive lung disease: do they enhance mucociliary clearance? Respir Care 52: 1159 – 1173
13. National Heart, Lung, and Blood Institute (NHLBI) (2008) Drug Study of Albuterol to Treat Acute Lung Injury (ALTA). Available at: http://clinicaltrials.gov/ct2/show/NCT00434993 Accessed 11 October 2010
14. The Beta-2 Agonist Lung Injury Trial 2 UK Clinical Research Network (2010) Balti-2 (Beta Agonist Lung injury TrIal – 2). Available at: http://www2.warwick.ac.uk/fac/med/research/ctu/trials/ecr/balti2 Accessed 11 October 2010
15. Ameredes BT, Calhoun WJ (2006) (R)-albuterol for asthma: pro [a.k.a. (S)-albuterol for asthma: con]. Am J Respir Crit Care Med 174: 965 – 969
16. Creagh-Brown BC, Ball J (2008) An under-recognized complication of treatment of acute severe asthma. Am J Emerg Med 26: 514, e1 – 3
17. Adam JS, Charles E, Douglas MC, et al (2008) Bronchodilator therapy in acute decompensated heart failure patients without a history of chronic obstructive pulmonary disease. Ann Emerg Med 51: 25 – 34
18. Camargo CA, Jr., Rachelefsky G, Schatz M (2009) Managing asthma exacerbations in the emergency department: Summary of the National Asthma Education and Prevention Program Expert Panel Report 3 Guidelines for the Management of Asthma Exacerbations. Proc Am Thorac Soc 6: 357 – 366
19. British Thoracic Society and the Scottish Intercollegiate Guidelines Network (2009) British Guideline on the Management of Asthma. Available at: http://www.brit-thoracic.org.uk/Portals/0/Clinical%20Information/Asthma/Guidelines/sign101 %20revised%20June%2009.pdf Accessed 11 October 2010
20. Mohammed S, Goodacre S (2007) Intravenous and nebulised magnesium sulphate for acute asthma: systematic review and meta-analysis. Emerg Med J 24: 823 – 830
21. Wiebe K, Rowe BH (2007) Nebulized racemic epinephrine used in the treatment of severe asthmatic exacerbation: a case report and literature review. CJEM 9: 304 – 308
22. Chong CF, Chen CC, Ma HP, Wu YC, Chen YC, Wang TL (2005) Comparison of lidocaine

and bronchodilator inhalation treatments for cough suppression in patients with chronic obstructive pulmonary disease. Emerg Med J 22: 429 – 432
23. Hunt LW, Frigas E, Butterfield JH, et al (2004) Treatment of asthma with nebulized lidocaine: A randomized, placebo-controlled study. J Allergy Clin Immunol 113: 853 – 859
24. Mannam P, Siegel MD (2010) Analytic review: Management of life-threatening asthma in adults. J Intensive Care Med 25: 3 – 15
25. Rogers DF (2007) Mucoactive agents for airway mucus hypersecretory diseases. Respir Care 52: 1176 – 1193
26. Voynow JA, Rubin BK (2009) Mucins, mucus, and sputum. Chest 135: 505 – 512
27. Nash EF, Stephenson A, Ratjen F, Tullis E (2009) Nebulized and oral thiol derivatives for pulmonary disease in cystic fibrosis. Cochrane Database Syst Rev: CD007168
28. Wark P, McDonald VM (2009) Nebulised hypertonic saline for cystic fibrosis. Cochrane Database Syst Rev: CD001506
29. Jaques A, Daviskas E, Turton JA, et al (2008) Inhaled mannitol improves lung function in cystic fibrosis. Chest 133: 1388 – 1396
30. Wills PJ, Greenstone M (2006) Inhaled hyperosmolar agents for bronchiectasis. Cochrane Database Syst Rev: CD002996
31. Prodhan P, Greenberg B, Bhutta AT, et al (2009) Recombinant human deoxyribonuclease improves atelectasis in mechanically ventilated children with cardiac disease. Congenit Heart Dis 4: 166 – 173
32. Riethmueller J, Kumpf M, Borth-Bruhns T, et al (2009) Clinical and in vitro effect of dornase alfa in mechanically ventilated pediatric non-cystic fibrosis patients with atelectases. Cell Physiol Biochem 23: 205 – 210
33. Afshari A, Brok J, Møller Ann M, Wetterslev J (2010) Aerosolized prostacyclin for acute lung injury (ALI) and acute respiratory distress syndrome (ARDS). Cochrane Database Syst Rev CD007733
34. Ivy DD (2010) Prostacyclin in the intensive care setting. Pediatr Crit Care Med 11: S41 – 45
35. Gomberg-Maitland M, Olschewski H (2008) Prostacyclin therapies for the treatment of pulmonary arterial hypertension. Eur Respir J 31: 891 – 901
36. Ichinose F, Erana-Garcia J, Hromi J, et al (2001) Nebulized sildenafil is a selective pulmonary vasodilator in lambs with acute pulmonary hypertension. Crit Care Med 29: 1000 – 1005
37. O'Callaghan DS, Savale L, Jaïs X, et al (2010) Evidence for the use of combination targeted therapeutic approaches for the management of pulmonary arterial hypertension. Respir Med 104: S74-S80
38. Torres A, Ewig S, Lode H, Carlet J (2009) Defining, treating and preventing hospital acquired pneumonia: European perspective. Intensive Care Med 35: 9 – 29
39. Craven DE, Chroneou A, Zias N, Hjalmarson KI (2009) Ventilator-associated tracheobronchitis. Chest 135: 521 – 528
40. Dhand R (2007) The role of aerosolized antimicrobials in the treatment of ventilator-associated pneumonia. Respir Care 52: 866 – 884
41. Palmer LB (2009) Aerosolized antibiotics in critically ill ventilated patients. Curr Opin Crit Care 15: 413 – 418
42. Toon MH, Maybauer MO, Greenwood JE, Maybauer DM, Fraser JF (2010) Management of acute smoke inhalation injury. Crit Care Resusc 12: 53 – 61
43. Aslan S, Kandis H, Akgun M, Cakir Z, Inandi T, Gorguner M (2006) The effect of nebulized NaHCO3 treatment on "RADS" due to chlorine gas inhalation. Inhal Toxicol 18: 895 – 900

VI Cardiac Crises

Cardiac Mitochondria and Heart Failure: The Chicken or the Egg?

S. Scolletta, B. Biagioli, and P. Giomarelli

Introduction

Current medical therapies for heart failure are aimed at suppressing the neurohormonal activation (e.g., angiotensin converting enzyme [ACE] inhibitors, angiotensin II receptor antagonists, beta-adrenergic receptor antagonists, aldosterone receptor antagonists) and/or treating fluid volume overload and hemodynamic symptoms (diuretics, digoxin, inotropic agents) [1, 2]. Evidence suggests that intense suppression of the neurohormonal systems does not provide further benefit compared with more modest therapy. There is a need for novel therapies for heart failure that are independent of the neurohormonal axis and can improve cardiac performance and prevent the progression of heart failure and heart remodeling [3]. Modulation of mitochondrial metabolism and the oxidative status of the myocardium may represent a new approach to the treatment of heart failure and could work additively with standard medical therapy while not exerting negative hemodynamic effects [4].

There are many reasons why a human heart can fail, but it is widely accepted that in the failing myocardium mitochondrial energy and antioxidant status are severely impaired, irrespective of the etiology of the heart failure [5]. The available evidence suggests that the failing heart is an engine out of fuel, highlighting the concept that myocardial energy plays an important role in the mechanisms of heart failure [6].

Cardiac Energy Metabolism

The heart consumes more energy than any other organ and is the greatest oxygen-consuming organ in the body (around 8 – 15 ml O_2 min/100 g heart), with the capacity to increase up to 70 ml under exercise conditions. Every day the heart beats about 100,000 times, pumps approximately 10 tons of blood through the body and cycles about 6 kg of adenosine-triphosphate (ATP) (20 – 30 times its own weight) [7].

The metabolic machinery (the mitochondrion) of the heart can be represented by three main components. The first component is substrate utilization, i.e., the use of fuel that comes from food. This process entails the cellular uptake of mainly fatty acids and glucose and then the breakdown of these components by beta-oxidation and glycolysis. These processes result in the formation of intermediary metabolite acetyl-CoA, which is fed into the Krebs cycle and produces NADH and carbon dioxide. The second component is oxidative phosphorylation,

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the production of energy by the mitochondrial respiratory chain. Respiratory-chain complexes (I through IV) transfer electrons from NADH to oxygen, thereby creating a proton electrochemical gradient across the inner mitochondrial membrane, as well as NAD and water. This gradient drives the F_0-F_1 ATP synthase, which produces ATP by phosphorylation of ADP. The third component is ATP transfer and utilization, the transport of energy to, and its consumption by, the heart's motor, the myofibrils. ATP transfer is achieved by an energy-transfer mechanism called the creatine kinase energy shuttle [8]. Mitochondrial creatine kinase catalyzes the transfer of the high energy phosphate bond in ATP to creatine to form phosphocreatine and ADP. Phosphocreatine, a smaller molecule than ATP, rapidly diffuses from the mitochondria to the myofibrils, where myofibrillar creatine kinase catalyzes the reformation of ATP from phosphocreatine. An important function of the creatine kinase system is to act as an energy buffer to keep ATP at normal levels. When the energy demand outstrips the energy supply, the phosphocreatine level falls, keeping ATP at a normal level, but the free ADP level rises. The increased level of free ADP inhibits the function of many intracellular enzymes (pyruvate dehydrogenase, sarcomeric ATPase, actomyosin ATPase, Na^+-K^+ ATPase), essential for excitation-contraction coupling), causing failure of the heart's contraction mechanism. Thus, a metabolic derangement in the cardiac myocyte can occur when phosphocreatine levels fall and free ADP levels rise, even if ATP levels remain unchanged [8]. The phosphocreatine to ATP ratio represents an excellent index of cardiac energy metabolism and a cut-off value less than 1.6 has been shown to be a good predictor of mortality in patients with dilated cardiomyopathy [9]. Unfortunately the analysis of ATP and phosphocreatine in tissue samples is problematic because of the instability of these molecules. The principal method for measuring ATP and phosphocreatine *in vivo* is phosphorus-31 magnetic resonance (31P-MR) spectroscopy [10].

Derangement of Myocardial Substrate Utilization

The heart is an omnivorous organ that utilizes amino acids, lactate, ketone bodies, and especially free fatty acids and glucose to produce oxygen and energy. Under normal conditions, 60–90 % of acetyl-CoA, which enters the Krebs cycle, comes from beta-oxidation of free fatty acids, and 10–40 % from oxidation of pyruvate, which comes from glycolysis. As a consequence, glycolysis contributes approximately 5 % to the total ATP generated. Conversely, fatty acid metabolism produces 95 % of the ATP via beta-oxidation in the mitochondria. The utilization of fatty acids costs 12 % more O_2 per unit of ATP generated than glucose and this is the reason why during myocardial ischemia there is a shift toward increased glucose uptake and utilization and decreased fatty acid oxidation. This can result in an up to 40 % reduction in myocardial oxygen consumption [11]. Similarly, in the early stage of heart failure, even in the absence of coronary artery disease, there is increased glucose uptake-and-oxidation and a reduced rate of fatty acid oxidation. The switch towards reduced fatty acid oxidation and increased glucose oxidation is termed "reversion to a fetal metabolic phenotype" because there is a re-expression of fetal forms of genes expressing contractile proteins, specifically myosin [12]. In the fetal and newborn heart, fatty acid oxidation rates are low and provide only a small proportion of overall ATP production (< 30 %). However, after birth, there is a dramatic 10-fold increase in fatty acid oxidation, which is

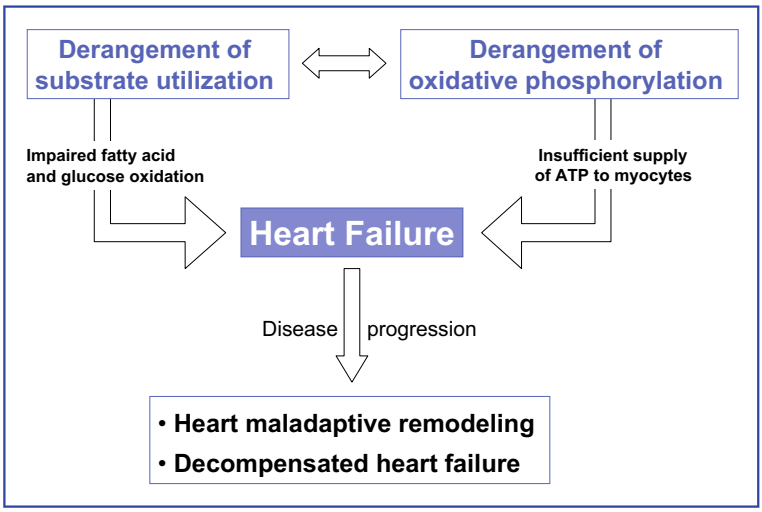

Fig. 1. Link between heart failure and derangement of substrate utilization and oxidative phosphorylation. **Derangement of substrate utilization:** In the early stage of heart failure there is increased glucose uptake-and-oxidation and a reduced rate of fatty acid oxidation. The switch towards reduced fatty acid oxidation and increased glucose oxidation is termed "reversion to a fetal metabolic phenotype". In advanced heart failure, there is a down-regulation of both fatty acid and glucose metabolic pathways. **Derangement of oxidative phosphorylation:** Impairment of mitochondrial oxidative phosphorylation can reduce cardiac function by providing an insufficient supply of ATP to myocytes. Furthermore, mitochondria exhibit defects of the electron transfer chain that increase generation of reactive oxygen species. This phenomenon is responsible for the disease progression and heart maladaptive remodeling (see text for more details).

accompanied by a parallel decrease in glycolytic rates. This process has been related to the down- or up-regulation or expression of specific nuclear receptors (peroxisome proliferator-activated receptors [PPAR]; PPAR coactivator-1, PGC-1; and PPAR specific response elements [ERRs]) that mediate these shifts in energy substrate utilization [13, 14]. In advanced heart failure, there is a downregulation of both fatty acid and glucose metabolic pathways (**Fig. 1**). A number of studies have demonstrated that in end stage heart failure the expression of all metabolic enzymes is repressed [11–14], and cardiomyocytes are insulin resistant [15]. However, interpretation of these findings is complicated by the substantial increases in the concentrations of plasma free fatty acids, glucose, and insulin that are common in heart failure and make it difficult to separate the changes in myocardial metabolic pathway capacities from indirect changes in the myocardium that are due to the altered metabolic milieu [16]. The low cardiac output of heart failure leads to a compensatory hyperadrenergic state that hyperphosphorylates the sarcoplasmic reticulum and increases the concentration of free fatty acids in the plasma. Enhanced fatty acid oxidation inhibits the key enzyme pyruvate dehydrogenase (PDH) and decreases the uptake of glucose and its oxidation [15, 16]. Direct demonstration of this pathophysiological mechanism comes from a model of pacing-induced heart failure, in which the administration of high doses of insulin did not improve myocardial glucose uptake in animals with heart failure [17]. Finally, reduced glycolysis results in less ATP to keep the sodium

pump functioning normally so that contractile activity and cardiac output are likely to decrease further [15, 16].

Modulation of Substrate Utilization: Therapeutic Potential for the Treatment of Heart Failure

Could substrate utilization be a specific therapeutic target in patients with heart failure? To answer this question it must be remembered that there is a controlled reciprocal relationship between the uptake of fatty acids and that of glucose in order to maintain the correct balance and coupling. Shifting myocardial substrate use from free fatty acids to glucose (more efficient in terms of energy production) should lead to an oxygen-sparing effect. On the other hand, partial inhibition of fatty acid beta-oxidation should stimulate glucose oxidation in the failing heart and, theoretically, improve aerobic efficiency [18]. There are several ways of achieving this end: 1) Inhibitors of circulating fatty acids (inhibitors of lipolysis, e.g., acipimox) improve PDH complex activity and accelerate the conversion of pyruvate to acetyl-CoA [19]; 2) inhibitors of free fatty acid uptake (e.g., perhexiline, oxfenicine, Etomoxir) prevent the uptake of free fatty acids *via* inhibition of CPT-I (carnitine palmitoyltransferase I), which is a key mitochondrial enzyme in this process [20]; 3) inhibitors of free fatty acid oxidation (e.g., trimetazidine) inhibit the enzyme 3-KAT (long chain 3-ketoacyl CoA thiolase), which is crucial in the beta-oxidation pathway [21]; 4) activators of the PDH complex (e.g., dichloroacetate) increase the conversion of pyruvate to acetyl-CoA [22]. Unfortunately, clinical trials using these metabolic modulators have in general been disappointing.

Oxidative Stress and Derangement of Oxidative Phosphorylation: The Key Role of Mitochondria

Impairment of oxidative phosphorylation can reduce cardiac function by providing an insufficient supply of ATP to myocytes. The mitochondrion plays an important role in this derangement (**Fig. 1**). In fact, in the failing heart, mitochondria have been shown to be structurally abnormal. They are smaller in size with membrane disruption and matrix depletion. Mitochondria exhibit defects in the electron transfer chain, which reduces ATP synthase capacity and increases generation of reactive oxygen species (ROS) [23]. Indeed, mitochondria have been shown to be the main source of ROS in heart failure. There are several factors that can influence mitochondrial ROS production (neurohumoral factors, catecholamines, increased cardiac sympathetic tone, increased basal oxygen requirement, hypoxia inducible-factor [HIF], increased angiotensin II, and tumor necrosis factor (TNF)-α stimulation) [24]. There is a complex pathophysiological link between ROS (and hence oxidative stress) and myocardial dysfunction. An increase in ROS production leads to electron transfer chain dysfunction which in turn reduces ATP turnover and causes myocardial contractile dysfunction [25]. ROS stimulate the production of non-mitochondrial proteins, other transcription factors, and inflammatory cytokines [26]. ROS can cause defects of cation pumps (Na^+-K^+ pump ATPase and Ca^{2+}-pump ATPase) leading to cellular and mitochondrial Ca^{++} overload, which is the main trigger for the opening of the mitochon-

drial permeability transition pore [27]; this determines mitochondrial depolarization and dysfunction which cause myocardial cell death via necrosis or apoptosis [28]. Finally, ROS activate the matrix metalloproteinases that can cause loss of collagen, slippage in myofibrillar alignment, left ventricular dilatation and heart maladaptive remodeling [29]. Under physiological conditions, there is an equilibrium between ROS production and breakdown. ROS toxicity can be prevented by several scavenging enzymes: Superoxide dismutase (SOD), glutathione peroxidase (GSHPx), and catalase, as well as by other non-enzymatic antioxidants (**Fig. 2**). However, when production of ROS becomes excessive there is an imbalance between ROS production and scavenger activity, thus oxidative stress may have a harmful effect on myocardial cells and tissue [30, 31]. This is particularly important in myocardial ischemia/reperfusion. Indeed, ROS play a central role in myocardial injury following ischemia/reperfusion phenomenon and can cause reversible (e.g., myocardial stunning) or irreversible (e.g., myocardial infarction) damage depending on the duration of the ischemic episode. In general, in myocardial stunning, ischemic damage is reversible because there is only a reduction in myocardial contractility after a brief period of ischemia followed by reperfusion (this condition is termed "flow-contractility mismatch"). Conversely, longer durations of ischemia can lead to cell death and myocardial infarction [32]. After a brief period of ischemia, during the early phase of reperfusion, the intracellular acidosis, the mitochondrial dysfunction, the Ca^{++} overload and the reduced sensitivity of contractile proteins are progressively corrected. The demonstration that oxida-

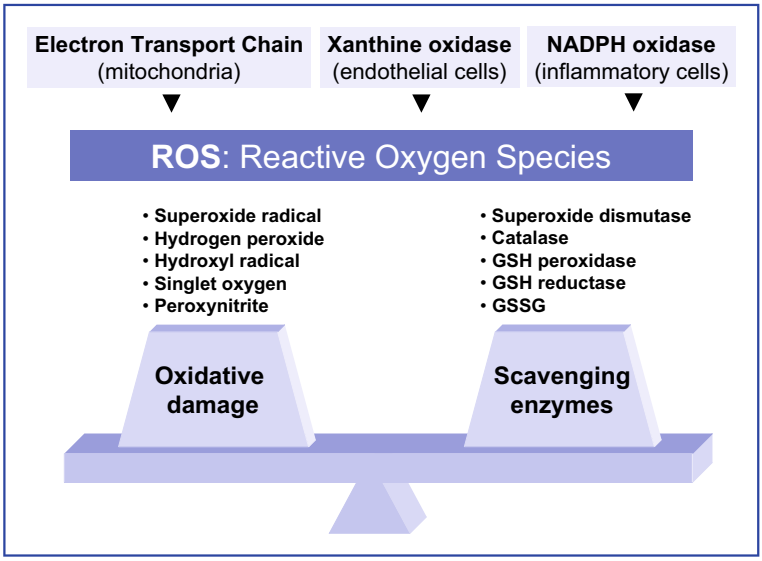

Fig. 2. Equilibrium between production and breakdown of reactive oxygen species (ROS). Under physiological conditions there is an equilibrium between ROS production and breakdown. ROS toxicity can be prevented by several scavenging enzymes: Superoxide dismutase (SOD), glutathione peroxidase (GSHPx), and catalase. When production of ROS becomes excessive there is an imbalance between ROS production and scavenger activity and the oxidative stress may have a harmful effect on myocardial cells. This is particularly important in myocardial ischemia/reperfusion phenomena where ROS can play a pivotal role in causing reversible (e.g., myocardial stunning) or irreversible (e.g., myocardial infarction) damage (see text for more details).

tive stress plays a significant role in the pathogenesis of myocardial stunning comes from animal experiments, which showed that in the conscious dog most of the myocardial stunning induced by a 15-min coronary occlusion could be prevented by antioxidant agents [33].

Oxidative stress also plays an important role in determining the extent of myocardial infarct size. In fact, transgenic over-expression of SOD has been shown to reduce infarct size in mice [34]. However, attempts to target SOD to improve outcome after myocardial infarction in other animal models have yielded mixed results. This suggests that ROS activation is only one contributor to post-myocardial infarction necrosis and reperfusion injury and that SOD alone is insufficient to neutralize the deleterious effects of ROS in this setting [35]. Finally, oxidative stress plays an important role in modulating the heart remodeling process after myocardial infarction. In fact, ROS can contribute to the remodeling processes in a number of ways (e.g., activation of matrix metalloproteinase, myocyte loss via apoptosis) [36]. Consequently, transgenic overexpression of GSHPx (a powerful scavenging enzyme) can improve left ventricular remodeling after myocardial infarction [37].

In contrast to the direct actions of ROS on cellular injury, ROS play a key role in cell protection as intracellular signaling molecules mediated by the activation and expression of antioxidant enzymes. The low-level oxidant production may be a trigger for ischemic preconditioning [38].

Oxidative Stress Studies: Pitfalls and Drawbacks

Contradictory results are often obtained in oxidative stress studies for a number of reasons: Different animal species are used; different durations of ischemia and timing of drug administration are considered; different drug delivery methods are applied; different end-points of cardioprotection are studied; 'clandestine' genetic artifacts in transgenic animals cannot be excluded; there is an interspecies heterogeneity of the response to myocardial ischemia/reperfusion; the agents used may not affect the status of only one antioxidant system [39]. Another problem is that it has been difficult to determine ROS activity *in vivo*. ROS are extremely reactive, therefore short-lived, which makes robust, reliable, and sensitive *in vivo* detection exceedingly difficult. Thus investigators and clinical studies have to rely on indirect measures of ROS, using biochemical markers of ROS activity (e.g., including indices of lipid peroxidation and stable end-products of free radical attack) with suboptimal reagents and methodologies. These pitfalls and drawbacks become particularly important in human models of ischemia/reperfusion phenomena.

Human Models of Ischemia/Reperfusion Phenomena

Ischemia/reperfusion phenomena in humans can occur spontaneously (variant and unstable angina, spontaneous coronary thrombolysis, transient coronary spasm) or during clinical interventions (percutaneous transluminal angioplasty, coronary artery bypass surgery, cardiopulmonary bypass [CPB], heart transplantation) (**Table 1**). Over recent years, several studies have demonstrated oxidative modification and release of the myocardial hydrophilic antioxidant in patients

Table 1. Human models of cardiac ischemia/reperfusion phenomena

Spontaneous	• Variant and unstable angina (also silent ischemia) • Spontaneous coronary thrombolysis • Transient coronary spasm
Clinical interventions (associated with global or local attenuation of coronary flow)	• PTCA (percutaneous transluminal angioplasty) • CABG (coronary artery bypass surgery) • CPB (cardiopulmonary bypass) • HTX (heart transplantation)

undergoing cardiac surgery with CPB utilizing aortic cross-clamping [40]. During cardiac surgery with CPB, the heart undergoes a three-step sequence of events: 1) Normal perfusion, before aortic cross-clamping; 2) cardiac arrest and global ischemia, after aortic cross-clamping; and 3) reperfusion, after aortic declamping. During this sequence of events, the lack of myocardial oxygen blocks mitochondrial NADH oxidation, this implies reduced mitochondrial ATP synthesis. Consequently, there is breakdown of high-energy phosphates in nucleosides and bases, as well as depletion of natural defenses against free radical damage. Ferrari and colleagues were the first to report the formation and release of oxidized glutathione (GSSG) in the coronary sinus following human myocardial ischemia/reperfusion in cardiac surgery. Reperfusion produced increased release of GSSG in a manner that was related to the duration of the ischemic period providing evidence for consumption of reduced glutathione (GSH) in humans subjected to cardiac surgery [41]. These observations have recently been extended to show changes in the myocardial content of glutathione and data from myocardial biopsies indicated that the cross-clamp period produced a massive loss of myocardial GSH [42]. The GSH/GSSG ratio represents an index of cellular redox modification. The balance between GSSG and GSH reflects cell defenses against oxidative stress: The higher the GSH/GSSG ratio, the better the antioxidant status of the myocardium and the defense against ROS toxicity. The GSH/GSSG ratio has been shown to correlate with indexes of cardiac performance after coronary surgery and heart transplantation [40–43]. Finally, the GSH/GSSG ratio has been shown to correlate with N-terminal pro-B-type natriuretic peptide (NT-proBNP), a biochemical marker that reflects the severity of myocardial stress and dysfunction [44].

Similar to hearts undergoing cardiac surgery with CPB, the transplanted heart undergoes a three-step sequence of events: 1) *In situ* heart function preservation in the brain-dead donor (normal perfusion), before aortic cross-clamping; 2) organ transport (cardiac arrest and global ischemia), after aortic cross-clamping; and 3) the implantation in the recipient (reperfusion), after aortic declamping. In these periods, the precautions adopted are not sufficient to maintain the energetic status because ATP is still being consumed, even if at a slower rate. The reduction in tissue ATP levels and oxygen free radical production could affect hemodynamic performance after heart transplantation [43]. Several studies have evaluated the influence of antioxidant agents (ascorbate, vitamin E, glutathione, allopurinol, thiol compounds alone or in various combinations, novel bioengineered compounds or low-molecular weight SOD mimetics) on ischemia/reperfusion injury in patients undergoing CPB and heart transplantation (**Table 2**). Unfortunately these studies are rather contradictory [45].

Table 2. Drugs and agents that have antioxidant effects or open mitochondrial K_{ATP} channels and exhibit pharmacological preconditioning

Antioxidants	**Exogenous** (thiol-containing compounds)	Probucol, allopurinol, hydralazine, propofol.
	Endogenous	SOD, catalase, GSHPx, CoQ, α-tocopherol, ascorbic acid, β-carotene, tezosentan.
K_{ATP} channels openers	**Anesthetic and narcotic agents**	Inhalational anesthetics, Opioids, ketamine, thiopental.
	Non-anesthetic agents	β-adrenergic blockers, ACE-I, Ca^{2+} channel antagonists, levosimendan, statins, cyclosporine A, adenosine, bradykinin, norepinephrine, small amount of ROS or TNF-α.

SOD: superoxide dismutase; GSHPx: glutathione peroxidase; CoQ: coenzyme Q; ACE-I: angiotensin-converting enzyme inhibitors; ROS: reactive oxygen species; TNF: tumor necrosis factor.

Ischemia/reperfusion Injury and Oxidative Stress: The Role of Mitochondrial ATP-Dependent Potassium (K_{ATP}) Channels on the Therapeutic Potential for the Treatment of Cardiac Dysfunction

The most powerful means of achieving cardiac protection against myocardial ischemia/reperfusion injury and oxidative stress is ischemic preconditioning. A number of studies have demonstrated that multiple short-term ischemic episodes interspersed by reperfusion make the heart more resistant to infarction during a subsequent acute coronary artery occlusion [46]. ATP-dependent potassium (K_{ATP}) channels have a pivotal role in ischemic preconditioning because they mediate the response to hypoxia and the hyperemic response to brief coronary occlusions. Sarcolemmal K_{ATP} channels open when ATP levels fall (during brief ischemic episodes), allowing potassium efflux so causing membrane hyperpolarization and reducing the action potential duration. These changes decrease the open probability of voltage-gated Ca^{2+} channels. The resulting reduction in Ca^{2+} concentration preserves ATP levels and reduces coronary vascular tone. The increase in extracellular potassium also facilitates coronary vasodilatation and increases blood flow to ischemic regions. Surface K_{ATP} channels were initially thought to mediate preconditioning. More recent evidence indicates that mitochondrial K_{ATP} channels play a crucial role in mediating cardiac preconditioning. Opening of mitochondrial K_{ATP} channels optimizes mitochondrial energy production, decreases mitochondrial Ca^{2+} overload, and prevents opening of mitochondrial permeability transition pores [47].

The mechanisms of preconditioning involve several types of trigger and mediator. Amongst them, adenosine A1- and A3-receptors, bradykinin 2-receptors, δ1-opioid receptors and α1-adrenoceptors play an important role. Via G-proteins, phospholipase C (PLC), and protein kinase C (PKC), these receptors act on mitochondrial and sarcolemmal K_{ATP} channels and reduce the opening probability of Ca^{2+} channels. Numerous studies have confirmed the important role of K_{ATP} channels in modulating ischemia/reperfusion phenomena [48]. The role of K_{ATP} channels in human preconditioning is evidenced by the observation that ischemic preconditioning does not occur in patients taking sulfonylurea, as this agent blocks K_{ATP} channels [49].

Several classes of drug have been shown to open mitochondrial K_{ATP} channels and to exhibit 'pharmacological' preconditioning (**Table 2**). In recent years, a number of experimental models have been conducted with these drugs and agents in an attempt to improve the oxidative stress following ischemia-reperfusion injury; unfortunately, results have not always been consistent [50].

Conclusion

To improve the prognosis of patients with heart failure, we need to develop therapeutic strategies based on novel insight into the pathophysiology of myocardial dysfunction and failure. Regulating myocardial energy metabolism and mitochondrial oxidative phosphorylation may contribute to the establishment of effective treatment strategies for patients with heart failure. Studies involving metabolic modulators and antioxidant agents have been small-scale, short-term trials looking at symptomatic benefits, and evidence of their efficacy has not yet been obtained. Large-scale clinical trials will have to prove or disprove the clinical efficacy of metabolic modulators and antioxidant agents in heart failure.

References

1. McMurray JJ, Pfeffer MA (2005) Heart Failure. Lancet 365: 1877 – 1889
2. Triposkiadis F, Parissis JT, Starling RC, Skoularigis J, Louridas G (2009) Current drugs and medical treatment algorithms in the management of acute decompensated heart failure. Expert Opin Investig Drugs 18: 695 – 707
3. Ormerod JOM, Ashrafian H, Frenneaux MP (2008) Impaired energetics in heart failure. A new therapeutic target. Pharmacology & Therapeutics 119: 264 – 274
4. Fragasso G, Salerno A, Spoladore R, Bassanelli G, Arioli F, Margonato A (2008) Metabolic therapy of heart failure. Curr Pharm Des 14: 2582 – 2591
5. Ingwall JS (2009) Energy metabolism in heart failure and remodelling. Cardiovasc Res 81: 412 – 419
6. Neubauer S (2007) The failing heart: an engine out of fuel. N Engl J Med 356: 1140 – 1151
7. Abozguia K, Shivu GN, Ahmed I, Phan TT, Frenneaux MP (2009) The heart metabolism: pathophysiological aspects in ischemia and failure. Current Pharmaceutical Design 15: 827 – 835
8. Bessman SP, Geiger PJ (1981) Transport of energy in muscle: the phosphocreatine shuttle. Science 211: 448 – 452
9. Neubauer S, Horn M, Cramer M, et al (1997) Myocardial phosphocreatine-to-ATP ratio is a predictor of mortality in patients with dilated cardiomyopathy. Circulation 96: 2190 – 2196
10. Conway MA, Allis J, Ouwerkerk R, Niioka T, Rajagopalan B, Radda GK (1991) Detection of low phosphocreatine to ATP ratio in failing hypertrophied human myocardium by 31P magnetic resonance spectroscopy. Lancet 338: 973 – 976
11. Stanley WC, Recchia FA, Lopaschuk GD (2005) Myocardial substrate metabolism in the normal and failing heart. Physiol Rev 85: 1093 – 1129
12. Luptak I, Yan J, Cui L, Jain M, Liao R, Tian R (2007) Long-term effects of increased glucose entry on mouse hearts during normal aging and ischemic stress. Circulation 116: 901 – 909
13. Madrazo JA, Kelly DP (2008) The PPAR trio: regulators of myocardial energy metabolism in health and disease. J Mol Cell Cardiol 44: 968 – 975
14. Sihag S, Cresci S, Li AY, Sucharov CC, Lehman JJ (2009) PGC-1alpha and ERRalpha target gene downregulation is a signature of the failing human heart. J Mol Cell Cardiol 46: 201 – 212
15. Opie LH (2004) The metabolic vicious cycle in heart failure. Lancet 364: 1733 – 1734

16. Ashrafian H, Frenneaux MP, Opie LH (2007) Metabolic mechanisms in heart failure. Circulation 116: 434–448
17. Nikolaidis LA, Sturzu A, Stolarski C, Elahi D, Shen YT, Shannon RP (2004) The development of myocardial insulin resistance in conscious dogs with advanced dilated cardiomyopathy. Cardiovasc Res 61: 297–306
18. Fragasso G (2007) Inhibition of free fatty acids metabolism as a therapeutic target in patients with heart failure. Int J Clin Pract 61: 603–610
19. Tuunanen H, Engblom E, Naum A, et al (2006) Free fatty acid depletion acutely decreases cardiac work and efficiency in cardiomyopathic heart failure. Circulation 114: 2130–2137
20. Ashrafian H, Horowitz JD, Frenneaux MP (2007) Perhexiline. Cardiovasc Drug Rev 25: 76–97
21. Fragasso G, Spoladore R, Cuko A, Palloshi A (2007) Modulation of fatty acids oxidation in heart failure by selective pharmacological inhibition of 3-ketoacyl coenzyme-A thiolase. Curr Clin Pharmacol 2: 190–196
22. Lopaschuk GD (2006) Optimizing cardiac fatty acid and glucose metabolism as an approach to treating heart failure. Semin Cardiothorac Vasc Anesth 10: 228–230
23. Marin-Garcia J, Goldenthal MJ, Moe GW (2001) Mitochondrial pathology in cardiac failure. Cardiovasc Res 49: 17–26
24. Di Lisa F, Kaludercic N, Carpi A, Menabò R, Giorgio M (2009) Mitochondrial pathways for ROS formation and myocardial injury: the relevance of p66(Shc) and monoamne oxidase. Basic Res Cardiol 104: 131–139
25. Tsutsui H (2001) Oxidative stress in heart failure: the role of mitochondria. Internal Medicine 40: 1177–1182
26. Hughes G, Murphy MP, Ledgerwood EC (2005) Mitochondrial reactive oxygen species regulate the temporal activation of nuclear factor kappaB to modulate tumour necrosis factor-induced apoptosis: evidence from mitochondria-targeted antioxidants. Biochem J 389: 83–89
27. Javadov S, Karmazyn M, Escobales N (2009) Mitochondrial permeability transition pore opening as a promising therapeutic target in cardiac diseases. J Pharmac Exp Ther 330: 670–678
28. Wagner M, Siddiqui MA (2009) Signaling networks regulating cardiac myocyte survival and death. Curr Opin Investig Drugs 10: 928–937
29. Tsutsui H, Kinugawa S, Matsushima S (2009) Mitochondrial oxidative stress and dysfunction in myocardial remodelling. Cardiovasc Res 81: 449–456
30. Huss JM, Kelly DP (2005) Mitochondrial energy metabolism in heart failure: a question of balance. J Clin Invest 115: 547–555
31. Jassem W, Fuggle SV, Rela M, Koo DDH, Heaton ND (2002) The role of mitochondria in ischemia/reperfusion injury. Transplantation 73: 493–499
32. Zaugg M, Schaub MC, Foex P (2004) Myocardial injury and its prevention in the perioperative setting. Br J Anaesth 93: 21–33
33. Bolli R (1998) Causative role of oxyradicals in myocardial stunning: a proven hypothesis. A brief review of the evidence demonstrating a major role of reactive oxygen species in several forms of postischemic dysfunction. Basic Res Cardiol 93: 156–162
34. Chen Z, Siu B, Ho YS, et al (1998) Overexpression of MnSOD protects against myocardial ischemia/reperfusion injury in transgenic mice. J Mol Cell Cardiol 30: 2281–2289
35. Suzuki K, Murtuza B, Sammut IA, et al (2002) Heat shock protein 72 enhances manganese superoxide dismutase activity during myocardial ischemia-reperfusion injury, associated with mitochondrial protection and apoptosis reduction. Circulation 106 (Suppl 1): 270–276
36. Tsutsui H, Ide T, Kinugawa S (2006) Mitochondrial oxidative stress, DNA damage, and heart failure. Antioxid Redox Signal 8: 1737–1744
37. Shiomi T, Tsutsui H, Matsusaka H, et al (2004) Overexpression of glutathione peroxidase prevents left ventricular remodeling and failure after myocardial infarction in mice. Circulation 109: 544–549
38. Klawitter PF, Murray HN, Clanton TL, Angelos MG (2002) Reactive oxygen species generated during myocardial ischemia enable energetic recovery during reperfusion. Am J Physiol Heart Circ Physiol 283: 1656–1661

39. Sheeran FL, Pepe S (2006) Energy deficiency in the failing heart: linking increased reactive oxygen species and disruption of oxidative phosphorilation rate. Biochim Biophys Acta 1757: 543 – 552
40. Carlucci F, Tabucchi A, Biagioli B, et al (2002) Cardiac surgery: myocardial energy balance, antioxidant status and endothelial function after ischemia-reperfusion. Biomed Pharmacother 56: 483 – 491
41. Ferrari R, Alfieri O, Curello S, et al (1990) Occurrence of oxidative stress during reperfusion of the human heart. Circulation 81: 201 – 211
42. Marczin N, El-Hbashi N, Hoare GS, Bundy RE, Yacoub M (2003) Antioxidants in myocardial ischemia-reperfusion injury: therapeutic potential and basic mechanisms. Archives of Biochemistry and Biophysics 420: 222 – 236
43. Biagioli B, Scolletta S, Marchetti L, Tabucchi A, Carlucci F (2003) Relationships between hemodynamic parameters and myocardial energy and antioxidant status in heart transplantation. Biomed Pharmacother 57: 156 – 162
44. Scolletta S, Carlucci F, Biagioli B, et al (2007) NT-proBNP changes, oxidative stress, and energy status of hypertrophic myocardium following ischemia/reperfusion injury. Biomed Pharmacother 61: 160 – 166
45. Boku N, Tanoue Y, Kajihara N, Eto M, Masuda M, Morita S (2006) A comparative study of cardiac preservation with Celsior or University of Wisconsin solution with or without prior administration of cardioplegia. J Heart Lung Transplant 25: 219 – 225
46. Kloner RA (2009) Clinical application of remote ischemic preconditioning. Circulation 119: 776 – 778
47. Baines CP (2009) The mitochondrial permeability transition pore and ischemia-reperfusion injury. Basic Res Cardiol 104: 181 – 188
48. Gross GJ, Peart JN (2003) KATP channels and myocardial preconditioning: an update. Am J Physiol Heart Circ Physiol 285: 921 – 930
49. Cleveland JC Jr, Meldrum DR, Cain BS, Banerjee A, Harken AH (1997) Oral sulfonylurea hypoglycaemic agents prevent ischemic preconditioning in human myocardium. Two paradoxes revisited. Circulation 96: 29 – 32
50. Frässdorf J, De Hert S, Schlack W (2009) Anaesthesia and myocardial ischaemia/reperfusion injury. Br J Anaesth 103: 89 – 98

Evolving Rationale for Minimally-interrupted Chest Compressions during Cardiopulmonary Resuscitation

J.G. Wigginton, A.H. Idris, and P.E. Pepe

Introduction

VI

This past year marked the 50th anniversary of the first scientific presentation describing the technique and resulting survival benefit of cardiopulmonary resuscitation (CPR) as we know it today [1]. When first described, the directives for the chest compression component were to "push hard, deep and fast". A half century later, the latest international guidelines for CPR have not only emphasized the timing, rate and quality of those chest compressions, but also the key notion of sustaining uninterrupted compressions whenever possible [1–6]. Today, those early caveats of hard, fast and deep are now further supported by an accumulating body of compelling scientific data, including those that indicate that chest compressions can even be "too fast" or too uneven with insufficient chest wall recoil [6]. Moreover, recent research efforts also have encouraged a strategy of early and sustained provision of minimally-interrupted chest compressions [7–11]. In many cases, resuscitation specialists have de-emphasized rescue ventilation altogether [7, 12–15]. Similarly, some investigators have recommended that the more invasive advanced life support (ALS) interventions (e.g., endotracheal intubation) should be deferred so that basic CPR (compressions) can be prioritized [7–10]. Furthermore, in view of this new emphasis on chest compressions, there has arisen a renewed focus on the quality of CPR using feedback loops for prospective rescuers, both in follow-up and real-time remediation [4–6]. In the following discussion, we will review the data that support this evolving emphasis on minimally-interrupted chest compressions and also provide a perspective on why 'compressions-only' CPR is a very feasible strategy for the majority of persons likely to survive a cardiac arrest.

Minimizing Interruptions in Chest Compressions

Many investigators have demonstrated that, following a cardiac arrest, attempts to re-establish and, most importantly, to maintain a certain degree of coronary artery perfusion pressure, even when only a fraction of normal levels, is the key factor in achieving restoration of spontaneous circulation (ROSC). This principle applies to all cases of cardiac arrest regardless of the precipitating cause, including those cases requiring defibrillation, and especially when too much time has elapsed from the onset of the ventricular fibrillation (VF) that led to the arrest [1, 2, 16, 17].

Therefore, the fundamental concept in CPR is that rescuers need to ensure constant delivery of what is hopefully an adequate degree of coronary artery per-

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fusion pressure. More importantly, it needs to be understood that when compressions are interrupted, coronary artery perfusion pressure rapidly declines and it then takes many seconds (and perhaps as much as a half minute) to build up and restore an adequate pressure head again [1, 7, 15]. In turn, it has been shown that if rescuers stop chest compressions too frequently, or if they do so for too long a period, the average coronary artery perfusion pressure calculated over a minute (minute-CAPP) is diminished dramatically and the chances for ROSC and ultimate survival are severely compromised [1, 7, 15, 16].

Ironically, with the current emphasis on harder, deeper, and faster compressions, rescuers can tire more readily and this can result in interruptions when rescuers providing the compressions are switched frequently. Although alternating rescuers to better ensure the most optimal compressions by avoiding fatigue, this switch is not always seamless. Likewise, if key tasks are not coordinated by team leaders, compressions may be recurrently and frequently halted, either to insert rescue breaths, make pulse assessments or deliver an attempted defibrillation. If not synchronized to avoid duplicate pauses, these frequent interruptions can significantly diminish the chances of attaining rapid ROSC and, ultimately, any hopes for long term survival without neurological impairment [1, 3 – 5, 7, 8].

Even more impressive in terms of demonstrating the pivotal role of providing continuous compressions is the observation that the length of the defibrillation 'hands-off' period is inversely proportional to achievement of ROSC [1, 3, 7]. Specifically, the hands-off period is defined as the time interval that begins when the rescuer's hands are removed from the chest (so that the cardiac rhythm can be analyzed) and extends until the defibrillator charges and chest compressions are resumed after delivery of the countershock. What is striking is that the critical interval for imposing significant compromise to resuscitation can be literally a matter of seconds [1, 3, 7]. Conversely, if chest compressions are maintained without significant interruption, a sufficient minute-CAPP may be sustained and the beneficial effects may be most pronounced in the early minutes following an abrupt loss of strong spontaneous circulation [1, 3, 7, 11]. For that reason, in most cases of sudden onset VF, there may be an increased chance of ROSC and ultimate survival with intact neurological status if chest compressions are not interrupted, especially in those critical first few minutes after sudden collapse [1, 7, 9, 12]. There are even clinical studies, including controlled trials, that compare 'compression-only' CPR versus traditional (airway, breathing, circulation) CPR and support this principle [12]. In such studies, not only are the all-important chest compressions started earlier, but there is better chance of achieving compliance in terms of getting bystanders to perform CPR [12].

From a physiological point of view, the early use of 'compression-only' (or minimally interrupted) CPR is most important in the early minutes after onset of a sudden cardiac arrest [11]. Not only does the peripheral vasculature still have a certain degree of residual vascular tone in the first few minutes after the sudden patient collapse (thus enhancing the pressure head at the base of the aorta during CPR), but the arterial blood is likely to be adequately saturated with oxygen [11 – 14, 17].

Concern Regarding Oxygen Desaturation

From a traditional and clearly intuitive perspective, rescuers might be concerned about desaturation of the circulating red blood cells if intermittent rescue breaths are not provided, particularly because patients can rapidly begin to turn cyanotic in appearance. However, what is often not appreciated by most care providers is that during CPR conditions, due to the markedly slower than normal circulation, tissue oxygen extraction may now be profoundly increased and thus manifests itself in many cases by profound cutaneous cyanosis. Still, despite appearances, the arterial bloodstream can stay fairly well-saturated for a few minutes after sudden cardiac arrests [13–15, 17].

For example, although cardiac arrest patients undergoing aggressive CPR may appear extremely ashen and cyanotic across their head and chest (until they achieved ROSC), a concurrent needle-syringe aspiration of the femoral artery can demonstrate bright red blood in the artery while simultaneously showing almost 'blackened' blood in the corresponding femoral vein site ('poor man's blood gas technique). While the patient's head and neck appear quite cyanotic due to the low flow state, the brain and heart may still be experiencing a steady (though unusually low) flow of well-oxygenated blood for the first four or five minutes [13–15, 17]. Considering that basic CPR can only provide a limited percentage of normal circulation, the larger arterial vessels can still retain blood with fairly reasonable oxygen content for several minutes before significant tissue extraction and eventual desaturation begins to occur [13–15, 17].

Excluding those cardiac arrests precipitated by respiratory compromise or a rapidly failing heart and flash pulmonary edema, a sudden circulatory arrest, such as that commonly caused by the sudden onset of VF, should be associated with well-saturated arterial red blood cells in the larger vessels at the time of the sudden circulatory arrest and this saturated state should remain intact for the first several critical minutes [1, 7, 8, 10, 12–15, 18].

Moreover, if arterial blood desaturation did begin to occur, it could be argued that the continuous, uninterrupted delivery of some fixed amount of oxygen, albeit from relatively desaturated red cells, is much more important for achieving ROSC than a circumstance in which red cells, even if 100 % saturated, are delivered infrequently and without a sustained pressure head. For example, mountain climbers and others who are respiring ambient atmosphere at altitudes above 18,000 feet can survive and even climb and mentate reasonably well with the resulting 75 % arterial blood saturation because they still have adequate circulation. However, they would not fair as well, even at 100 % saturation, if there was not enough coronary artery perfusion pressure to maintain coronary artery blood flow, especially in a low flow state. Taking such a non-traditional perspective, many would now argue that uninterrupted compressions should continue, even after several minutes of basic CPR, and even when professional rescuers are on-scene with airway equipment [7, 8].

Enhanced Oxygenation, Ventilation and Circulation – by Not Ventilating

One of the traditional concerns over letting desaturated blood flow to the tissues (by not breathing for the cardiac patient) is the potential resulting effects of low

oxygen tensions in critical tissues such as the heart and brain. The concerns also involve the inadequate elimination of carbon dioxide and other normal functions that may lead to additional acidosis and impaired end-organ function. However, it has also been noted that mouth-to-mouth ventilation by bystanders not only causes a maldistribution of ventilation to the lungs and increases the risk of gastric insufflation and subsequent regurgitation and aspiration, but rescuers are delivering their own expired air that already has a relatively low oxygen (and relatively high carbon dioxide) tension [15]. Moreover, rescue breaths provided by bystanders and professional responders alike all involve positive pressure ventilation techniques which not only interfere with venous return and cardiac preload, but also interrupt chest compressions for significant periods of time thus diminishing the minute-CAPP significantly [1, 7, 15, 16]. Thus, rescue breaths can not only create an additional risk for aspiration and airway compromise, but also impair alveolar oxygenation, carbon dioxide elimination and also interfere with cardiac output and maintenance of coronary artery perfusion pressure [15].

There is, therefore, an interesting paradox that may occur during CPR by not providing rescue ventilations. With chest compression-only CPR, particularly in the first few minutes after a sudden VF cardiac arrest, one may actually provide better oxygenation (arterial saturation), better ventilation (carbon dioxide elimination), and even better circulation (enhanced preload) by not ventilating. The rationale for this viewpoint is further enhanced by the frequent presence of gasping respirations in those cardiac arrest patients who are most likely to survive [19–31].

Gasping Enhances Continuous Chest Compressions – and *Vice Versa*

Gasping is a physiological entity that, among other conditions, is seen typically in mammals who have sustained a global ischemic insult such as sudden cardiac arrest or severe hemorrhagic shock [19–31]. Scientists have defined a gasp formally in nomenclature consensus processes as “an abrupt, sudden, transient inspiratory effort” [32]. The classic gasping that occurs after sudden cardiac arrest is also sometimes referred to as “agonal breaths” or “agonal respirations” in various investigations [20, 21, 23]. However, agonal breathing may also be used by some when referring to a broader variety of respiratory efforts or abnormal conditions. Classic gasps, according to strict definition, however, are usually sudden, abrupt, and much brisker and larger than normal respiratory efforts [32].

Gasping respirations are not found in all cardiac arrest patients, even when the duration of cardiac arrest is short. This observation may reflect the underlying etiology of the event, the individual’s specific tolerance to global anoxia, or some predetermined individual propensity for gasping [19–31]. For example, gasping is found much more often in out-of-hospital cardiac arrest patients presenting with scenarios that reflect a shorter period of anoxia, such as cardiac arrests that have been directly witnessed by bystanders (witnessed arrests), shorter emergency medical services (EMS) response intervals, and an initial presenting electrocardiographic (EKG) rhythm of VF or ventricular tachycardia [20, 23, 24].

Accordingly, it is not surprising that the presence of gasping in out-of-hospital cardiac arrest is also associated with a higher rate of survival [19, 20, 23, 24]. The higher survival rate may be a reflection of other co-existing surrogate variables, such as easier ability to resuscitate and restore full circulation in persons present-

ing with VF. However, gasping is also a clear marker that there is continued activity of critical respiratory system cells including those in the medulla stimulating the inspiration, those in the spinal cord and phrenic nerves conducting the impulses, and those in the relevant respiratory musculature. Therefore, the observation of gasping also may simply mean the individual organism with the global ischemic insult, be it human or animal, was better developed to tolerate anoxia. Also, as described in the subsequent discussion, gasping itself may also be an active and independent factor in the ability to achieve successful resuscitation [19].

Although the need to excrete carbon dioxide (CO_2) using standard basic CPR techniques generally will remain low throughout this low perfusion circumstance, normal systemic arterial O_2 saturation still requires maintenance of the inflation (or re-inflation) of certain dependent lung zones subject to alveolar closure [9, 19, 27]. Considering the lung compressing force of vigorous chest compressions and progressive lung deflation due to absence of normal spontaneous breathing, oxygen desaturation of red blood cells eventually becomes a problem. The pivotal concern for most clinicians is to determine the point at which assisted lung inflation (i.e., alveolar recruitment) truly may be required and, when that time comes, what respiratory rate and tidal volume should be delivered [10].

One mechanism for providing ventilation in and out of the chest is the thoracic squeeze and recoil process that occurs during the chest compressions of CPR. During chest compressions, air is expelled from the thorax during the down-stroke phase and then, to some degree, air is passively inhaled during the elastic recoil of the chest wall, assuming an open airway is present [33]. This technique may work to some extent for the purposes of removing CO_2, but it may not maintain adequate oxygenation, particularly in the absence of spontaneous respiratory activity [33].

Therefore, relevant to this conversation is the impact of gasping as a secondary mechanism of ventilation. Considering that the brainstem, the peripheral nervous system and respiratory apparatus usually remain oxygenated up until the actual moment of a sudden cessation of circulation, it is understandable that some form of respiration might still occur during the early minutes following sudden cardiac arrest [19, 20, 23, 24]. Considering that gasping is associated with better survival rates, its presence probably reflects, at least in part, a shorter or lesser ischemic insult to the brain and the rest of the respiratory apparatus. This hypothesis is logical considering the fact that gasps are most often observed in witnessed collapses and non-asystole presentations [19, 20, 23, 24]. Relevant to the current discussion, therefore, is the belief that gasping may be preserved for longer periods of time with early, effective and minimally interrupted basic CPR [19].

This reasonable speculation stems from the notion that there is more preservation of oxygenation of the brainstem and respiratory apparatus with optimal chest compressions, such as that provided in experimental models [27–31]. However, in a recent clinical study of agonal respirations, the relative proportions of patients who had received bystander CPR was not different when comparing those who were gasping and those who were not, regardless of the relative length of the EMS response intervals. Nevertheless, survival rates for those receiving bystander CPR was 39 % among gasping patients versus 9 % among the non-gaspers [24]. But while gasping may be a surrogate marker for better tolerance of the ischemic insult among those cases that were witnessed by bystanders and thus received CPR, there are also a number of animal studies with data to support the

concept that gasping itself may independently improve survival chances as well [25–31].

While these spontaneous gasping ventilations eventually deteriorate due to the less than optimal perfusion of the brain and respiratory muscles during cardiac arrest and prolonged CPR (particularly when continually interrupted for ventilations and other activities), it is believed that they may still provide relatively effective respirations during the first few minutes after a sudden cardiac arrest [27–31]. Ironically, when rescue breaths are not delivered so that chest compressions can remain uninterrupted, the special mechanics of gasping may actually improve the effectiveness of CPR for several sound physiological reasons. First, the physical nature of gasps can potentially generate a larger and more powerful respiratory effort than a normal resting breath with a much stronger inspiratory effort, at least in the first few minutes following sudden cardiac arrest [27–31]. As a result, in the initial phases following circulatory collapse, this type of respiratory effort can result in larger, more efficient lung inflations. In turn, such respiratory efforts can better ensure the inflation of dependent lung zones and thus behave more like normal breathing. Also, with a greater percentage of each of these larger than normal breaths going toward alveolar ventilation (and a lesser percentage to dead space), more CO_2 is cleared, even when compared to typical normal resting breaths [10, 15].

In addition, these unique and extraordinary inspiratory efforts can often generate enhanced negative intrathoracic pressures, thus augmenting venous return to the heart and, in some cases, diminishing intracranial pressure (ICP) as well [27–31]. In fact, in one experimental study, gasping significantly increased carotid blood flow during untreated cardiac arrest in a pig model of VF [29]. Consequently, gasping may have an independent positive effect that is not directly related to its overt respiration function.

In contrast to gasping, the provision of mouth-to-mouth rescue breaths is a technique that provides maldistributed and relatively hypoxic gas into the lungs. Perhaps more importantly, as a ventilatory mechanism that uses positive pressure to inflate the lungs, assisted rescue breaths, either by mouth-to-mouth or a bag-valve device, will raise intrathoracic pressure and transiently inhibit venous return, particularly in the low flow state of CPR conditions [10]. Teleologically, gasping may be the best ventilatory response during the first few minutes following cessation of circulation as it not only will likely increase oxygenation and ventilation (much larger tidal volume and better physiological distribution of that volume), but it also improves circulation [10, 15, 29, 30].

Even in asphyxial arrest models, and despite poorer saturation, overall oxygen delivery to the tissues may be matched by the improved flows attained with uninterrupted compressions [34]. Assimilating all of the available experimental information, one could argue that with earlier, uninterrupted chest compressions, coronary perfusion pressures remain in a better range, and, in turn, perfusion of the brain and respiratory apparatus are better sustained. This will theoretically prolong the period of gasping and its additional positive physiological benefits [19, 27–31]. By not providing ventilations, the rescuer may paradoxically be providing better oxygenation, ventilation and circulation in the resuscitative effort.

If sustaining better perfusion of the brainstem and respiratory apparatus can be accomplished by uninterrupted chest compressions and ‘no (assisted) ventilation’, then gasps may very well be sustained longer (at least in theory) and, in turn, the enhanced circulation from gasping may also delay other aspects of car-

diovascular deterioration such as that occurring when the peripheral vasculature begins to lose tone from under-perfusion [11]. When vascular tone is rapidly lost, coronary perfusion is diminished because of a declining aortic pressure and resuscitation chances diminish as well. Gasping may help to defer that rate of decline, especially when accompanied by well-performed and minimally-interrupted chest compressions. In essence, continuous chest compressions may have other indirect effects that go beyond simple out-thrusts of blood from the thorax and they may actually result in better and more prolonged respiratory and circulatory function as facilitated by the gasping process (when present).

With this presumption, international standards for dispatchers who provide CPR instruction over the telephone to bystanders at the scene now emphasize compressions-only in their protocols, particularly in the first few minutes after a sudden cardiac arrest with no obvious precipitating cause for the arrest [9]. More recently, these same international consensus groups are also now adopting protocols involving the identification of agonal breaths to detect cardiac arrest and persons who therefore need the initiation of basic CPR [1, 20]; it has also become a topic in recent training materials for laypersons learning basic CPR techniques [1, 7, 35].

New Technologies to Minimize Interruptions in CPR

With the new CPR mantra to "push hard, push fast" on the chest and allow full recoil while also curtailing interruptions in compressions, recent research has led to the concept of "hands-on" defibrillation. In one study, it was shown that the typical gloves worn by most rescuers appear to be protective from the effects of the shock, allowing the rescuer to continue compressions during the delivery of a shock [36]. Other recent research has demonstrated that 'noise reduction' automated external defibrillator (AED) and cardiac monitor analysis may now allow advanced devices to distinguish VF from CPR artifact [37]. This technology may now allow AED devices to identify the need to provide shocks without interrupting chest compressions [37]. With advances such as these, rescuers may never need to take their hands off the chest altogether, be it for rhythm analysis, shock delivery or any other reason beyond switching out a chest compressor.

In addition, the scientific community and federal research funding organizations have begun to place a higher priority on providing quality chest compressions. A good example of this evolution is the founding and funding of the Resuscitation Outcomes Consortium (ROC) in North America by the National Institutes of Health (NIH), the Canadian Institutes of Health Research and other relevant, related organizations [38]. This initiative has involved the use of specialized devices that continuously monitored second-to-second performance of CPR, including rate, depth, recoil and interruptions in chest compressions. These recordings initially demonstrated frequent disruptions and sub-optimal performance in 9-1-1 first responders (**Fig. 1**). However, using the electronically-recorded CPR measurements, investigators and the respective EMS medical directors were able to give routine follow-up and feedback with appropriate remediation of CPR performance for individual rescuers over a period of time. This performance improvement process resulted in substantial progress in training rescuers to avoid interruptions in chest compressions (**Fig. 1**). In turn, there were concomitant profound increases in the population-based survival rates throughout

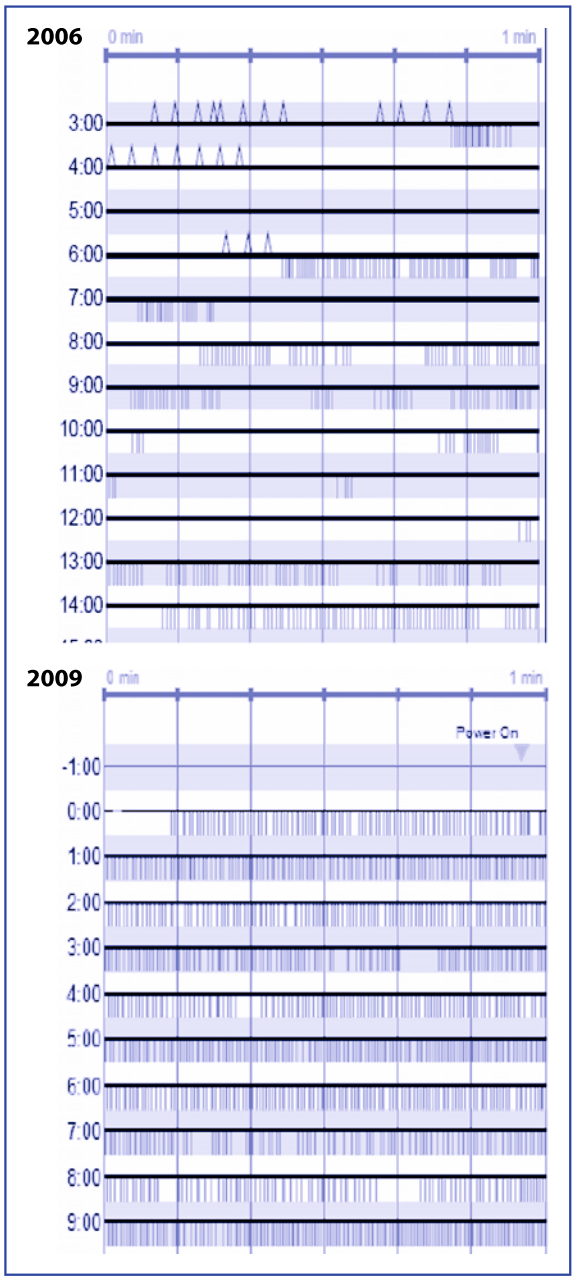

Fig. 1. Improving the quality of chest compressions. The figure demonstrates electronically-stored chest compression tracings used as feedback for 9-1-1 medical first responders. Each spike on the tracing represents a chest compression. The data indicate dramatic improvements in the frequency/quality of chest compressions provided by rescuers from before (2006) to after (2009) repeated feedback and training sessions to remediate and better ensure minimal interruptions in the provision of chest compressions. As similarly demonstrated in other communities, these findings were associated with profound improvements in patient survival rates.

the participating cities including one large municipality with nearly a four-fold improvement in the numbers of patients returning home neurologically intact following cardiac arrest. At the same time, the researchers were able to demonstrate that improving CPR effectiveness by simply teaching rescuers to "push,

hard, fast and deep" without more specific guidance could also have a downside. Specifically, they found that overzealous compressions (those delivered at far too great a rate) were also deleterious. In essence, improving the overall quality of CPR and minimizing its interruption should constitute a comprehensive approach that involves numerous components [1–11, 16].

But beyond technologies, success in effecting minimally-interrupted chest compressions should also involve logistical and clinical strategies to synchronize activities that might disrupt continuous delivery of the compressions. In other words, potential disruptions such as defibrillation, pauses for pulse and rhythm checks, and the alternation of rescuers should be coordinated and consolidated. For example, anticipating that the chest compressor should soon be relieved by another rescuer, resuscitation team leaders should have that substitute ready to go and have their hands ready in position while another rescuer is already palpating over the pulse check region (e.g., femoral artery) and someone else is simultaneously running an EKG rhythm strip. The concept is that all of these potential interruptions should be synchronized into one instance of interruption, not several.

Pediatric Arrests and Cases of Presumed Respiratory Etiology

The clear caveat to the concept of continuous chest compressions or 'compression-only' CPR is its applicability to sudden cardiac arrest when it is believed that the arterial vessels remain fully saturated with oxygenated red cells during the first few minutes. The question remains as to whether or not rescue breaths should still be delivered in cardiac arrest cases likely to be precipitated by a respiratory compromise such as water submersion, pediatric scenarios, and underlying pulmonary disease in which hypoxemia may have led to the cardiac arrest. Whereas the general consensus is to still provide rescue breaths as part of the resuscitation effort, one might still question the potential detrimental effects of interrupting chest compressions once pulselessness has occurred using the same rationale that continuously delivering blood flow to vital organs, even if desaturated blood, is more important than trying to insert rescue breaths that will dissipate the coronary perfusion pressures and, in turn, the chances of achieving ROSC. In fact, the classic practice of trying to provide more frequent breaths to pulseless children may, therefore, account for the poor outcomes traditionally observed in population-based studies of pediatric cardiac arrest [10, 39].

Conclusion

Maintaining an adequate level of coronary artery perfusion pressure is the key factor in achieving ROSC following cardiac arrest. When compressions are interrupted, the coronary artery perfusion pressure rapidly dissipates and it may take as much as half a minute to again build up and restore an adequate pressure head. If rescuers stop chest compressions too frequently, or if they do so for too long a period, survival chances are profoundly diminished. Conversely, many clinical studies, including controlled trials, have confirmed that 'compression-only' CPR is superior to traditional approaches that include rescue breaths. Therefore, the fundamental concept is to provide minimally-interrupted chest compressions. In addition to interrupting compressions and dissipating coronary

perfusion pressure, rescue breaths also reduce circulation by inhibiting venous return and subsequent cardiac pre-load. Fortunately, the presence of gasping respirations is common in those cardiac arrest patients most likely to survive and their presence may enhance oxygenation (better lung inflation of dependent lung zones) and facilitate adequate ventilation (more efficient breaths) while also boosting circulation (augmented venous return). In turn, continuous chest compressions, by better supplying a more sustained cardiac output to the brain and respiratory apparatus, may protract the presence of gasping and thus improve oxygenation, ventilation and circulation for a longer period of time during CPR. Technologies designed to minimize interruptions in chest compressions and improve the quality of the CPR delivered can improve survival rates dramatically.

References

1. Berg RA, Hemphill R, Abella BS, et al (2010) Part 5: Adult basic life support: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation 122 (suppl 3): S685 – 705
2. Wik L, Hansen TB, Fylling F, et al (2003) Delaying defibrillation to give basic cardiopulmonary resuscitation to patients with out-of-hospital ventricular fibrillation: a randomized trial. JAMA 289: 1389 – 1395
3. Koster RW (2003) Limiting 'hands-off' periods during resuscitation. Resuscitation 58: 275 – 276
4. Wik L, Kramer-Johansen J, Myklebust H, et al (2005) Quality of cardiopulmonary resuscitation during out-of-hospital cardiac arrest. JAMA 293: 299 – 304
5. Abella BS, Alvarado JP, Myklebust H, et al (2005) Quality of cardiopulmonary resuscitation after in-hospital cardiac arrest. JAMA 293: 305 – 310
6. Aufderheide TP, Pirallo RG, Yannopoulos D, et al (2005) Incomplete chest wall compressions: a clinical evaluation of CPR performance by EMS personnel and assessment of alternate manual chest compression-decompression techniques. Resuscitation 64: 353 – 362
7. Sayre MR, Berg RA, Cave DM, Page RL, Potts J, White RD (2008) Hands-only (compression-only) cardiopulmonary resuscitation: A call to action for bystander response to adults who experience out-of-hospital sudden cardiac arrest. Circulation 117: 2162 – 2167
8. Bobrow BJ, Clark LL, Ewy GA, et al (2008) Minimally interrupted cardiac resuscitation by emergency medical services for out-of-hospital cardiac arrest. JAMA 299: 1158 – 1165
9. Roppolo LP, Pepe PE, Cimon N, et al (2005) Modified cardiopulmonary resuscitation (CPR) instruction protocols for emergency medical dispatchers rationale and recommendations. Resuscitation 65: 203 – 210
10. Pepe PE, Roppolo LP, Fowler RL (2005) The detrimental effects of ventilation during low-blood-flow states. Curr Opin Crit Care 11: 212 – 219
11. Lee SK, Vaageres P, Safar P, Stezoski SW, Scanlon M (1989) Effect of cardiac arrest time on cortical cerebral blood flow during subsequent standard external cardiopulmonary resuscitation in rabbits. Resuscitation 17: 105 – 117
12. Hallstrom A, Cobb L, Johnson E, Copass M (2000) Cardiopulmonary resuscitation by chest compression alone or with mouth-to-mouth ventilation. N Engl J Med 342: 1546 – 1553
13. Chandra NC, Gruben KG, Tsitlik JE, et al (1994) Observations of ventilation during resuscitation in a canine model. Circulation 90: 3070 – 3075
14. Idris AH, Florete Jr. O, Melker RJ, Chandra NC (1996) The physiology of ventilation, oxygenation, and carbon dioxide elimination during cardiac arrest. In: Paradis NA, Halperin HR, Nowak RM (eds) Cardiac Arrest: The Science and Practice of Resuscitation Medicine, 1st edn. Williams & Wilkins, Baltimore, pp 391 – 392
15. Becker LB, Berg RA, Pepe PE, et al (1997) A reappraisal of mouth-to-mouth ventilation during bystander-initiated cardiopulmonary resuscitation. Circulation 96: 2102-2112
16. Christenson J, Andrusiek D, Everson-Stewart S, et al (2009) Chest compression fraction determines survival in patients with out-of-hospital ventricular fibrillation. Circulation 120: 1241 – 1247

17. Tucker KJ, Idris AH, Wenzel V, Orban DJ (1994) Changes in arterial and mixed venous blood gases during untreated ventricular fibrillation and cardiopulmonary resuscitation. Resuscitation 28: 137–141
18. Caffrey SL, Willoughby PJ, Pepe, PE, Becker LB (2002) Public use of automated defibrillators. N Engl J Med 347: 1242–1247
19. Roppolo LP, Pepe PE, Bobrow BJ (2010) The role of gasping in resuscitation. In: Vincent JL (ed) 2010 Yearbook of Intensive Care and Emergency Medicine. Springer-Verlag, Heidelberg, pp 83–95
20. Roppolo LP, Westfall AH, Pepe PE, et al (2009) Dispatcher assessments for agonal breathing improve detection of cardiac arrest. Resuscitation 80: 769–772
21. Clark JJ, Larsen MP, Culley LL, Graves JR, Eisenberg MS (1992) Incidence of agonal respirations in sudden cardiac arrest. Ann Emerg Med 21: 1464–1467
22. Noc M, Weil MH, Sun S, Tang W, Bisera J (1994) Spontaneous gasping during cardiopulmonary resuscitation without mechanical ventilation. Am J Respir Crit Care Med 150: 861–864
23. Eisenberg MS (2006) Incidence and significance of gasping or agonal respirations in cardiac arrest patients. Curr Opin Crit Care 12: 204–206
24. Bentley J, Bobrow BJ, Zuercher M, et al (2008) Gasping during cardiac arrest in humans is frequent and associated with improved survival. Circulation 118: 2550–2554
25. Suzuki M, Funabiki T, Hori S, Aikawa N (2009) Spontaneous gasping increases cerebral blood flow during untreated fatal hemorrhagic shock. Resuscitation 80: 109–112
26. St John WM (1990) Neurogenesis, control, and functional significance of gasping. J Appl Physiol 68: 1305–1315
27. Yang L, Weil MH, Noc M, Tang W, Turner T, Gazmuri RJ (1994) Spontaneous gasping increases the ability to resuscitate during experimental cardiopulmonary resuscitation. Crit Care Med 22: 879–883
28. Xie J, Weil MH, Sun S, Yu T, Tang W (2004) Spontaneous gasping generates cardiac output during cardiac arrest. Crit Care Med 32: 238–240
29. Ristagno G, Tang W, Sun S, Weil MH (2007) Spontaneous gasping produces carotid blood flow during untreated cardiac arrest. Resuscitation 75: 366–371
30. Srinivasan V, Nadkarni VM, Yannopoulos D, et al (2006) Spontaneous gasping decreases intracranial pressure and improves cerebral perfusion in a pig model of ventricular fibrillation. Resuscitation 69: 329–334
31. Manole MD, Hickey RW, Momoi N, et al (2006) Preterminal gasping during hypoxic cardiac arrest increases cardiac function in immature rats. Pediatr Res 60: 174–179
32. Schaefer H, Tenney SM for the International Union of Physiological Sciences Commitee on Nomenclature (1973) Glossary on respiration and gas exchange. J Appl Physiol 34: 549–558
33. Idris AH, Banner MJ, Wenzel V, Fuerst RS, Becker LB, Melker RJ (1994) Ventilation caused by external chest compression is unable to sustain effective gas exchange during CPR: a comparison with mechanical ventilation. Resuscitation 28: 143–150
34. Kern KB, Hilwig RW, Berg RA, Ewy GA (1998). Efficacy of chest compression-only BLS CPR in the presence of an occluded airway. Resuscitation 39: 179–188
35. Roppolo LP, Pepe PE, Campbell L, et al (2007) Prospective, randomized trial of the effectiveness and retention of 30-minute layperson training for cardiopulmonary resuscitation and automated external defibrillators. Resuscitation 74: 276–285
36. Lloyd MS, Heeke B, Walter PF and Langberg JJ (2008) Rescuers in direct contact with patients during biphasic external hands-on defibrillation: An analysis of electrical current flow through defibrillation. Circulation 117: 2510–2514
37. Berger R, Palazzolo J. Halperin H (2007) Rhythm discrimination during uninterrupted CPR using motion artifact reduction system. Resuscitation 75: 145–152
38. National Institutes of Health (2006) New federally-funded research program aims to improve survival from cardiac arrest and severe trauma. Available at: http://www.nhlbi.nih.gov/new/press/06-03-24.htm. Accessed Oct 27, 2010
39. Sirbaugh PE, Pepe PE, Shook JE, et al (1999) A prospective, population-based study of the demographics, epidemiology, management and outcome of out-of-hospital pediatric cardiopulmonary arrest. Ann Emerg Med 33: 174–184

VII Renal Aspects

Hypoalbuminemia as a Risk Factor for Acute Kidney Injury

M. Joannidis and C.J. Wiedermann

Introduction

Acute kidney injury (AKI) is associated with significant morbidity and mortality in critically ill patients [1, 2]. Risk factors leading to this complication are under active investigation [3]. Independent risk factors for AKI that have already been identified include age, body mass index, baseline renal function, acute circulatory or respiratory failure, liver disease, infection, peripheral vascular occlusive disease, chronic obstructive pulmonary disease (COPD), chronic heart failure, lymphoma or leukemia, prior invasive procedures, and higher-risk surgery [2, 4, 5]. Although hypoalbuminemia is well established as a potent independent risk factor for morbidity and mortality [6], its role, if any, as a specific predictor of AKI remains poorly defined. There is also the possibility that hypoalbuminemia may augment the risk of AKI. This narrative mini-review describes hypoalbuminemia as a novel risk factor for AKI.

Albumin

Albumin is a multifunctional protein of 69 kDa molecular weight with both colloidal and pharmacological activity. Its colloidal activity is essential in maintaining fluid balance between the intravascular and interstitial compartments. Because it is the predominant plasma protein, albumin accounts for approximately 75 – 80 % of plasma colloid osmotic pressure (COP). In addition, albumin is endowed with diverse biologically specific capabilities such as ligand binding, antioxidant, free radical-scavenging and anti-inflammatory activity, inhibition of apoptosis, and cell signaling [7]. Albumin binds to a wide array of endogenous ligands, including metabolites, lipids, hormones, metal ions and high-affinity endothelial cell albumin receptors [8]. Binding itself may serve multiple purposes such as transport, sequestration and transcytosis. Additionally, albumin binds numerous drugs and in many cases can modify their bioavailability and pharmacokinetics [9]. For example, albumin administration increases the effects of loop diuretics by augmenting drug delivery to the renal tubule [10]. Evidence concerning the non-oncotic pharmacological properties of albumin continues to accumulate rapidly.

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Antioxidant Activity

Albumin can function directly as an antioxidant by virtue of its reduced thiol moiety on cysteine 34. *In vivo*, 77 % of circulating albumin thiol is present in reduced form, whereas a smaller proportion of the reduced form (43 %) can be found in commercially available human serum albumin preparations [11]. Despite the lower proportion of reduced thiol, purified albumin solutions effectively augment antioxidant capacity. Thus, in a double-blinded randomized trial of 20 patients with acute lung injury (ALI) due to trauma, pneumonia, sepsis and other predisposing insults, administration of 25 g of 25 % albumin solution for a total of 9 doses increased plasma thiol concentration ($p = 0.0001$) and total antioxidant capacity ($p = 0.033$) compared with normal saline placebo [12].

Albumin can also serve as an indirect antioxidant by binding and inactivating mediators of oxidant damage or by binding and delivering antioxidant molecules [13, 14]. Hence, some antioxidant effects of albumin have been proven to be thiol-independent. For instance, treatment of bovine aortic endothelial cells with human serum albumin protected against HOCl-induced oxidative damage ($p< 0.05$) [15]. The effect was dose-related and independent of protein thiol status. Another indirect antioxidant role is modulation of inflammatory processes that involve oxidation, as described below.

Inflammation

In vitro investigations have indicated anti-inflammatory properties of albumin by demonstrating decreased ($p< 0.05$) binding of activated polymorphonuclear leukocytes to aortic endothelial cells [15]. Furthermore, in contrast to artificial colloids like HES 670/0.7, which significantly augmented the binding of neutrophil-derived myeloperoxidase, a mediator of multiple oxidative and nitric oxide (NO)-consuming reactions, to aortic endothelial cells, albumin did not display such pro-oxidant activity [15].

In a rodent model of hemorrhagic shock, albumin exerted systemic and pulmonary anti-inflammatory actions [16]. Both 5 % and 25 % albumin reduced levels of macrophage inflammatory protein (MIP)-2 and increased levels of the anti-inflammatory cytokine, interleukin (IL)-10, in plasma and bronchoalveolar lavage (BAL) fluid compared with Ringer's lactate ($p < 0.05$ for all comparisons). These effects were accompanied by reductions in plasma ($p < 0.05$) and BAL fluid ($p < 0.05$) concentrations of H_2O_2, thus, indicating protection against oxygen free radical formation. Additionally, pulmonary edema was reduced by albumin, as evidenced by a reduction in lung wet/dry ratio ($p < 0.05$).

In a rat endotoxemia model, 5 % albumin decreased NO synthase (NOS) II mRNA ($p < 0.05$) and protein expression ($p < 0.05$) in the heart [17]. NO is a known modulator of inflammation. Albumin was also effective in preventing lipopolysaccharide (LPS)-induced fractional shortening of isolated cardiac myocytes, indicative of myocardial dysfunction ($p < 0.01$) [17].

In a swine model of hemorrhagic shock, neither 5 % nor 25 % albumin exhibited any pro-inflammatory effect. On the other hand, resuscitation with hydroxyethyl starch (HES) 450/0.7 resulted in marked neutrophil activation measured by oxidative burst activity [18]. Earlier *in vitro* data also showed marked neutrophil activation after the addition of HES 450/0.7 but not of albumin to blood specimens from 10 healthy volunteers [19].

Microcirculation

Possibly, at least partly by virtue of its anti-inflammatory activity, albumin may reduce fluid leakage and enhance microcirculatory performance, thus helping preserve major organ function. In a study of isolated perfused guinea pig hearts, albumin attenuated fluid extravasation both before and after ischemia compared with either saline ($p< 0.05$) or HES 130/0.4 ($p< 0.05$) under conditions of controlled flow rate [20]. A difference between albumin and HES 200/0.5 was not apparent in a similar earlier study; however, in that investigation the flow rate was much higher in the albumin than in the HES 200/0.5 group [21]. In rodent mesenteric venules, 5 % albumin prevented LPS-induced leukocyte rolling and firm adhesion and albumin leakage [22].

Hypoalbuminemia

Acutely ill patients frequently develop hypoalbuminemia. In patients undergoing cardiopulmonary bypass (CPB) surgery, for example, serum albumin declined from preoperative levels in the normal range of 3.8 ± 0.5 g/dl (mean ± standard deviation) to 2.6 ± 0.5 g/dl, indicative of moderately severe hypoalbuminemia, by the time of extubation [23]. Low serum albumin levels have long been known to be associated with poor outcome, and hypoalbuminemia has been a traditional indication for administration of exogenous albumin. In recent years, some commentators have expressed skepticism about the effectiveness of correcting hypoalbuminemia [24, 25]. They have argued that low serum albumin may be merely a marker, for instance of nutritional status or inflammation, rather than a cause of poor outcome. This view was not affirmed in a meta-analysis of 90 clinical studies with 291433 total patients evaluating hypoalbuminemia as an outcome predictor by multivariate analysis [6]. Each 10.0 g/l decline in serum albumin concentration increased the odds of mortality (odds ratio [OR], 2.37; confidence interval [CI], 2.10 – 2.68), morbidity (OR, 1.89; CI, 1.59 – 2.24), prolonged stay in the intensive care unit (ICU) (OR, 1.28; CI, 1.16 – 1.40) and hospital (OR, 1.71; CI, 1.33 – 2.21), and increased resource utilization (OR, 1.66; CI, 1.17 – 2.36). Importantly, the association between hypoalbuminemia and poor outcome was found to be independent of both nutritional status and inflammation. The results of the meta-analysis supported a causative role for low serum albumin in producing poor outcomes.

Additional contemporary studies have highlighted the relationship between hypoalbuminemia and outcome. A prospective study in 688 patients with sepsis, trauma, aspiration and hypertransfusion demonstrated increased odds of developing acute respiratory distress syndrome (ARDS) in patients with serum albumin ≥ 2.3 g/dl (OR, 1.80; CI, 1.18 – 2.73) [26]. In a randomized trial of 152 intra-abdominal surgery patients, liberal use of lactated Ringer's solution increased complications ($p = 0.046$) and body weight gain ($p < 0.01$), delayed postoperative recovery ($p < 0.001$) and prolonged hospital stay ($p = 0.01$) compared with a protocol restricting recourse to lactated Ringer's solution [27]. Associated with these poorer outcomes was more marked postoperative hypoalbuminemia in the liberal protocol group ($p < 0.01$). In a study of 31 pediatric patients with portal hypertensive ascites, lower serum albumin levels were associated with the presence of infected ascites, a potentially life-threatening complication in this population

($p = 0.01$) [28]. A retrospective analysis of 455 ICU patients included in a sepsis trial, 178 of whom developed ARDS, showed that reduced initial total serum protein levels and protein change over time were the most significant predictors of ARDS development (OR 2.8, CI 1.5–4.9 and 1.7. CI 0.9–3.2, respectively) and prolonged mechanical ventilation [29]. In accordance with these findings, a prospective randomized, placebo controlled trial in 40 patients with ALI and a serum protein < 6 g/l demonstrated sustained improvement in oxygenation in patients given albumin plus diuretic therapy with furosemide compared to placebo plus furosemide (mean change in PaO_2/FiO_2: + 43 vs. – 24 mmHg at 24 h and +49 vs. -13 mmHg at day 3); the albumin-treated patients also had a greater increase in total serum protein (1.5 vs. 0.5 g/dl at day 3) [30]. A meta-analysis supported the concept that correction of hypoalbuminemia may improve patient outcome [31], and these results were substantiated by a recent randomized controlled study in 100 critically ill patients [32]. Repetitive administration of human serum albumin to patients with a serum albumin < 3 g/dl resulted in significant improvement in organ function compared to controls (delta SOFA 3.1 ± 1.0 vs. 1.3 ± 1.1, $p < 0.03$) and was associated with significantly increased albumin concentrations [32].

VII

Hypoalbuminemia and Acute Kidney Injury

Recently, a meta-analysis was performed of observational clinical studies evaluating the relationship between serum albumin level and the occurrence of AKI by multivariate methods [33]. Additionally, the impact of lower serum albumin on mortality in patients who developed AKI was assessed. Eligible studies were sought by multiple methods, and adjusted odds ratios were quantitatively combined using a random effects model (**Table 1**). Seventeen clinical studies with 3,917 total patients were included: 11 studies (6 in surgical or ICU patients and 5 in other hospital settings) evaluating the influence of serum albumin on AKI incidence and 6 studies describing the relationship between serum albumin and mortality among patients who had developed AKI. Lower serum albumin was an independent predictor both of AKI and of death after AKI development. With each 10 g/l serum albumin decrement, the odds of AKI increased by 134 %. The pooled OR for AKI was 2.34 with a 95 % CI of 1.74–3.14. Among patients who had developed AKI, the odds of death increased by 147 % (pooled OR, 2.47; CI, 1.51–4.05) with each 10 g/l serum albumin decrement. This meta-analysis provided evidence that hypoalbuminemia is a significant independent predictor both of AKI and of death following AKI development [33].

This meta-analysis [33] focused on serum albumin level as a predictor rather than on the effects of administering exogenous albumin. Controlled studies are needed to assess interventions aimed at correcting hypoalbuminemia. Studies of albumin administration are relevant to the question of whether low serum albumin may play a causal role in poor renal outcomes [34, 35]. A large multicenter randomized controlled trial in which 4 % albumin was compared to crystalloid for fluid resuscitation failed to demonstrate any difference in outcome parameters including renal function, but proved that albumin itself was safe [36].

Whether administration of exogenous albumin protects renal function is unknown. Hyopalbuminemia has been associated with diuretic resistance [10] and several studies have demonstrated improved response to loop diuretics in conjunction with albumin administration. This effect was demonstrated in

Table 1. Studies on hypoalbuminemia as a predictor of AKI development or death after development of AKI, as analyzed by Wiedermann et al. [33]

Study [ref]	Albumin[a]	Number of Patients	Odds Ratio[b]	Confidence Interval[b]
AKI Development				
Rich et al. 1989 [47]	38	92	2.23	1.34 – 3.71
Rich & Crecelius 1990 [48]	40.7	183	3.24	1.37 – 7.67
Contreras et al. 1994 [34]	34.4	104	11.20	1.01 – 124.72
Létourneau et al. 2002 [49]	27.1	57	1.20	0.92 – 1.57
Kim et al. 2003 [50]	23.7	147	1.53	0.53 – 4.41
Chawla et al. 2005 [51]	30	194	2.17	1.17 – 4.02
Boyle et al. 2006 [52]	38	774	2.94	1.83 – 4.72
Cabezuelo et al. 2006 [53]	35.6	184	2.70	2.01 – 3.62
Drawz et al. 2008 [54]	35	540	1.47	0.67 – 3.22
Park et al. 2008 [55]	35.7	183	3.24	1.37 – 7.67
Hung et al. 2009 [56]	37.7	234	3.33	2.04 – 5.44
Total		2,745	2.34	1.74 – 3.14
Mortality after AKI Development				
Chertow et al. 1998 [57]	27	256	1.37	0.96 – 1.96
Obialo et al. 1999 [58]	31	100	2.86	0.92 – 8.90
Lins et al. 2000 [59]	32	197	2.25	1.30 – 3.90
Dharan et al. 2005 [60]	–[c]	459	1.65	0.63 – 4.31
Mahajan et al. 2006 [61]	–[c]	45	7.83	2.12 – 28.91
Sezer et al. 2006 [62]	33.8	115	4.39	2.08 – 9.25
Total		1,172	2.47	1.51 – 4.05

[a] Mean baseline serum albumin level (g/l)
[b] Adjusted odds ratio (95 % confidence interval) for AKI per 10 g/l decrement in serum
[c] Not reported

patients with ALI who achieved higher negative fluid balances [30]. Both adults and children with nephrotic syndrome exhibited increased urine output and sodium excretion after co-administration of furosemide and human serum albumin [37, 38]. The design of these studies, however, does not allow the question as to whether exogenous albumin may improve renal function in terms of glomerular filtration to be answered; this aspect is addressed by the trials discussed in the next section, most of which were performed in patients with liver cirrhosis.

In three randomized trials of hypoalbuminemic patients with spontaneous bacterial peritonitis, albumin infusion reduced the odds of renal impairment by 70 – 79 % compared either with no albumin [39, 40] or with HES 200/0.5 [41]. Although only one of the three trials was powered to show statistical significance [42], the magnitudes of the albumin effects closely coincided in all three.

In a prospective study of 21 consecutive patients with hepatorenal syndrome (HRS), complete responses, defined as 1.5 mg/dl serum creatinine or lower, were achieved in 77 % of patients receiving albumin as an adjunct to terlipressin vs. 25 % of those treated with terlipressin alone [43]. Survival was also improved in the albumin recipients. Based on studies of extracorporeal albumin dialysis, HRS appears to be another indication in which the benefit of albumin may derive from its specific ligand-binding properties. Extracorporeal albumin dialysis is designed to take advantage of toxin binding by albumin. In a randomized trial, extracorporeal albumin dialysis improved survival of hypoalbuminemic HRS patients and

reduced levels of both creatinine and bilirubin [44]. Animal evidence exists of direct nephrotoxicity by unconjugated bilirubin [45]. Nevertheless, systemic toxicity arising from unbound ligands, like uremic toxins, in hypoalbuminemic patients might be a major indirect contributor to renal dysfunction.

In a recent report of 10 patients with recurrent focal segmental glomerulosclerosis, 2.5 l of plasma was exchanged with 5 % albumin in multiple plasmapheresis sessions over 10–12 weeks [46]. Nine patients achieved a complete or partial response to therapy as evidenced by reduced proteinuria or, in the case of prophylactic treatment, lack of recurrence.

The results of these studies, within their limitations, illustrate the apparent capacity of albumin to improve kidney function even in the presence of pre-existing renal impairment. The meta-analysis by Wiedermann et al. [33] provided evidence for hypoalbuminemia as an independent risk factor for AKI and for post-AKI death. Currently available data support a causal role for serum albumin, not only in overcoming diuretic resistance, but even in maintaining kidney integrity and function. Hence, controlled clinical studies are warranted to evaluate the effects on renal function of interventions aimed at correcting hypoalbuminemia. Further evaluation of serum albumin in identifying patients at increased risk for AKI and for death after AKI would also be justified.

Conclusion

Despite the multitude of studies devoted to albumin for over 60 years, albumin-related research shows little sign of abating. Recent studies have further delineated mechanisms of action and addressed clinical effectiveness and safety, both in broad patient populations and specific indications. These investigations have made it increasingly clear that albumin can help preserve physiological homeostasis not only by maintenance of COP but also by additional mechanisms, such as ligand binding and antioxidant and anti-inflammatory activity.

Although new data have been plentiful, further studies are needed. In the clinical arena morbidity should be considered as well as mortality. Despite its extensive clinical usage, the optimal doses and administration schedules for albumin remain to be fully elucidated in many indications, its role in AKI included. Hence, additional basic pharmacology studies will be essential, and dose and regimen should be considered in future meta-analyses of albumin therapy. Whereas the benefits of albumin in liver disease are well-established, pertinent data in other indications, such as AKI in hypoalbuminemia, are much more limited. Nevertheless, while new investigations will be welcome, the data compiled thus far provide support for many of the current uses of albumin in clinical fluid management.

References

1. Joannidis M, Metnitz B, Bauer P, et al (2009) Acute kidney injury in critically ill patients classified by AKIN versus RIFLE using the SAPS 3 database. Intensive Care Med 35: 1692–1702
2. Metnitz PG, Krenn CG, Steltzer H, et al (2002) Effect of acute renal failure requiring renal replacement therapy on outcome in critically ill patients. Crit Care Med 30: 2051–2058
3. de Mendonça A, Vincent JL, Suter PM, et al (2000) Acute renal failure in the ICU: risk factors and outcome evaluated by the SOFA score. Intensive Care Med 26: 915–921

4. Joannidis M, Metnitz PG (2005) Epidemiology and natural history of acute renal failure in the ICU. Crit Care Clin 21: 239 – 249
5. Uchino S, Kellum JA, Bellomo R, et al (2005) Acute renal failure in critically ill patients: a multinational, multicenter study. JAMA 294: 813 – 818
6. Vincent JL, Dubois MJ, Navickis RJ, Wilkes MM (2003) Hypoalbuminemia in acute illness: is there a rationale for intervention? A meta-analysis of cohort studies and controlled trials. Ann Surg 237: 319 – 334
7. Quinlan GJ, Martin GS, Evans TW (2005) Albumin: biochemical properties and therapeutic potential. Hepatology 41: 1211 – 1219
8. Mitzner S, Stange J, Klammt S, et al (2001) Albumin-bound substances--a new target in liver failure therapy. Z Gastroenterol 39 (Suppl 2): 6 – 7
9. Bertucci C, Domenici E (2002) Reversible and covalent binding of drugs to human serum albumin: methodological approaches and physiological relevance. Curr Med Chem 9: 1463 – 1481
10. Inoue M, Okajima K, Itoh K, et al (1987) Mechanism of furosemide resistance in analbuminemic rats and hypoalbuminemic patients. Kidney Int 32: 198 – 203
11. Bar-Or D, Bar-Or R, Rael LT, Gardner DK, Slone DS, Craun ML (2005) Heterogeneity and oxidation status of commercial human albumin preparations in clinical use. Crit Care Med 33: 1638 – 1641
12. Quinlan GJ, Mumby S, Martin GS, Bernard GR, Gutteridge JM, Evans TW (2004) Albumin influences total plasma antioxidant capacity favorably in patients with acute lung injury. Crit Care Med 32: 755 – 759
13. Neuzil J, Stocker R (1994) Free and albumin-bound bilirubin are efficient co-antioxidants for alpha-tocopherol, inhibiting plasma and low density lipoprotein lipid peroxidation. J Biol Chem 269: 16712 – 16719
14. Satoh K, Ida Y, Kimura S, et al (1997) Chelating effect of human serum proteins on metal-catalyzed ascorbate radical generation. Anticancer Res 17: 4377 – 4380
15. Lang JD Jr, Figueroa M, Chumley P, et al (2004) Albumin and hydroxyethyl starch modulate oxidative inflammatory injury to vascular endothelium. Anesthesiology 100: 51 – 58
16. Zhang H, Voglis S, Kim CH, Slutsky AS (2003) Effects of albumin and Ringer's lactate on production of lung cytokines and hydrogen peroxide after resuscitated hemorrhage and endotoxemia in rats. Crit Care Med 31: 1515 – 1522
17. Walley KR, McDonald TE, Wang Y, Dai S, Russell JA (2003) Albumin resuscitation increases cardiomyocyte contractility and decreases nitric oxide synthase II expression in rat endotoxemia. Crit Care Med 31: 187 – 194
18. Alam HB, Stanton K, Koustova E, Burris D, Rich N, Rhee P (2004) Effect of different resuscitation strategies on neutrophil activation in a swine model of hemorrhagic shock. Resuscitation 60: 91 – 99
19. Rhee P, Wang D, Ruff P, et al (2000) Human neutrophil activation and increased adhesion by various resuscitation fluids. Crit Care Med 28: 74 – 78
20. Jacob M, Bruegger D, Rehm M, Welsch U, Conzen P, Becker BF (2006) Contrasting effects of colloid and crystalloid resuscitation fluids on cardiac vascular permeability. Anesthesiology 104: 1223 – 1231
21. Rehm M, Zahler S, Lotsch M, et al (2004) Endothelial glycocalyx as an additional barrier determining extravasation of 6 % hydroxyethyl starch or 5 % albumin solutions in the coronary vascular bed. Anesthesiology 100: 1211 – 1223
22. Anning PB, Finney SJ, Singh S, Winlove CP, Evans TW (2004) Fluids reverse the early lipopolysaccharide-induced albumin leakage in rodent mesenteric venules. Intensive Care Med 30: 1944 – 1949
23. Mohnle P, Schwann NM, Vaughn WK, et al (2005) Perturbations in laboratory values after coronary artery bypass graft surgery with cardiopulmonary bypass. J Cardiothorac Vasc Anesth 19: 19 – 25
24. Wilkes MM, Navickis RJ (2001) Patient survival after human albumin administration. A meta-analysis of randomized, controlled trials. Ann Intern Med 135: 149 – 164
25. Pulimood TB, Park GR (2000) Debate: Albumin administration should be avoided in the critically ill. Crit Care 4: 151 – 155
26. Gong MN, Thompson BT, Williams P, Pothier L, Boyce PD, Christiani DC (2005) Clinical

predictors of and mortality in acute respiratory distress syndrome: potential role of red cell transfusion. Crit Care Med 33: 1191 – 1198
27. Nisanevich V, Felsenstein I, Almogy G, Weissman C, Einav S, Matot I (2005) Effect of intraoperative fluid management on outcome after intraabdominal surgery. Anesthesiology 103: 25 – 32
28. Vieira SM, Matte U, Kieling CO, et al (2005) Infected and noninfected ascites in pediatric patients. J Pediatr Gastroenterol Nutr 40: 289 – 294
29. Mangialardi RJ, Martin GS, Bernard GR, et al (2000) Hypoproteinemia predicts acute respiratory distress syndrome development, weight gain, and death in patients with sepsis. Ibuprofen in Sepsis Study Group. Crit Care Med 28: 3137 – 3145
30. Martin GS, Moss M, Wheeler AP, Mealer M, Morris JA, Bernard GR (2005) A randomized, controlled trial of furosemide with or without albumin in hypoproteinemic patients with acute lung injury. Crit Care Med 33: 1681 – 1687
31. Vincent JL, Navickis RJ, Wilkes MM (2004) Morbidity in hospitalized patients receiving human albumin: a meta-analysis of randomized, controlled trials. Crit Care Med 32: 2029 – 2038
32. Dubois MJ, Orellana-Jimenez C, Melot C, et al (2006) Albumin administration improves organ function in critically ill hypoalbuminemic patients: A prospective, randomized, controlled, pilot study. Crit Care Med 34: 2536 – 2540
33. Wiedermann CJ, Wiedermann W, Joannidis M (2010) Hypoalbuminemia and acute kidney injury: a meta-analysis of observational clinical studies. Intensive Care Med 36: 1657 – 1665
34. Contreras AM, Ramírez M, Cueva L, Alvarez S, de Loza R, Gamba G (1994) Low serum albumin and the increased risk of amikacin nephrotoxicity. Rev Invest Clin 46: 37 – 43
35. Joannidis M, Druml W, Forni LG, et al (2010) Prevention of acute kidney injury and protection of renal function in the intensive care unit Expert opinion of the working group for nephrology, ESICM. Intensive Care Med 36: 392 – 411
36. Finfer S, Bellomo R, Boyce N, French J, Myburgh J, Norton R (2004) A comparison of albumin and saline for fluid resuscitation in the intensive care unit. N Engl J Med 350: 2247 – 2256
37. Fliser D, Zurbruggen I, Mutschler E, et al (1999) Coadministration of albumin and furosemide in patients with the nephrotic syndrome. Kidney Int 55: 629 – 634
38. Dharmaraj R, Hari P, Bagga A (2009) Randomized cross-over trial comparing albumin and frusemide infusions in nephrotic syndrome. Pediatr Nephrol 24: 775 – 782
39. Chen TA, Tsao YC, Chen A, et al (2009) Effect of intravenous albumin on endotoxin removal, cytokines, and nitric oxide production in patients with cirrhosis and spontaneous bacterial peritonitis. Scand J Gastroenterol 44: 619 – 625
40. Sort P, Navasa M, Arroyo V, et al (1999) Effect of intravenous albumin on renal impairment and mortality in patients with cirrhosis and spontaneous bacterial peritonitis. N Engl J Med 341: 403 – 409
41. Fernández J, Monteagudo J, Bargallo X, et al (2005) A randomized unblinded pilot study comparing albumin versus hydroxyethyl starch in spontaneous bacterial peritonitis. Hepatology 42: 627 – 634
42. Ortega R, Ginès P, Uriz J, et al (2002) Terlipressin therapy with and without albumin for patients with hepatorenal syndrome: Results of a prospective, nonrandomized study. Hepatology 36: 941 – 948
43. Mitzner SR, Stange J, Klammt S, et al (2000) Improvement of hepatorenal syndrome with extracorporeal albumin dialysis MARS: results of a prospective, randomized, controlled clinical trial. Liver Transpl 6: 277 – 286
44. Elias MM, Comin EJ, Grosman ME, Galeazzi SA, Rodriguez Garay EA (1982) Inhibitory effect of unconjugated bilirubin on p-aminohippurate transport in rat kidney cortex slices. Biochim Biophys Acta 693: 265 – 272
45. Elias MM, Comin EJ, Grosman ME, Galeazzi SA, Rodriguez Garay EA (1987) Possible mechanism of unconjugated bilirubin toxicity on renal tissue. Comp Biochem Physiol A Comp Physiol 87: 1003 – 1007
46. Valdivia P, Gonzalez RF, Gentil MA, et al (2005) Plasmapheresis for the prophylaxis and treatment of recurrent focal segmental glomerulosclerosis following renal transplant. Transplant Proc 37: 1473 – 1474

47. Rich MW, Keller AJ, Schechtman KB, Marshall WG Jr, Kouchoukos NT (1989) Increased complications and prolonged hospital stay in elderly cardiac surgical patients with low serum albumin. Am J Cardiol 63: 714–718
48. Rich MW, Crecelius CA (1990) Incidence, risk factors, and clinical course of acute renal insufficiency after cardiac catheterization in patients 70 years of age or older. A prospective study. Arch Intern Med 150: 1237–1242
49. Létourneau I, Dorval M, Bélanger R, Légaré M, Fortier L, Leblanc M (2002) Acute renal failure in bone marrow transplant patients admitted to the intensive care unit. Nephron 90: 408–412
50. Kim GH, Oh KH, Yoon JW, et al (2003) Impact of burn size and initial serum albumin level on acute renal failure occurring in major burn. Am J Nephrol 23: 55–60
51. Chawla LS, Abell L, Mazhari R, et al (2005) Identifying critically ill patients at high risk for developing acute renal failure: a pilot study. Kidney Int 68: 2274–2280
52. Boyle JM, Moualla S, Arrigain S, et al (2006) Risks and outcomes of acute kidney injury requiring dialysis after cardiac transplantation. Am J Kidney Dis 48: 787–796
53. Cabezuelo JB, Ramírez P, Ríos A, et al (2006) Risk factors of acute renal failure after liver transplantation. Kidney Int 69: 1073–1080
54. Drawz PE, Miller RT, Sehgal AR (2008) Predicting hospital-acquired acute kidney injury – a case-controlled study. Ren Fail 30: 848–855
55. Park J, Chung HC, Lee JS, et al (2008) Acute kidney injury after transarterial chemoembolization for hepatocellular carcinoma: a retrospective analysis. Blood Purif 26: 454–459
56. Hung CC, Liu WC, Kuo MC, Lee CH, Hwang SJ, Chen HC (2009) Acute renal failure and its risk factors in Stevens-Johnson syndrome and toxic epidermal necrolysis. Am J Nephrol 29: 633–638
57. Chertow GM, Lazarus JM, Paganini EP, Allgren RL, Lafayette RA, Sayegh MH (1998) Predictors of mortality and the provision of dialysis in patients with acute tubular necrosis. The Auriculin Anaritide Acute Renal Failure Study Group. J Am Soc Nephrol 9: 692–698
58. Obialo CI, Okonofua EC, Nzerue MC, Tayade AS, Riley LJ (1999) Role of hypoalbuminemia and hypocholesterolemia as copredictors of mortality in acute renal failure. Kidney Int 56: 1058–1063
59. Lins RL, Elseviers M, Daelemans R, et al (2000) Prognostic value of a new scoring system for hospital mortality in acute renal failure. Clin Nephrol 53: 10–17
60. Dharan KS, John GT, Antonisamy B, Kirubakaran MG, Jacob CK (2005) Prediction of mortality in acute renal failure in the tropics. Ren Fail 27: 289–296
61. Mahajan S, Tiwari S, Bharani R, et al (2006) Spectrum of acute renal failure and factors predicting its outcome in an intensive care unit in India. Ren Fail 28: 119–124
62. Sezer MT, Demir M, Gungor G, Senol A (2006) Predictors of mortality in patients with acute renal failure. Acta Medica (Hradec Kralove) 49: 183–188

Developing Biological Markers: The Case of Urinary Neutrophil Gelatinase-associated Lipocalin in Acute Kidney Injury

A.A.N.M. Royakkers, P.E. Spronk, and M.J. Schultz

Introduction

Despite important improvements in general care, acute kidney injury (AKI) remains a frequent and major complication in intensive care unit (ICU) patients, with persistently high morbidity and mortality rates [1–3]. AKI requiring renal replacement therapy occurs in up to 5 % of those cases in whom the mortality rate approaches 80 % [3]. One reason for the failure to define an effective treatment for AKI is the paucity of sensitive and early biological markers for renal injury [4]. Such markers could assist in timely patient management decisions, including administration of potentially effective therapeutic agents.

Over the last decade, several novel and promising biological markers for AKI have been identified, including serum and urinary proteins [5]. Some markers estimate renal function, while others reflect renal injury or inflammation associated with AKI. Commercial assays for these biological markers have become available, and numerous studies of their diagnostic accuracy have been published in recent years. However, large-scale cohort studies in the ICU setting are sparse and results of interventional trials using the aforementioned novel biological markers (e.g., for screening, or as an outcome variable) in critically ill patients are not available yet. In this chapter, we describe the process of developing biological markers for AKI, using the case of urinary neutrophil gelatinase-associated lipocalin (NGAL) as an example.

Conventional Measures of Renal Function

Glomerular Filtration Rate

There are several gold standard methods for determining glomerular filtration rate (GFR), including inulin clearance and isotope clearance techniques. These techniques are expensive and laborious and, therefore, not routinely used in clinical practice. Serum creatinine and urea concentrations, and clearance of creatinine using 24-hour urine collections, are frequently used indicators of GFR. However, serum creatinine concentrations are affected by muscle mass and diet, and vary with age and gender. In addition, a rising serum creatinine concentration is related to an increase in its tubular secretion, leading to overestimation of GFR in patients with moderate to severe renal injury. Similarly, serum urea concentrations are affected by various disease states, hepatic function and diet.

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Tubular Function

Tubular concentrating ability and sodium conservation have both been advocated to test for tubular function. The urine to plasma osmolar ratio is a sensitive index of tubular concentrating ability, and thus tubular function, since the ability to concentrate urine may be lost 24 to 48 hours before serum creatinine and urea concentrations start to increase. The urine to serum creatinine ratio, representing the proportion of water filtered by the glomerulus that is abstracted by the distal tubule, is another index of the tubular concentrating ability. Urine sodium concentrations may indicate the tubular ability to conserve sodium. Whereas in prerenal states of renal insufficiency, urine sodium concentrations fall, in established acute tubular necrosis the ability to conserve sodium is lost, and urine sodium concentrations increase. All these measures, however, are influenced by the use of diuretics, which are frequently administered to ICU patients.

Renal Function versus Renal Injury

Concentrations of creatinine and urea in serum and/or urine are insensitive, nonspecific, and change only significantly after substantial kidney injury with a substantial time delay. It should, therefore, be realized that these markers are only useful to determine global renal function, which is not the same as renal injury. Indeed, concentrations of creatinine and/or urea in serum and/or urine are not specific for, nor directly related to, underlying pathophysiological processes such as inflammation, apoptotic and necrotic cell death, and tubule regeneration.

Classification Schemes for Acute Kidney Injury

As part of the Acute Dialysis Quality Initiative 2nd International Consensus Conference, the RIFLE (Risk of kidney dysfunction, Injury to the kidney, Failure of Kidney function, Loss of kidney function, and End stage kidney disease) classification scheme was derived to provide standardized criteria for defining AKI [6]. More recently, the acute kidney injury network (AKIN) modified the RIFLE risk criteria slightly to include an absolute increase in serum creatinine concentrations ≥ 0.3 mg/dl [7]. This modification was performed in recognition of increasing data that suggest that even small changes in serum creatinine concentrations are associated with poorer outcome as measured by mortality [1, 8].

Although clear progress has been made in formulating a classification scheme for AKI, it is notable that the criteria rely heavily on changes in serum creatinine concentrations as a marker of renal function. This is important in view of the aforementioned thoughts regarding creatinine as a suboptimal marker for renal function. In addition, because the classification schemes only depend on creatinine concentrations, these schemes neither monitor nor define renal injury, and do not differentiate between different forms of renal injury.

Biological Markers

In general, biological markers can be used as indicators of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic inter-

Table 1. Phases of biological marker development in AKI

Goals	Phase	Study Designs	Aims
Discover	Phase 1	Preclinical exploratory	Identification of promising markers of AKI
Translate	Phase 2	Assay development and validation	Development of assays for clinical samples; detection of established AKI
	Phase 3	Retrospective longitudinal studies	Early detection of AKI
Validate	Phase 4	Prospective screening	Use of a biological marker of AKI to screen populations
	Phase 5	Disease control	Impact of screening on reducing the burden of AKI

Modified from [9].

vention. Five phases of biological marker development have been proposed (**Table 1**) [9]. Focusing on biological marker development for AKI in critically ill patients, these phases can be described as follows:

- Phase 1 – This phase involves preclinical studies. The aim of this phase is to identify genes and/or proteins that are over-expressed in AKI compared to no AKI. Tissues from organs of experimental animals could be used, but specimens that can be obtained easily to assay concentrations of proteins expressed by the identified genes (e.g., serum or urine) are preferable.
- Phase 2 – This phase involves clinical studies and focuses on assay development. The aim of this phase is to estimate the true positive rate and the false positive rate or receiver operating characteristic (ROC) curve of assays for biological markers, usually ELISAs or immunoassays, and to assess the ability of these assays to distinguish individuals with AKI from individuals without AKI. This phase could involve comparing the results from diverse control groups, such as a healthy population, and patients with chronic or other kidney diseases. Other observations, such as behavior of the biological marker with patient characteristics like age, gender and race, and variations in biological marker concentration with the spectrum of AKI and other AKI characteristics could also be noted. Phase 2 studies typically do not allow determination of whether AKI can be detected early with the proposed biomarkers. It is essential that specimens to assay concentrations of biological markers can be obtained easily (e.g., serum and/or urine).
- Phase 3 – Phase 3 is somewhat similar to phase 2, but biological markers are now evaluated for their capacity to detect AKI at earlier time points than established AKI. One other goal of phase 3 could be to define the cut-offs for a positive screening test that can be validated in future studies.
- Phase 4 – This phase involves large-scale validation of the biological markers in prospective cohort studies. The primary questions addressed in phase 4 studies include the understanding of the performance of the biological marker-based 'screening' test in a relevant population by determining the true positive rate and false positive rate. Phase 4 studies could also help to determine the severity of AKI. For example, the ability of the biological marker to detect and differentiate early between RIFLE stadiums, such as

injury, failure, need for renal replacement therapy, and definite renal failure. Studies in phase 4 can also help with understanding of the feasibility of applying the newer test and make preliminary assessments of costs.

- Phase 5 – This phase usually involves post-marketing studies in which the assessment of reduction of (burden of) AKI is made as a result of the availability of a new test. For AKI, it could be essential that availability of a biological marker reduce progress of AKI, need for renal replacement therapy or mortality associated with AKI.

Novel Biological Markers of AKI

Novel biomarkers include, but are not limited to, mRNA, proteins and peptides, and lipid molecules. In AKI, important pathophysiological processes such as inflammation, apoptotic and necrotic cell death, and tubular regeneration may be reflected in blood or urine and indicated by the assay of a biomarker. Over the last decade, several promising novel biological markers for AKI have been identified, including serum proteins (cystatin C and NGAL) and urinary proteins (cystatin C, NGAL, interleukin [IL]-18 and kidney injury molecule [KIM]-1) (**Fig. 1**) [5]. Some of these markers estimate renal function (serum cystatin C), some reflect on renal injury (urinary cystatin C, serum and urinary NGAL, and urinary KIM-1), and some show inflammation associated with AKI (urinary IL-18). Here we will focus on urinary NGAL.

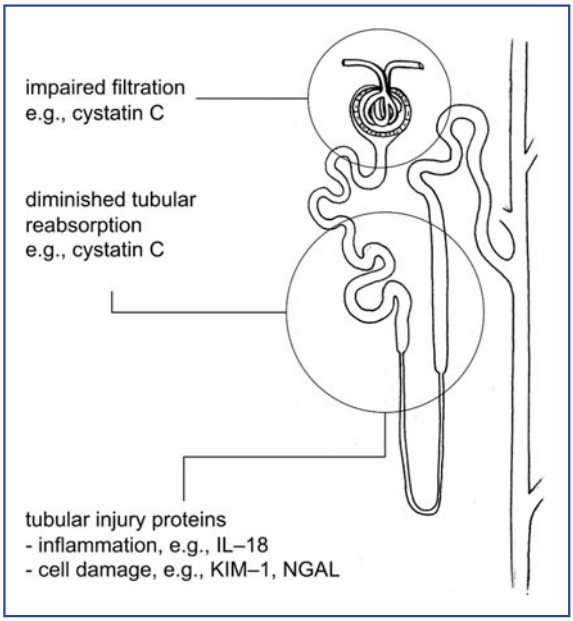

Fig. 1. Biological markers may aid in understanding the pathophysiology of AKI, allowing localization of injury to specific segments of the nephron. IL: interleukin; KIM: kidney injury molecule; NGAL: neutrophil gelatinase-associated lipocalin

The Case of Urinary NGAL

NGAL, also known as lipocalin-2, is a ubiquitous 25-kDa protein that is covalently bound to gelatinase from human neutrophils. It is normally expressed in very low concentrations in several human tissues, such as the lungs, stomach, colon and the kidney. While the functions of NGAL are not fully understood, it appears to be upregulated in cells under 'stress' (e.g., from infection, inflammation, or ischemia). NGAL possibly has an antibacterial role, since NGAL binds enterobactin and other siderophores, depriving the microorganisms of Fe^{3+}, an important nutritional requirement. Urinary levels correlate with serum levels whatever the cause of increased NGAL production. High urinary levels can be expected when NGAL is released directly into the urine by the kidney tubules.

Phase 1: Discovery of NGAL

It was discovered that the gene for NGAL was upregulated more than 10-fold in a murine model of AKI [10]. Mice underwent unilateral renal artery clamping for 45 minutes resulting in tubule cell apoptosis. By microarray analysis, consistent patterns of altered gene expression were identified, including transcription factors, growth factors, signal transduction molecules, and apoptotic factors. NGAL was identified as one of the most upregulated transcripts in the early post-ischemic mouse kidney, a finding that has now been confirmed in several other animal studies [11, 12]. The results of these preclinical studies indicate that NGAL could represent an early and quantitative urinary biomarker for AKI.

Phase 2: Assay Development

Several studies have tested assays for NGAL in diverse control groups, such as a healthy population, and patients with chronic or other kidney diseases. For example, in a cross-sectional study, adults with established AKI (defined by a doubling of serum creatinine) displayed a marked increase in urine NGAL by Western blotting when compared to normal controls [13]. Urine and serum NGAL levels correlated with serum creatinine. Other studies have tested ELISA for NGAL in similar cohorts.

The availability of a standardized clinical platform for NGAL measurements could revolutionize diagnostics, especially in the ICU setting. In this regard, a major step forward has been the development of a standardized point-of-care kit for the clinical measurement of plasma NGAL In children undergoing cardiac surgery, 2-hour plasma NGAL measurement measured by the Triage NGAL Device (Biosite Inc., San Diego, CA, USA) showed an area under the curve (AUC) of 0.96, sensitivity of 0.84 and specificity of 0.94 for the prediction of AKI using a cut-off value of 150 ng/ml [14]. The Triage NGAL Device is easy with quantitative results available in 15 min, and requires only μl-quantities of whole blood or plasma. One urinary NGAL immunoassay has been developed for a standardized clinical platform (ARCHITECT analyzer, Abbott Diagnostics, Abbott Park, IL, USA). In children undergoing cardiac surgery, 2-hour urine NGAL measurement by ARCHITECT analyzer showed an AUC of 0.95, sensitivity of 0.79 and specificity of 0.92 for prediction of AKI using a cut-off value of 150 mg/ml [15]. In another study with urine samples (NGAL range, 0.3 – 815 ng/ml) and 6 calibration standards (NGAL range 0 – 1000 ng/ml), NGAL measurements by research ELISA

and by ARCHITECT were highly correlated (r = 0.99) [15]. ARCHITECT is easy to perform, with no manual pretreatment steps, a first result available within 35 min, and requires only 150 μl of urine. Both kits are currently undergoing multicenter validation in adult populations.

Phases 3 and 4: Early Detection and Risk Stratification

In a study of children undergoing cardiopulmonary bypass (CPB), NGAL measurements by ELISA and by Western blotting revealed a 10-fold or more increase in urine within 2–6 hours of surgery in patients who subsequently developed AKI [16]. Urine NGAL was a powerful independent predictor of AKI, with an AUC of 0.99 for the 2-hour urine NGAL [16]. These findings were confirmed in a study of adults undergoing cardiac surgery [17]. In patients who developed AKI, urinary NGAL levels were significantly elevated within 1–3 hours after surgery. However, patients who did not develop AKI also displayed a significant increase in urinary NGAL in the early post-operative period, although to a much lesser degree than in those who subsequently developed AKI. The AUC reported in this study was 0.74 for the 3-hour urinary NGAL level and 0.80 for the 18-hour urinary NGAL level. NGAL has also been evaluated as a biological marker of AKI in kidney transplantation [18, 19] and AKI following contrast administration [20, 21].

Subsequent studies were recently reviewed in a large meta-analysis [22]. The primary outcome of this meta-analysis was AKI (defined as an increase in serum creatinine level > 50 % from baseline within 7 days). Secondary outcomes were initiation of renal replacement therapy and in-hospital mortality. Diagnostic odds ratio (DOR) and sample size-weighted AUC for the ROC curve (AUC-ROC) were calculated using a hierarchical bivariate generalized linear model (**Fig. 2**). Overall, the DOR/AUC-ROC of NGAL to predict AKI was 18.6 (95 % confidence interval [CI] 9.0–38.1)/0.82 (95 % CI 0.73–0.89). The DOR/AUC-ROC of NGAL was 13.1 (95 % CI 5.7–34.8)/0.78 (95 % CI 0.67–0.87) in cardiac surgery patients, and 10.0 (95 % CI 3.0–33.1)/0.73 (95 % CI 0.62–0.83) in critically ill patients. The DOR/AUC-ROC of NGAL was higher in children (25.4 [95 % CI, 8.9–72.2]/0.93 [95 % CI, 0.88–0.97]) compared to adults (10.6 [95 % CI, 4.8–23.4]/0.782 [95 % CI, 0.69–0.87]). Notably, the diagnostic accuracy of serum NGAL (17.9 [95 % CI, 6.0–53.7]/0.78 [95 % CI, 0.68–0.87]) was similar to that of urine NGAL (18.6 [95 % CI 7.2–48.4]/0.84 [95 % CI 0.76–0.91]). The meta–analysis found that NGAL was a useful prognostic tool with regard to the prediction of renal replacement therapy initiation (12.9 [95 % CI 4.9–33.9]/0.78 [95 % CI 0.65–0.97]) and in-hospital mortality (8.8 [95 % CI 1.9–40.8]/0.706 [95 % CI 0.530–0.747]).

A recently published study confirmed the diagnostic accuracy of serum NGAL for early detection of AKI and need for renal replacement therapy in adult ICU patients [23]. Indeed, plasma NGAL was a good diagnostic marker for AKI development within the next 48 hours (AUC-ROC 0.78, 95 % CI 0.65–0.90), and for renal replacement therapy initiation (AUC-ROC 0.82, 95 % CI 0.70–0.95). In addition, peak plasma NGAL levels increased with worsening AKI severity. Notably, this study did not study urinary NGAL levels.

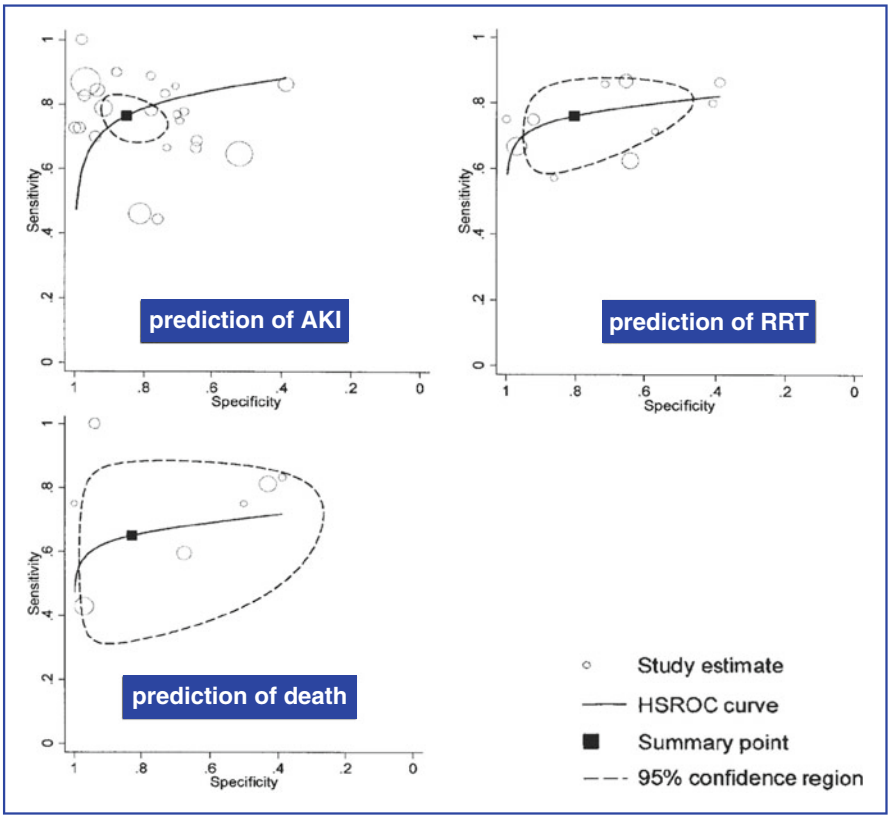

Fig. 2. Hierarchical summary receiver operating characteristic (HSROC) plot of neutrophil gelatinase-associated lipocalin (NGAL) to predict acute kidney injury (AKI), renal replacement therapy (RRT) initiation, and in-hospital mortality. Based on combined sensitivity (95 % confidence interval [CI]) and specificity (95 % CI) weighted for sample size of each dataset reflected by the size of the circles, showing average sensitivity and specificity estimate of the study results (solid square) and a 95 % confidence region around it. Adapted from [22] with permission.

Phase 5: Reduction in (burden of) AKI with the use of NGAL

Because of its predictive properties for AKI, NGAL could also serve as an early biological marker in interventional trials. Two clinical trials using a reduction in urine NGAL as an endpoint, demonstrated the improved efficacy of a modern hydroxyethyl starch (HES) preparation over albumin or gelatin in maintaining renal function in cardiac surgery patients [24, 25]. In a study of adult cardiac surgery patients, the response of urinary NGAL was attenuated in patients who experienced a lower incidence of AKI after sodium bicarbonate therapy when compared to sodium chloride [26]. In addition, adults who developed AKI after aprotinin use during cardiac surgery displayed a rise in urine NGAL in the immediate postoperative period [27].

Without doubt, the approach of using NGAL as a trigger to initiate and monitor novel therapies will soon be evaluated in clinical trials.

Conclusion

The discovery of several novel biological markers for renal injury, including NGAL, adds to the diagnostic armamentarium of ICU physicians. Indeed, we need biological markers that monitor and define renal inflammation and/or injury more than markers of renal function, as administration of potentially effective therapeutic agents may only be effective or may be more effective in the early stages of renal injury.

However, most studies of novel biological markers of AKI are preliminary and require validation in large multicenter trials. Once valid biological markers for early detection have been identified, we should evaluate them in combination. The pattern of urinary excretion of these markers may potentially aid in understanding the pathophysiology of AKI, allowing localization of injury to specific segments of the nephron (**Fig. 1**). This combination of markers could eventually lead to differentiated preventive and/or therapeutic approaches.

References

1. Chertow GM, Burdick E, Honour M, Bonventre JV, Bates DW (2005) Acute kidney injury, mortality, length of stay, and costs in hospitalized patients. J Am Soc Nephrol 16: 3365–3370
2. Hoste EA, Lameire NH, Vanholder RC, Benoit DD, Decruyenaere JM, Colardyn FA (2003) Acute renal failure in patients with sepsis in a surgical ICU: predictive factors, incidence, comorbidity, and outcome. J Am Soc Nephrol 14: 1022–1030
3. Uchino S, Kellum JA, Bellomo R, et al (2005) Acute renal failure in critically ill patients: a multinational, multicenter study. JAMA 294: 813–818
4. Jo SK, Rosner MH, Okusa MD (2007) Pharmacologic treatment of acute kidney injury: why drugs haven't worked and what is on the horizon. Clin J Am Soc Nephrol 2: 356–365
5. Briggs JP (2008) The hunt for the perfect biomarker for acute kidney injury: back to gamma-trace? Kidney Int 74: 987–989
6. American Society of Nephrology (2005) Renal Research Report. J Am Soc Nephrol 16: 1886–1903
7. Mehta RL, Kellum JA, Shah SV, et al (2007) Acute Kidney Injury Network: Report of an initiative to improve outcomes in acute kidney injury. Crit Care 11: R31
8. Lassnigg A, Schmidlin D, Mouhieddine M, et al (2004) Minimal changes of serum creatinine predict prognosis in patients after cardiothoracic surgery: a prospective cohort study. J Am Soc Nephrol 15: 1597–1605
9. Coca SG, Parikh CR (2008) Urinary biomarkers for acute kidney injury: perspectives on translation. Clin J Am Soc Nephrol 3: 481–490
10. Supavekin S, Zhang W, Kucherlapati R, Kaskel FJ, Moore LC, Devarajan P (2003) Differential gene expression following early renal ischemia/reperfusion. Kidney Int 63: 1714–1724
11. Mishra J, Ma Q, Prada A, et al (2003) Identification of neutrophil gelatinase-associated lipocalin as a novel early urinary biomarker for ischemic renal injury. J Am Soc Nephrol 14: 2534–2543
12. Mishra J, Mori K, Ma Q, Kelly C, Barasch J, Devarajan P (2004) Neutrophil gelatinase-associated lipocalin: a novel early urinary biomarker for cisplatin nephrotoxicity. Am J Nephrol 24: 307–315
13. Mori K, Lee HT, Rapoport D, et al (2005) Endocytic delivery of lipocalin-siderophore-iron complex rescues the kidney from ischemia-reperfusion injury. J Clin Invest 115: 610–621
14. Dent CL, Ma Q, Dastrala S, et al (2007) Plasma neutrophil gelatinase-associated lipocalin predicts acute kidney injury, morbidity and mortality after pediatric cardiac surgery: a prospective uncontrolled cohort study. Crit Care 11: R127
15. Bennett M, Dent CL, Ma Q, et al (2008) Urine NGAL predicts severity of acute kidney injury after cardiac surgery: a prospective study. Clin J Am Soc Nephrol 3: 665–673

16. Mishra J, Dent C, Tarabishi R, et al (2005) Neutrophil gelatinase-associated lipocalin (NGAL) as a biomarker for acute renal injury after cardiac surgery. Lancet 365: 1231–1238
17. Wagener G, Jan M, Kim M, et al (2006) Association between increases in urinary neutrophil gelatinase-associated lipocalin and acute renal dysfunction after adult cardiac surgery. Anesthesiology 105: 485–491
18. Parikh CR, Jani A, Mishra J, et al (2006) Urine NGAL and IL-18 are predictive biomarkers for delayed graft function following kidney transplantation. Am J Transplant 6: 1639–1645
19. Mishra J, Ma Q, Kelly C, et al (2006) Kidney NGAL is a novel early marker of acute injury following transplantation. Pediatr Nephrol 21: 856–863
20. Bachorzewska-Gajewska H, Malyszko J, Sitniewska E, Malyszko JS, Dobrzycki S (2006) Neutrophil-gelatinase-associated lipocalin and renal function after percutaneous coronary interventions. Am J Nephrol 26: 287–292
21. Bachorzewska-Gajewska H, Malyszko J, Sitniewska E, Malyszko JS, Dobrzycki S (2007) Neutrophil gelatinase-associated lipocalin (NGAL) correlations with cystatin C, serum creatinine and eGFR in patients with normal serum creatinine undergoing coronary angiography. Nephrol Dial Transplant 22: 295–296
22. Haase M, Bellomo R, Devarajan P, Schlattmann P, Haase-Fielitz A (2009) Accuracy of neutrophil gelatinase-associated lipocalin (NGAL) in diagnosis and prognosis in acute kidney injury: a systematic review and meta-analysis. Am J Kidney Dis 54: 1012–1024
23. Cruz DN, de Cal M, Garzotto F, et al (2010) Plasma neutrophil gelatinase-associated lipocalin is an early biomarker for acute kidney injury in an adult ICU population. Intensive Care Med 36: 444–451
24. Boldt J, Brosch C, Ducke M, Papsdorf M, Lehmann A (2007) Influence of volume therapy with a modern hydroxyethylstarch preparation on kidney function in cardiac surgery patients with compromised renal function: a comparison with human albumin. Crit Care Med 35: 2740–2746
25. Boldt J, Brosch C, Rohm K, Papsdorf M, Mengistu A (2008) Comparison of the effects of gelatin and a modern hydroxyethyl starch solution on renal function and inflammatory response in elderly cardiac surgery patients. Br J Anaesth 100: 457–464
26. Haase M, Haase-Fielitz A, Bellomo R, et al (2009) Sodium bicarbonate to prevent increases in serum creatinine after cardiac surgery: a pilot double-blind, randomized controlled trial. Crit Care Med 37: 39–47
27. Wagener G, Gubitosa G, Wang S, Borregaard N, Kim M, Lee HT (2008) Increased incidence of acute kidney injury with aprotinin use during cardiac surgery detected with urinary NGAL. Am J Nephrol 28: 576–582

Biomarkers of Acute Kidney Injury in Cardiorenal Syndromes

A.K. Roy, B.A. McMahon, and P.T. Murray

Introduction

Renal dysfunction in association with congestive heart failure (CHF) is common, both chronically (chronic kidney disease, CKD) and in the setting of acute decompensated heart failure. Acute kidney injury (AKI) occurs in up to 20–45 % of admissions for acute heart failure [1, 2], and is associated with increased short- and long-term mortality and morbidity. Thus, there is a need to develop improved biomarkers of early renal injury and function to guide the management of patients with CHF, reduce adverse renal events, and improve outcomes.

The recent Acute Dialysis Quality Initiative (ADQI) consensus guidelines define 5 subtypes of cardiorenal syndrome [3], and provide a framework to understanding the complexity of the heart-kidney interaction, emphasizing the degree to which dysfunction in one organ may precipitate a sequence of injury affecting both systems, and often other distant organ systems as well. Worsening renal function, defined as a serum creatinine increase of $\geq 0.3-0.5$ mg/dl during hospitalization [4], has been validated in multiple heart failure populations to identify patients with AKI-associated increased morbidity and mortality in the setting of acute decompensated heart failure, but the ultimate goal is to define those at risk of significant renal dysfunction before irreversible injury occurs, and offer alternative or tailored therapies to improve outcomes. Aspects of patient care that may be improved by earlier and/or more accurate AKI diagnosis include: Differentiating between CKD, (reversible) pre-renal azotemia, acute tubular necrosis, or other causes of AKI; deciding on the cessation of essential therapies known to improve mortality (such as angiotensin-converting enzyme [ACE] inhibitors or beta-adrenergic antagonists); and preventing or postponing nephrotoxic insults (iodinated contrast or gadolinium).

The Pathophysiology of the Cardiorenal Interaction

The pathophysiology of the cardiorenal interaction is complex, characterized by a variety of hemodynamic alterations, including more recently identified phenomena such as raised central venous pressures (CVPs) causing renal congestion and abnormal filtration gradients, in addition to hypoperfusion caused by inadequate renal perfusion pressures initially triggered by impaired cardiac output [5, 6]. These hemodynamic insults are exacerbated by neurohormonal activation and inflammation (cytokine activation). Specifically, systemic and renal vasoconstriction are caused by increased sympathetic and neurohormonal activity, including

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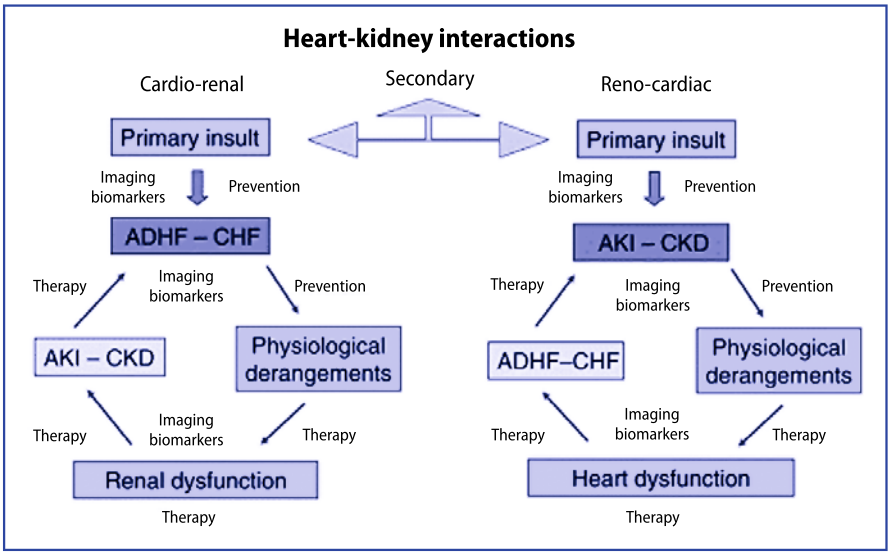

Fig. 1. Schematic of heart kidney interaction in cardiorenal syndrome. The figure demonstrates the dynamic interrelation between the heart and kidneys in cardiorenal syndrome, indicating the importance of the sequence of organ injury. At each stage, a combination of the most appropriate diagnostic and therapeutic modalities should be considered, in an attempt to prevent further injury. AKI: acute kidney injury; CKD: chronic kidney disease; ADHF: acute decompensated heart failure; CHF: congestive hear failure. From [3] with permission

activation of the renin-angiotensin-aldosterone-system (RAAS), and altered tubuloglomerular feedback systems (adenosine signaling via A1 receptors), which can also lead to long-term renal and cardiac structural and functional abnormalities, such as CKD and left ventricular remodeling. **Figure 1** highlights the inter-relation between heart and kidney, and how injury to one can precipitate a cascade of biological reactions involving the other. Ronco et al. [3] also demonstrate in **Figure 1** various points at which diagnosis and intervention are possible.

Current Definitions of Acute Kidney Injury

The limitations of serum creatinine in diagnosing AKI, which have been well described, become most apparent when early diagnosis of tubular injury is an essential trigger to initiate effective interventions designed to attenuate further injury. Serum creatinine and glomerular filtration rate (GFR) are biomarkers of renal function, with GFR often deteriorating by 25 – 50 % before there has been any significant change in serum creatinine, which may be days after the tubular insult has occurred, when steady-state equilibrium is achieved [7, 8]. Creatinine is also dependent on other factors, such as muscle mass, age, gender and hydration status – all of which may result in underestimation of the presence and severity of renal dysfunction, particularly in elderly heart failure patients with cardiac cachexia, for example. When AKI develops in patients with CHF, the utility of urine biochemistries to differentiate between reversible prerenal azotemia

and acute tubular necrosis is unproven. Specifically, diuretics invalidate the diagnosis of acute tubular necrosis in the presence of a high fractional excretion of sodium (FENa); and the putative superiority of the FEUrea in this setting has not been conclusively demonstrated.

In recent years, interdisciplinary consensus groups have proposed standardized systems to define and stage AKI. Both the RIFLE (Risk, Injury, Failure, Loss of Kidney Function, and End-stage Kidney Disease (RIFLE), and Acute Kidney Injury Network (AKIN) criteria, were designed for the purpose of accurately diagnosing and assessing the severity and progression of AKI in critically ill patients, as well as providing some predictive ability for mortality [9]. Both systems rely on changes in creatinine or GFR, while also incorporating urinary output criteria [9]. Although the RIFLE criteria have been validated in over 550,000 patients, few studies have examined the ability of RIFLE or AKIN systems to predict mortality and AKI outcomes in heart failure patients, who receive a variety of acute and chronic therapies (diuretics, ACE inhibitors, inotropes and vasodilators that may differentially alter GFR or urine output and morbidity/mortality). Studies such as ADHERE (Acute Decompensated Heart Failure National Registry) demonstrated the ability of clinical and biochemical markers such as systolic blood pressure, serum creatinine, or blood urea nitrogen (BUN) to independently predict mortality in acute decompensated heart failure, but did not use current definitions of AKI. The modification of the RIFLE definition to the AKIN system primarily reflected the recognition of the prognostic and diagnostic importance of even small variations in serum creatinine seen in acutely ill patients. Specifically in CHF, Hata et al. were able to demonstrate the prognostic significance of AKI staging using the RIFLE criteria; in 376 patients with acute decompensated heart failure, hospital mortality increased in a stepwise manner with progression from Risk or Injury, to Failure [10].

Biomarker Features

Novel biomarkers should ideally be able to satisfy several criteria, including the ability to identify risk, allow for early diagnosis, provide prognostic information, determine the likelihood of response to treatment, or perhaps even serve as a treatment target or surrogate outcome to guide therapy. The key to understanding the specific role of any novel biomarker is also to understand its limitations, and what specific additive clinical information it may provide, either alone, or in combination with other markers. Does the biomarker improve the predictive accuracy of the best available standard of care, incorporating other known predictors of AKI or filtration function, such as serum creatinine or GFR? The varied pathophysiologic mechanisms causing AKI point towards a multimarker approach to diagnosing risk or occurrence of AKI, examining markers which may reflect both proximal and distal sites of tubular injury, perhaps in complementary combination with more sensitive real-time measurement of GFR. As advances in understanding the role of the natriuretic peptides have shown, the road to a biomarker-guided patient management scheme can be long, and highlighting the care with which one should interpret study results, particularly in subsets of patients with potentially confounding biological interactions, such as cardiorenal syndrome. **Table 1** summarizes some features of the key biomarkers currently under development for use in cardiorenal syndromes.

Table 1. Selected cardiorenal biomarkers

Cardiac markers of myocyte injury (necrosis and apoptosis)	Cardiac troponins – Troponin I, high-sensitivity troponin CPK-MB
Neurohormones	(i) Natriuretic peptides: ANP, mid-regional pro-atrial natriuretic peptide (MR-proANP) BNP and NT-proBNP CNP (ii) Vasodilatory hormones: mid-region pro-adrenomedullin (MR-proADM)
Novel AKI biomarkers	Cystatin C NGAL KIM-1 GST Interleukin-18 N-acetyl-β-(D) glucosaminidase (NAG) Urinary albumin
Standard clinical AKI biomarkers	Serum creatinine Blood urea nitrogen Uric acid eGFR Urea Serum sodium Systolic blood pressure

AKI: acute kidney injury; CPK: creatine phosphokinase; ANP: atrial natriuretic peptide; BNP: b-type natriuretic peptide; CNP: C-type natriuretic peptide; NGAL: neutrophil gelatinase-associated lipocalin; KIM: kidney injury molecule; GST: glutathione-S-transferase

Biomarkers of Myocyte Necrosis and Wall Stress

As depicted in **Figure 1**, the interaction between the heart and kidneys in cardiorenal syndrome is dynamic, and interdependent. Thus any review or interpretation of the clinical utility of biomarkers in cardiorenal syndrome should also mention the importance of biomarkers of cardiac myocyte necrosis, such as cardiac troponin, which should alert the clinician to possible ongoing ischemic myonecrosis in the setting of acute or chronic heart failure. The phenomenon of subclinical ischemic cardiac myocyte damage will become increasingly recognized with the advent of high-sensitivity troponin assays. However, a detailed review of the role of cardiac troponin monitoring in heart failure is beyond the scope of this chapter.

Natriuretic peptides, such as B-type natriuretic peptide (BNP), are released in response to increased atrial and ventricular wall stretch due to pressure or volume overload, and correlate well with echocardiographic markers of LV end-diastolic wall stress (LVEDWS) in patients with heart failure and normal serum creatinine [1]. By acting as counterregulatory hormones, they modulate the effects of the RAAS and the sympathetic nervous system, causing vasodilation, improved salt and water excretion, and favorable ventricular remodeling [5]. The active hormone component, BNP, and the inactive NT-proBNP, have been extensively studied as biomarkers in heart failure with significant prognostic and diagnostic

utility (Breathing Not Properly study, REDHOT-Rapid Emergency Department Heart failure Outpatient Trial), along with older standard biomarkers such as uric acid, creatinine, and BUN [7, 11, 12].

Measurement of BNP is incorporated in the European Society of Cardiology clinical practice guidelines for the management of CHF with left ventricular failure and of pulmonary hypertension and right heart failure [13, 14], has excellent negative predictive value in the ICU setting, and also excellent overall test performance: A BNP level > 144 pg/ml predicts cardiac dysfunction with high sensitivity and specificity (92 % and 86 %, respectively) [15]. The combination of NT-proBNP and cardiac troponin T (cTnT), markers of myocardial wall stretch and myonecrosis, respectively, have also been shown to be strong independent predictors of mortality, particularly when measured at discharge [16].

In the subset of patients with heart failure and severe or end-stage renal disease (cardiorenal syndromes types 2 – 5), it is apparent that alternative BNP cutoff values may be needed, because the diagnostic accuracy of plasma BNP and NT-proBNP is reduced compared with patients with GFR > 60 ml/min [16]. Whether this relates more to impaired renal clearance or ongoing hemodynamic stimulation by volume overload remains unclear.

The evolution of data concerning the use of natriuretic peptides has led to trials such as SURVIVE (levosimendan vs dobutamine for patients with acute decompensated heart failure), and REVIVE-2 (Randomized multicenter EValuation of Intravenous leVosimendan Efficiency), both designed to use BNP-guided endpoints to monitor the effectiveness of levosimendan in heart failure [17]. TIME-CHF (Trial of Intensified vs Standard Medical Therapy in Elderly Patients With Congestive Heart Failure), and the recent BATTLESCARRED (NT-proBNP–Assisted Treatment To Lessen Serial Cardiac Readmissions and Death) study, also raised the issue of older age (in this case > 75 years) as a possible confounder when interpreting BNP levels in heart failure. The combination of physiologic changes seen during aging, such as diastolic ventricular stiffness, impaired endothelial function, as well alterations in pharmacodynamic responses to standard heart failure therapies, highlights the ongoing need for data that are specific to the majority of heart failure and cardiorenal patients being tested.

Cystatin C

Cystatin C is a 13 kDa cysteine protease inhibitor, produced by all functioning nucleated cells in the human body. It is released into the plasma at a constant rate, where it is filtered at the glomerulus and subsequently reabsorbed and almost completely degraded in the proximal convoluted tubule [18]. Thus, it is not generally measurable in the urine in significant amounts under normal conditions, although serum cystatin is easily measured in serum, and used as an index of GFR. Some studies suggest that extrarenal factors, such as inflammation, cancer, steroids, and thyroid disease, may affect serum concentrations; however it is not known to what degree this may occur.

Of all the new biomarkers of AKI, cystatin C has been the most extensively studied in patients with heart failure, and lessons learned from these studies are being applied to other AKI biomarker trial designs. Increased serum cystatin C concentrations are associated with adverse cardiovascular outcomes and prognosis [19]. There is still limited information regarding demographic-specific normal

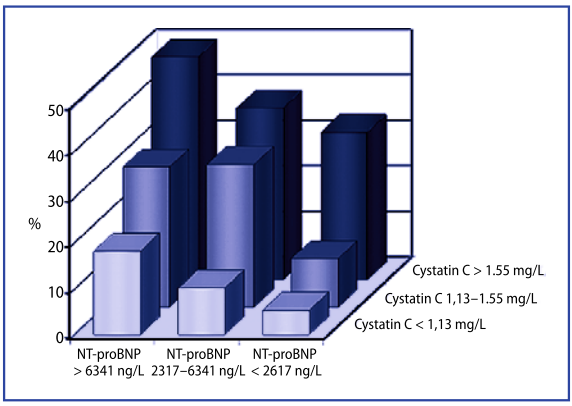

Fig. 2. Risk stratification of acute decompensated heart failure by combining tertiles of cystatin C and NT-proBNP. Mortality at 1 year increases from 5.2 % in patients in the first tertile of both biomarkers (n = 77) to 48.7 % in patients in the third tertile (n = 76) of cystatin C and NT-proBNP [7]. From [7] with permission.

ranges for urine and serum cystatin C values in heart failure, with many of the earlier studies instead examining tertiles of cystatin C values. The prognostic ability of cystatin C in predicting all-cause mortality in acute decompensated heart failure was demonstrated by Lassus et al. [7] in a multicenter study of 480 patients, with average age 74.8 years and mean NT-proBNP 3916 ng/l. Renal dysfunction was present in 20 % of patients (serum creatinine > 120 μmol/l) at presentation, with 7.9 % patients known to have chronic kidney disease before admission. All-cause mortality at 12 months was three-fold higher at 39 % in patients with raised serum cystatin C above a median of 1.3 mg/l, compared with 12 % of patients with cystatin C levels below the median (log rank $p < 0.0001$). Elevated serum cystatin C in patients with normal creatinine clearance (CrCl) was also a powerful predictor of mortality (50 % v 3 %, log rank $p < 0.0001$), compared with those with normal values for both CrCl and cystatin C. The combination of tertiles of cystatin C and NT-proBNP allowed for greater prognostic risk stratification of 12 month mortality, from 5 % in the lowest combination tertile group to 49 % of patients in the highest cystatin C and NT-proBNP group (**Fig. 2**). Similarly powerful prognostic cardiovascular mortality indicators using combination cystatin C and NT-proBNP in stable elderly CHF patients studied over a 10-year period were described by Alehagan et al. [19].

Neutrophil Gelatinase-Associated Lipocalin (NGAL)

NGAL (previously called lipocalin-2) is a 25 kDa glycoprotein identified by microarray analysis in early post-ischemic kidney mouse models as an early marker of tubular injury. Further translational studies have shown that NGAL is covalently bound with matrix metalloproteinase-9 (MMP-9) in association with human neutrophils [20], and also plays a role in innate immunity towards exogenous bacterial infections by acting as a shuttle for iron and siderophores. The NGAL gene and proteins are upregulated in response to renal tubular injury, to enhance tubular epithelial cell proliferation. In the arena of AKI, NGAL has been studied as an AKI biomarker in a variety of clinical settings, including cardiac surgery, coronary angiography with contrast media, the emergency department [21], and more recently in the first prospective heart failure studies [4, 22].

NGAL, in various other complexes with iron and MMP-9, has also been identified in association with adenocarcinomas, cisplatin nephrotoxicity, and degree of severity of coronary artery disease, highlighting the importance and diversity of the lipocalin family in cellular proliferation and differentiation.

In children undergoing congenital cardiac surgery, Mishra et al. [23] demonstrated that urinary NGAL levels greater than 50 μg/l within 2–4 hours after cardiopulmonary bypass (CPB) were 100 % sensitive and 98 % specific for identifying AKI (defined by 50 % increase in serum creatinine) that developed 1–2 days postoperatively (area under the curve [AUC] 0.99 at 2 and 1.0 at 4 hours post-bypass, respectively). Further studies in adults undergoing CPB (**Table 2**) have shown AUCs between 0.53–0.80 for prediction of AKI [24], with sensitivity and specificity being affected by age, comorbidities not commonly seen in pediatric populations, as well as the influence of other methodologic problems (sample storage temperature, lack of standardized definitions of AKI) seen in several of these studies.

Further explanations for the variability in AUC performance for NGAL in adult cardiac surgery were explored by Haase-Fielitz et al. [24], who performed sensitivity analyses on 100 postoperative patients, to determine the influence of AKI definition (RIFLE, AKIN) on predictive value of plasma NGAL. They found that the predictive value of plasma NGAL was increased with AKI class, from an AUC of 0.64 for a 25 % increase in serum creatinine to an AUC of 0.83 for the prediction of progression to renal replacement therapy [24]. The authors also proposed that newer criteria, such as AKIN, which are designed to acknowledge the importance of smaller variations in creatinine, may still be relatively insensitive to detect tubular stress or injury, as indicated by mild NGAL increases.

Table 2. Impact of definition of acute kidney injury (AKI) after cardiac surgery on the predictive value of neutrophil gelatinase-associated lipocalin (NGAL) measurement. From [24] with permission

Reference	No. patients	Setting	Creatinine increase	Timing of postoperative creatinine increase days (d)	Timing of NGAL measurement (after end of CPB)	AUC-ROC to predict AKI (plasma/urine)
Mishra et al. [23]	71	Pediatric	> 50 %	Within 5 d	At 2h	0.91/0.99
Dent et al [30]	120	Pediatric	> 50 %	Within 5 d	At 2h	0.96/–
Bennett et al [31]	196	Pediatric	> 50 %	Within 5 d	At 2h	–/0.95
Wagener et al [32]	81	Adult	> 50 %	Within 5 d	At 3h	–/0.74
Wagener et al [33]	426	Adult	> 50 % or > 0.3mg/dl	Within 2 d	At 3h	–/0.60
Koyner et al [8]	72	Adult	> 25 % or need for RRT	Within 3 d	At –2 h*	0.53/0.70
Haase-Fielitz et al [34]	100	Adult	> 50 %	Within 5 d	At –2 h*	0.80/–

AUC: area under the curve; ROC: receiver operating characteristic; RRT: renal replacement therapy; CPB: cardiopulmonary bypass; *- six hours after CPB or intensive care unit arrival.

Table 3. Recent studies examining urine and serum neutrophil gelatinase-associated lipocalin (NGAL) in acute and chronic heart failure

Reference	Sample size (n)	HF type	Average age (yr)	Biomarkers used in multivariate analysis
Damman et al (2008) [35]	90 + 20 controls	CHF	59 ± 11	Urinary NGAL, NT-proBNP, eGFR, SCr
Yndestad et al (2009) [36]	150 + 20 controls	CHF	56 ± 12	Serum NGAL
Aghel et al (2010) [4]	91	ADHF	65 ± 15 (AKI group)	Serum NGAL
Damman et al (2010) [37]	90	CHF	59 ± 11	Urine NGAL, NAG, KIM-1, urinary albumin excretion, eGFR, effective renal plasma flow

CHF: congestive heart failure; ADHF: acute decompensated heart failure

There are also emerging data regarding the utility of NGAL as a biomarker of AKI in settings apart from cardiac surgery (**Table 3**). For example, in 635 patients presenting to a busy urban emergency department, mean urinary NGAL levels were able to differentiate between patients with no renal impairment, pre-renal azotemia, or CKD (low NGAL concentrations), and AKI caused by acute tubular necrosis, outperforming three other AKI biomarkers and serum creatinine (**Fig. 3**) [23]. In one of the few acute decompensated heart failure studies to date, admission serum NGAL concentrations > 140 ng/ml had an AUC of 0.70 to predict worsening renal failure (creatinine rise ≥ 0.3 mg/dl), which occurred in 38 % of patients with acute decompensated heart failure. Admission serum creatinine was not associated with worsening renal failure in a logistic regression analysis [4]. Damman et al. recently showed that stable chronic heart failure patients, compared with age-matched controls, demonstrated marked evidence of urinary NGAL elevation (indicative of tubular dysfunction), with decreased GFR and, more impor-

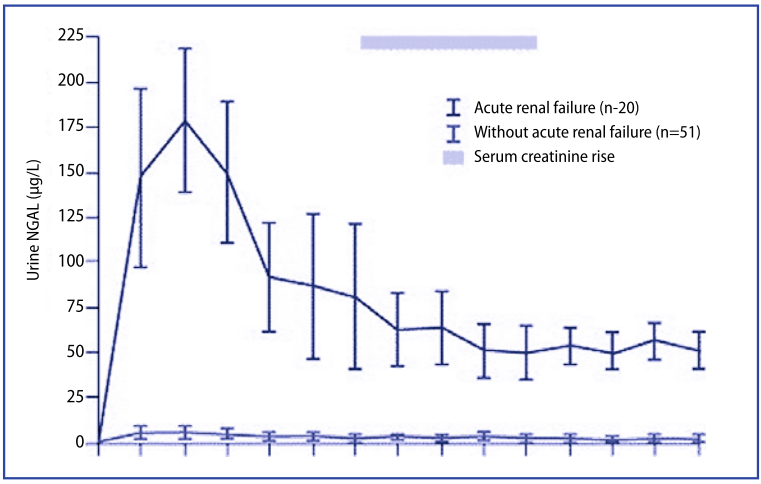

Fig. 3. Performance of urine NGAL in pediatric patients with AKI (with error bars) and without AKI compared to serum creatinine rise (solid gray bar). From [23] with permission.

tantly, a positive association with increased levels of NT-proBNP and urinary albumin excretion [35].

There have been enough studies of NGAL in AKI to permit a more comprehensive analysis than is available for other putative AKI biomarkers. A systematic review and meta-analysis of the predictive value of NGAL for the early diagnosis of AKI was carried out by the NGAL Meta-analysis Investigator Group and studied 2,500 patients in 19 studies [25]. These investigators found that serum and urine NGAL levels performed similarly well, and suggested a cut-off NGAL concentration > 150 ng/ml for clinical laboratory platforms [25]. The performance of NGAL levels as early predictors of AKI was robust, including direct comparisons with serum creatinine level, also demonstrating prognostic value for adverse outcomes such as renal replacement therapy and mortality. Haase et al. appear to have addressed many of the inconsistencies seen in smaller studies, while providing further direction for the development of NGAL for use in studies assessing the effects of therapeutic interventions initiated for early AKI. As the authors point out, in this early phase of AKI biomarker development, one cannot overlook the comparisons of performance (AUC ~ 0.70) of another biomarker in its early clinical development: serum troponin. Among the remaining issues concerning the use of NGAL as an AKI biomarker, the role of NGAL for this purpose in patients with pre-existing CKD remains to be determined.

Kidney Injury Molecule-1 (KIM-1)

KIM-1 is a glycoprotein found on the proximal renal tubular epithelial cell membrane, where it is markedly induced in response to ischemia-reperfusion injury. In a recent study of 123 cardiac surgery patients, Koyner et al. demonstrated the ability of KIM-1 to detect Stage 1 and 3 AKI (along with NGAL, cystatin C, and α-glutathione-S-transferase [GST]), as well as, interestingly, predicting AKI prior to the initiation of surgery, suggesting a possible role in early warning of subclinical proximal tubular insults which may allow for tailored management [26]. Several other studies have suggested that the utility of KIM-1 for AKI diagnosis may be GFR- or time-dependent. KIM-1 expression has also been described in malignancies such as renal cell carcinoma.

Urinary α- and π-GST

GST proteins are constitutive markers normally found in renal tubular epithelium, involved in modulating the oxidative tubular injury caused by reactive oxygen species (ROS). Compared to the smaller proteins such as creatinine or cystatin C, the GSTs are of larger molecular weights ranging from 47 – 51 kDa, thus largely preventing glomerular filtration. α-GST is found in proximal tubular cells, while π-GST is found in distal tubular cells, both demonstrating site-specific release in response to injury. The pattern of GST release has been shown to correlate to site of injury and aid in differentiation between proximal tubular injury (for example, due to calcineurin-inhibitors), and distal tubular injury seen (caused by acute renal allograft rejection). In one of the largest published KIM-1 studies to date, examining various potential biomarkers of AKI in CPB patients (n = 123), Koyner et al. [26] suggest a potential role for π- and α-GST as markers

of occurrence and progression of AKI following cardiac surgery, demonstrating an AUC of 0.86 (0.74–0.99), p = 0.002, for π-GST in predicting progression to Stage 3 AKI at time of initial creatinine rise and AKI diagnosis (Stage 1). Furthermore, the authors noted increases in GST in 11 patients who received preoperative intravenous iodinated contrast for cardiac catheterization, despite no associated clinical AKI, suggesting that GST may also have a role in the diagnosis of subclinical tubular oxidant stress and injury. However, the role of GST as biomarkers to predict, diagnose, and assess AKI in cardiorenal syndromes (acute decompensated heart failure, contrast-induced nephropathy, cardiac surgery) has yet to be fully investigated, and requires further large-scale studies.

Urinary Albumin

The role of proteinuria as an independent predictor of outcome, such as death or readmission for heart failure in SOLVD (Studies of Left Ventricular Dysfunction), or mortality in SAVE (Survival and Ventricular Enlargement), correlates with the recent CHARM (Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity) analysis [28, 29] in which the prevalence and prognostic value of a spot urinary albumin to creatinine ratio (UACR) was studied in 2,310 patients presenting with heart failure [29]. Microalbuminuria (defined as UACR 2.5–25 mg/mmol in men and 3.5–25 mg/mmol in women) and macroalbuminuria (UACR > 25 mg/mmol in men and women) were robust independent predictors of clinical outcomes, with a 60–80 % adjusted increase in risk of death, and 30–70 % increase in risk of admission for heart failure, with either systolic left ventricular (LV) dysfunction or preserved LV systolic function. Furthermore, while the authors note that renal venous congestion causes proteinuria in experimental animal models, the hazard related to albuminuria in the CHARM study was independent of renal dysfunction (severe renal dysfunction patients were excluded), assessed using both estimated GFR (eGFR) and serum creatinine. Taken together, these findings underscore the important bi-directional nature of cardiorenal syndrome, while also demonstrating the independent predictive ability for adverse outcome of urinary albumin measurement, compared to serum creatinine and eGFR.

Conclusion

Ongoing large-scale prospective trials are currently in analysis or underway (GALLANT, AKINESIS) examining the role of new biomarkers in detecting AKI in heart failure and cardiorenal syndromes, as well as shedding more light on the performance of AKI biomarkers in specific patient subsets, such as those with CKD, acute coronary syndromes, the elderly, or other ‘real-world’ patients with multiple co-morbidities. As we learn more about the value of biomarkers in detecting early evidence of tubular injury, it seems clear that our ability to assess short-term renal risk will improve. Challenges remain, however, in the validation of early AKI biomarkers to facilitate appropriate clinical trials to study successful interventions to prevent or treat AKI and improve outcomes in a variety of high-risk clinical settings, including cardiorenal syndromes such as acute decompensated heart failure.

References

1. Iwanaga Y, Miyazaki S (2010) Heart failure, chronic kidney disease, and biomarkers--an integrated viewpoint. Circ J 74: 1274 – 1282
2. House AA, Haapio M, Lassus J, Bellomo R, Ronco C (2010) Therapeutic strategies for heart failure in cardiorenal syndromes. Am J Kidney Dis 56: 759 – 773
3. Ronco C, McCullough P, Anker SD, et al (2010) Cardiorenal syndromes: report from the consensus conference of the Acute Dialysis Quality Initiative. Eur Heart J 31: 703 – 711
4. Aghel A, Shrestha K, Mullens W, Borowski A, Tang WH (2010) Serum neutrophil gelatinase-associated lipocalin (NGAL) in predicting worsening renal function in acute decompensated heart failure. J Card Fail 16: 49 – 54
5. Manzano-Fernandez S, Boronat-Garcia M, Albaladejo-Oton MD, et al (2009) Complementary prognostic value of cystatin C, N-terminal pro-B-type natriuretic peptide and cardiac troponin T in patients with acute heart failure. Am J Cardiol 103: 1753 – 1759
6. Mullens W, Abrahams Z, Francis G, et al (2009) Importance of venous congestion for worsening of renal function in advanced decompensated heart failure. J Am Coll Cardiol 53: 589 – 596
7. Lassus J, Harjola VP, Sund R, et al (2007) Prognostic value of cystatin C in acute heart failure in relation to other markers of renal function and NT-proBNP. Eur Heart J 28: 1841 – 1847
8. Koyner JL, Bennett MR, Worcester EM, et al (2008) Urinary cystatin C as an early biomarker of acute kidney injury following adult cardiothoracic surgery. Kidney Int 74: 1059 – 1069
9. Hoste EA, Clermont G, Kersten A, et al (2006) RIFLE criteria for acute kidney injury are associated with hospital mortality in critically ill patients: a cohort analysis. Crit Care 10: R73
10. Hata N, Yokohama S, Shinada T, et al (2010) Acute kidney injury and outcomes in acute decompensated heart failure: evaluation of the RIFLE criteria in an acutely ill heart failure population. Eur J Heart Fail 12: 32 – 37
11. Maisel A (2009) Natriuretic peptide-guided therapy for heart failure: ready for “battle” or too “scarred” by the challenges of trial design? J Am Coll Cardiol 55: 61 – 64
12. Maisel A (2007) Biomarkers in heart failure. Does prognostic utility translate to clinical futility? J Am Coll Cardiol 50: 1061 – 1063
13. European Society of Cardiology (2008) ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008. Available at: http://www.escardio.org/guidelines-surveys/esc-guidelines/GuidelinesDocuments/guidelines-HF-FT.pdf Accessed Nov 2010
14. European Society of Cardiology (2009) Guidelines for the diagnosis and treatment of pulmonary hypertension. Available at: http://www.escardio.org/guidelines-surveys/esc-guidelines/GuidelinesDocuments/guidelines-PH-FT.pdf. Accessed Nov 2010
15. Mclean AS, Tang B, Nalos M, et al (2003) Increased B-type natriuretic peptide level is a strong predictor for cardiac dysfunction in intensive care unit patients. Anaesth Intensive Care 31: 21 – 27
16. Metra M, Nodari S, Parrinello G, et al (2007) The role of plasma biomarkers in acute heart failure. Serial changes and independent prognostic value of NT-proBNP and cardiac troponin-T. Eur J Heart Fail 9: 776 – 786
17. Gheorghiade M, Pang PS (2009) Are BNP changes during hospitalization for heart failure a reliable surrogate for predicting the effects of therapies on post-discharge mortality? J Am Coll Cardiol 53: 2349 – 2352
18. McIlroy DR, Wagener G, Lee HT (2010) Biomarkers of acute kidney injury: an evolving domain. Anesthesiology 112: 998 – 1004
19. Alehagen U, Dahlstrom U, Lindahl TL (2009) Cystatin C and NT-proBNP, a powerful combination of biomarkers for predicting cardiovascular mortality in elderly patients with heart failure: results from a 10-year study in primary care. Eur J Heart Fail 11: 354 – 360
20. Devarajan P (2008). Neutrophil gelatinase-associated lipocalin – an emerging troponin for kidney injury. Nephrol Dial Transplant 23: 3737 – 3743
21. Nickolas TL, O’Rourke MJ, Yang J, et al (2008) Sensitivity and specificity of a single emergency department measurement of urinary neutrophil gelatinase-associated lipocalin for diagnosing acute kidney injury. Ann Intern Med 148: 810 – 819

22. Lassus JP, Nieminen MS, Peuhkurinen K, et al (2010) Markers of renal function and acute kidney injury in acute heart failure: definitions and impact on outcomes of the cardiorenal syndrome. Eur Heart J 31: 2791–2798
23. Mishra J, Dent C, Tarabishi R, et al (2005) Neutrophil gelatinase-associated lipocalin (NGAL) as a biomarker for acute renal injury after cardiac surgery. Lancet 365: 1231–1238
24. Haase-Fielitz A, Bellomo R, Devarajan P, et al (2009) The predictive performance of plasma neutrophil gelatinase-associated lipocalin (NGAL) increases with grade of acute kidney injury. Nephrol Dial Transplant 24: 3349–3354
25. Haase M, Bellomo R, Devarajan P, Schlattmann P, Haase-Fielitz A (2009) Accuracy of neutrophil gelatinase-associated lipocalin (NGAL) in diagnosis and prognosis in acute kidney injury: a systematic review and meta-analysis. Am J Kidney Dis 54: 1012–1024
26. Koyner JL, Vaidya VS, Bennett MR, et al (2010) Urinary biomarkers in the clinical prognosis and early detection of acute kidney injury. Clin J Am Soc Nephrol 5: 2154–2165
27. Bonventre JV (2009) Kidney injury molecule-1 (KIM-1): a urinary biomarker and much more. Nephrol Dial Transplant 24: 3265–3268
28. Damman K, Hillege HL, van Veldhuisen DJ (2009) Albuminuria in heart failure: a CHARMing new risk factor? Lancet 374: 506–508
29. Jackson CE, Solomon SD, Gerstein HC, et al (2009) Albuminuria in chronic heart failure: prevalence and prognostic importance. Lancet 374: 543–550
30. Dent CL, Ma Q, Dastrala S, et al (2007) Plasma neutrophil gelatinase-associated lipocalin predicts acute kidney injury, morbidity and mortality after paediatric cardiac surgery; a prospective uncontrolled cohort study. Crit Care 11: R127
31. Bennett M, Dent CL, Ma Q, et al (2008) Urine NGAL predicts severity of acute kidney injury after cardiac surgery: a prospective study. Clin J Am Soc Nephrol 3: 665–673
32. Wagener G, Jan M, Kim M, et al (2006) Association between increases in urinary neutrophil gelatinase-associated lipocalin and acute kidney injury after adult cardiac surgery. Anaesthesiology 105: 485–491
33. Wagener G, Gubitosa G, Wang S, et al (2008) Urinary neutrophil gelatinase-associated lipocalin and acute kidney injury after cardiac surgery. Am J Kidney Dis 52: 425–433
34. Haase-Fielitz A, Bellomo R, Devarajan P, et al (2009) Novel and conventional serum biomarkers predicting acute kidney injury in adult cardiac surgery- a prospective cohort study. Crit Care Med 37: 553–560
35. Damman K, Veldhusen DJ, Navis G, et al (2008) Urinary neutrophil gelatinase associated lipocalin (NGAL), a marker of tubular damage, is increased in patients with chronic heart failure. Eur J Heart Fail 10: 997–1000
36. Yndestad A, Landro L, Ueland T, et al (2009) Increased systemic and myocardial expression of neutrophil gelatinase-associated lipocalin in clinical and experimental heart failure. Eur Heart J 30: 1229–1236
37. Damman K, Van Veldhuisen DJ, Navis G, et al (2010) Tubular damage in chronic systolic heart failure is associated with reduced survival independent of glomerular filtration rate. Heart 96: 1297–1302

Cardio-renal Syndromes: A Complex Series of Combined Heart/Kidney Disorders

C.Y. Goh and C. Ronco

Introduction

Cardio-renal syndrome is broadly defined as a condition characterized by the initiation and/or progression of renal insufficiency secondary to heart failure [1] and has also been used to describe the negative cardiac effects of declining renal function (reno-cardiac syndrome) [2]. A recent definition and classification system has been generated to include a vast array of acute or chronic conditions in these two important organs, where the primary failing organ can be either the heart or the kidneys [3]. This classification has been endorsed and further developed by the ADQI (Acute Dialysis Quality Initiative) consensus group leading to a comprehensive characterization of the complex heart-kidney organ cross-talk [4]. This new classification represents a step forward to a better understanding of the pathophysiology and management strategies of the bidirectional heart-kidney interactions.

The Definition or Classification of Cardio-renal Syndromes

Any direct and indirect insult to heart or kidneys can initiate and perpetuate the combined disorder of these two organs through several complex mechanisms. Therefore, the large umbrella term 'cardio-renal syndromes' should be used to describe a series of heart and kidney disorders "whereby acute or chronic dysfunction in one organ may induce acute or chronic dysfunction (structural or functional abnormalities) of the other" [4]. A more descriptive classification into different subtypes would permit recognition of the primary organ dysfunction (cardiac versus renal) as well as the acute versus chronic nature of the condition [4].
Five subtypes of the CRS can be identified (**Table 1**) and defined as follows:

- Acute cardio-renal syndrome (CRS Type 1): An acute worsening of heart function (acute heart failure-acute coronary syndrome [ACS]) leading to kidney injury and/or dysfunction;
- Chronic cardio-renal syndrome (CRS Type 2): Chronic abnormalities in heart function (chronic heart failure-coronary heart disease) leading to kidney injury and/or dysfunction;
- Acute reno-cardiac syndrome (CRS Type 3): Acute worsening of kidney function (acute kidney injury [AKI]) leading to heart injury and/or dysfunction;
- Chronic reno-cardiac syndrome (CRS Type 4): Chronic kidney disease leading to heart injury, disease, and/or dysfunction;

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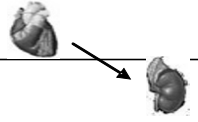
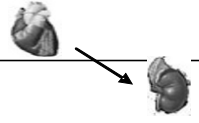
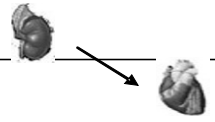
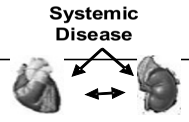
Table 1. Modern definition of cardio-renal syndromes.

	Type 1	Type 2	Type 3	Type 4	Type 5
Organ failure sequence					
Definition	Abrupt worsening of cardiac function leading to acute kidney injury	Chronic abnormalities in cardiac function causing progressive and permanent chronic kidney disease	Abrupt worsening of renal function causing acute cardiac disorders	CKD contributing to decreased cardiac function, cardiac hypertrophy and/or increased risk of cardiovascular events	Systemic condition (e.g., diabetes mellitus, sepsis) causing both cardiac and renal dysfunction
Primary events	Acute decompensated heart failure, ischemic insult, coronary angio, cardiac surgery	LV remodeling and dysfunction Diastolic dysfunction Chronic abnormalities in cardiac function	AKI (e.g., acute kidney ischemia or glomerulonephritis)	CKD (e.g., chronic glomerular disease)	Sepsis
Criteria for primary events	Severe arrythmia Troponin/ ST elevation ECHO: dilatation	Decreased EF Increased CVP NYHF class 3-4	RIFLE R.I.F. or AKIN stage 1-2-3 or AKI requiring RRT	CKD stage 1-5 or CKD requiring RRT	APACHE 2 > SOFA SCORE > No. of failing organs
Sequelae	Inadequate renal perfusion Reduced diuretic responsiveness Worsening renal function	Nephroangiosclerosis, chronic interst. nephr.	ADHF, severe arrythmias, shock	LVH, Dilatative myocardiopathy, CHF	ADHF - AKI
Criteria for sequelae	RIFLE R,I,F by creatinine or urine output.	CKD stage 1-5	Pulmonary edema, electrolyte imbalance arrythmias, cardiac arrest, reduced myocardiac contractility ADHF, AHF, pericarditis	CHF Decreased EF Increased CVP NYHF class 3-4	RIFLE R,I,F or RRT
Cardiac markers	Troponin, BNP, MPO	BNP, CRP	BNP, CRP	CRP	CRP, procalcitonin,
Renal markers	Serum cystatin, creatinine, NGAL. Urinary KIM-1, IL-18, NGAL, NAG	Creatinine, cystatin C, urea, uric acid, CRP Decreased GFR	Serum cystatin, creatinine, NGAL. Urinary KIM-1, IL-18, NGAL, NAG	Creatinine, cystatin C, urea, uric acid, CRP Decreased GFR	Creatinine, NGAL, IL-18, KIM-1, NAG

BNP: brain natriuretic peptide; EF: ejection fracton; LV: left ventricular; CVP: central venous pressure; AKI: acute kidney injury; ADHF: acute decompensated heart failure; CRP: C-reactive protein; IL: interleukin; NGAL: neutrophil gelatinase-associated lipocalin; AHF: acute heart failure; GFR: glomerular filtration rate; CKD: chronic kidney disease; CHF: chronic heart failure; KIM: kidney injury molecule; NAG: N-acetyl-beta-D-glucosaminidase

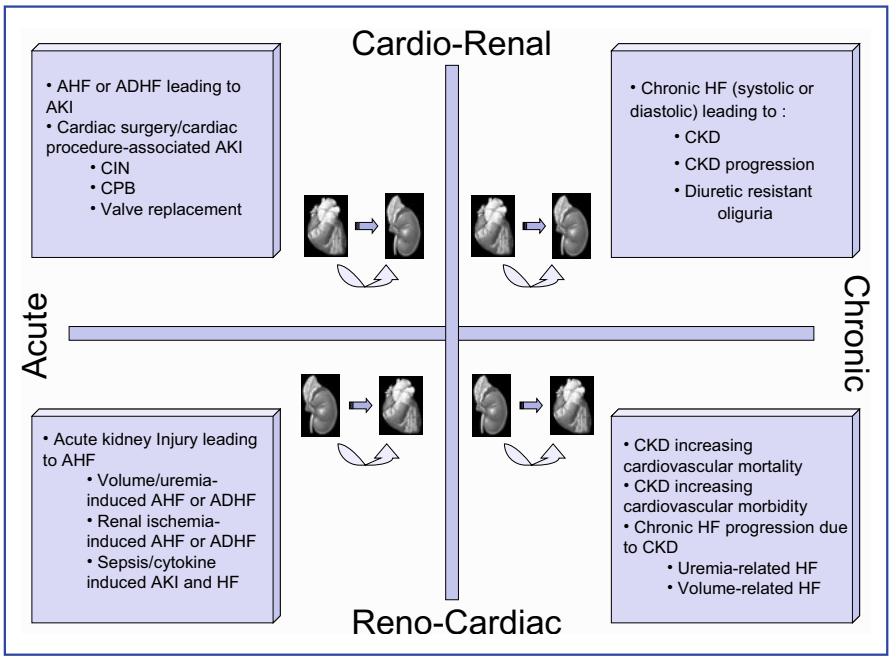


Fig. 1. Cardio-renal syndrome domain map. The time frame and the bidirectionality of the different syndromes are described in the different subtypes (acute and chronic/cardio-renal and reno-cardiac). Every syndrome is then susceptible to transformation into another due to development of vicious circles. HF: heart failure; CKD: chronic kidney disease; AHF: acute heart failure; ADHF: acute decompensated heart failure; CIN: contrast-induced nephropathy; CPB: cardiopulmonary bypass; AKI: acute kidney injury

- Secondary cardio-renal syndromes (CRS Type 5): Systemic conditions causing simultaneous injury, and/or dysfunction of both the heart and kidneys.

The relevant mechanisms are summarized in **Figure 1**.

Epidemiology and Pathophysiology of Cardio-Renal Syndromes

Cardio-renal Syndrome Type I or Acute Cardio-renal Syndrome

Pre-morbid renal dysfunction is common in heart failure patients (*de novo* acute heart failure or acute decompensated heart failure) and predisposes them to AKI, which has been associated with higher risk of prolonged/re-hospitalization, cardiovascular and all-cause mortality, and faster progression to chronic kidney disease (CKD) stage 4–5 [5–9]. Incidence estimates for AKI or worsening renal function associated with acute heart failure and ACS range between 24–45 % and 9–19 %, respectively [4]. The broad range in reported incidence is largely attributable to variations in the definitions of worsening renal function as well as retrospective and/or *post hoc* analyses of data [5–9]. The mechanisms by which the onset of acute heart failure or acute decompensated heart failure leads to AKI are multiple and complex [6]. They have been described in detail in recent publications [3, 4]. The clinical importance of each of these mechanisms is likely to vary

from patient to patient. The mechanisms that have been identified as being involved include: Hemodynamic mechanisms in which a reduced cardiac output, together with an increased renal venous congestion may affect intra-renal circulation and glomerular filtration rate (GFR); neurohormonal biofeedback mechanisms including activation of the renin-angiotensin-aldosterone system (RAAS). A non-osmotic secretion of vasopressin and a parallel sympathetic nervous system-mediated vasoconstriction may lead to perpetuation and extension of the primary insult. We may also suggest immune-mediated damage in which the activation of monocytes and the direct effect of pro-inflammatory mediators may play an important role in renal tissue apoptosis and damage [10]. Finally, exogenous nephrotoxic agents such as contrast media, aminoglycosides, diuretics or angiotensin converting enzyme (ACE) inhibitors may represent another important source of kidney insult in patients with acute heart failure or acute decompensated heart failure.

Cardio-renal Syndrome Type 2 or Chronic Cardio-renal Syndrome

Patients with chronic heart failure with secondary worsening renal failure have significantly increased adverse cardiovascular mortality and prolonged hospitalization. However, chronic heart disease and CKD frequently coexist in the same patient, and often the clinical scenario does not allow one to distinguish which disease came first. Notably, about 45 to 64 % of patients with chronic heart failure have evidence of CKD with estimated GFR (eGFR) < 60 ml/min/1.73m^2 [11, 12]. The mechanisms causing secondary worsening renal failure in these patients likely differ from those in cardio-renal syndrome type 1. Concomitant hemodynamic alterations with poor cardiac contractility, and neurohormonal abnormalities with excessive production of vasoconstrictive mediators (epinephrine, angiotensin, endothelin) as well as altered sensitivity and/or release of endogenous vasodilatory factors (natriuretic peptides, nitric oxide [NO]) are commonly present in patients with chronic heart failure. Hence, kidneys that are chronically hypoperfused will be highly susceptible to any minor or major insults. Genetic and acquired micro- or macrovascular risk factors, such as diabetic mellitus, hypertension, dyslipidemia, may contribute to initiate and perpetuate the kidney damage. Moreover, subclinical inflammation, endothelial dysfunction and accelerated atherosclerosis, determine progressive sclerosis and fibrosis in the kidney tissue with a progressive loss of nephrons. These processes result in an initial phase of CKD that contributes to pathological conditions such as anemia, calcium-phosphate abnormalities, reduction in vitamin D receptor activation, hyperparathyroidism and hypertension. A vicious cycle is activated and a combined worsening of heart and kidney function inevitably occurs.

Cardio-renal Syndrome Type 3 or Acute Reno-cardiac Syndrome

The development of AKI as a primary event subsequently leading to cardiac injury and/or dysfunction has been recently observed with high prevalence. Type 3 cardio-renal syndrome is associated with poor short- and long-term outcomes. Unfortunately, it has not been systematically evaluated or studied because of the heterogeneity in the etiology of AKI, variability in the definition of AKI, and the failure of many clinical studies of AKI to report the occurrence of acute cardiac dysfunction as an outcome. AKI can affect the heart through several pathways.

Fluid overload can contribute to the development of pulmonary edema. Electrolyte imbalances, such as hyperkalemia, can contribute to arrhythmias, which may cause cardiac arrest. Untreated uremia affects myocardial contractility through the accumulation of myocardial depressant factors, pulmonary vasoconstriction and/or pericarditis [13]. In addition, renal ischemia itself may induce inflammatory-mediated cardiac injury via cytokine induction, leukocyte infiltration, apoptosis [14]; a central role of the monocyte may also be envisaged. If AKI is severe and renal replacement therapy (RRT) is necessary, conventional hemodialysis with rapid fluid and electrolyte shifts can induce hypotension, arrhythmias, and myocardial ischemia. Continuous RRT (CRRT), which minimizes such cardiovascular instability, appearsd physiologically safer and more logical in this setting.

Cardio-renal Syndrome Type 4 or Chronic Reno-cardiac Syndrome

CKD is classified in five stages. Several studies have evaluated the cardiovascular outcomes in selected CKD-specific populations [15–18]. Increasing evidence shows that CKD leads to myocardial interstitial fibrosis, ventricular hypertrophy, systolic and diastolic dysfunction [17, 18]. CKD is an independent risk factor for cardiovascular outcomes in patients with and without chronic heart failure and post-cardiac surgery. Even moderate degrees of renal insufficiency are independently associated with an increased risk of death in patients with heart failure and left ventricular (LV) systolic dysfunction. It is well understood that patients with moderate to severe renal insufficiency not only carry a high burden of traditional cardiovascular risk factors, but also are exposed to uremia-specific risk factors that in concert induce an excessively increased cardiovascular mortality [18]. Uremia, acidosis, inflammation, malnutrition, endothelial dysfunction, anemia and calcium-phosphate abnormalities seems to play an important role in this setting. When patients are on dialysis, specific cardiovascular events may arise from subclinical inflammation, chronic exposure with artificial biomaterials, dialysate impurity and infection at the vascular access site.

Cardio-renal Syndrome Type 5 or secondary Cardio-renal Syndrome

There are limited data on the epidemiology of secondary cardio-renal syndrome in general due to the large number of potentially contributing acute and chronic systemic conditions affecting the kidneys and the heart. Although there is an appreciation that, as more organs fail, mortality increases in critical illness, there is limited insight into how combined renal and cardiovascular failure may differently affect such outcome compared to, for example, combined pulmonary and renal failure. Nonetheless, it is clear that several acute and chronic diseases can affect both organs simultaneously and that the disease induced in one can affect the other and *vice versa*. In the acute setting, severe sepsis represents the most common and serious condition that can affect both organs. Severe sepsis can induce AKI while leading to profound myocardial depression. The mechanisms responsible for such changes are poorly understood but they may involve the effects of tumor necrosis factor (TNF) and other humoral mediators on both organs [19, 20]. A different series of mechanisms are involved in chronic systemic disorders, such as amyloidosis or diabetes, where the combined damage is likely to be due to severe endothelial dysfunction and accelerated atherosclerosis.

A description of the epidemiology and pahophysiology of heart-kidney interaction, stratified by the cardio-renal syndrome subtypes, is a critical initial step towards understanding the overall burden of disease for each cardio-renal syndrome subtype, their natural history, associated morbidity and mortality, potential prevention or treatment strategies and health resource implications.

Biomarkers in Cardio-renal Syndromes

Recent studies have attempted to evaluate the utility of biomarkers for assessing CKD risks in cardiovascular disease patients and cardiovascular risks in CKD patients [21–25]. There seems to be a crucial role of biomarkers in the early diagnosis of evolving heart failure or AKI in different subtypes of cardio-renal syndrome. Evaluation of biomarkers may allow earlier changes in management, such as stopping harmful interventions or starting therapeutic interventions and protective/preventive strategies. Biomarkers could also help make a more accurate differential diagnosis of heart failure and AKI facilitating prognostic stratification of the disorders, staging of disease, and assessment of current and future severity of injury.

Several cardiac biomarkers, like brain natriuretic peptides (BNPs), troponins, myeloperoxidase, asymmetric dimethylarginine, plasminogen-activator inhibitor type I, homocysteine, C-reactive protein (CRP), creatine kinase (CK)-MB, myoglobin, serum amyloid A protein, ischemia modified albumin and advanced glycation end-products, have been demonstrated to correlate with cardiovascular outcomes in CKD patients [21–27]. It is well known that troponins correlate with the severity of cardiac injury, even in the absence of typical clinical features [23, 25]. BNPs are elevated in patients with cardio-renal syndrome type 1 in which AKI occurs as a consequence of acute heart failure or acute decompensated heart failure. Importantly, both troponins and BNPs have shown prognostic utility in patients with various stages of renal insifficiency [22–24, 26–28]. Recently, Hayashi et al. reported that troponin T (TnT) was a useful screening tool for asymptomatic coronary artery disease in patients with CKD [29]. Furthermore, elevated TnT and NT-pro BNP levels were correlated with hypervolemia and could identify a subgroup of end-stage renal disease patients with 2 to 5 fold increase in mortality, despite being asymptomatic [30]. In chronic peritoneal dialysis patients, NT-pro BNP was a marker of LV dysfunction and cardiovascular congestion, which was associated with high cardiovascular and all-cause mortality [31].

Renal biomarkers like cystatin C and neutrophil gelatinase-associated lipocalin (NGAL) have recently been evaluated as diagnostic and prognostic markers for cardiovascular outcomes in CKD patients [32–36]. Higher levels of cystatin C have been showed to be directly involved in the atherosclerotic process [36] and were associated with increased LV mass and concentricity independent of renal function [37]. Cystatin C appears to be a marker of cardiovascular risk at intermediate term follow-up of patients with ACS or acute decompensated heart failure [38, 39]. Similarly, increased NGAL expression has been demonstrated in atherosclerotic plaque and failing myocardium in patients with coronary artery disease or heart failure [40, 41]. NGAL levels were significantly higher in the presence of these disorders and were correlated with disease severity independent of coexisting renal injury [41, 42]. Patients with acute decompensated heart failure with an elevated admission serum NGAL had a higher risk of worsening renal

failure [33]. In a small study on 46 elderly chronic heart failure patients, higher levels of plasma NGAL were found in parallel with the clinical severity of chronic heart failure, the highest levels being reached in NYHA class IV patients and these were associated with higher mortality [35]. Several studies have demonstrated a significant rise in NGAL levels in AKI patients secondary to cardiac surgery, sepsis, ischemia, or nephrotoxins [43].

Management of Cardio-renal Syndromes

Because the pathophysiology of cardio-renal syndromes is complex, multimodality preventive and therapeutic strategies working via multiple targets are needed. Currently, there are no guidelines for managing patients with AKI or cardio-renal syndromes. Physicians should rely on knowledge accumulated for the treatment of the individual organ diseases [44–46]. Hopefully, the new cardio-renal syndrome classification will help in the design of trials necessary to generate the missing evidence in this field.

In patients with cardio-renal syndromes type 1 and 2, elimination of cause and/or disease leading to cardiac damage and heart failure progression, coronary artery disease risk factor modification, blood pressure control, compliance with dietary sodium restriction, and drug treatments are crucial steps in management. The main drugs consist of RAAS blockers and beta-adrenergic blockers to mitigate the overactivation of the RAAS and sympathetic system in these groups of patients, unless contraindicated [44, 47–49]. Vasodilators and loop diuretics are widely used in cases of acute decompensated heart failure [50]. However, these drugs do carry some risks in worsening renal function. Other drugs, like vasopressin receptor 2 antagonists, phosphodiesterase inhibitors (milrinone), and lusitropic agents (levosimendan) have been used in some cases but without any clear survival benefit. Extracorporeal ultrafiltration may be useful in acute heart failure associated with diuretic resistance, resulting in significant fluid removal and weight loss. If systemic hypotension persists, then inotropic agents may be considered, along with elective ventilation and/or intra-aortic balloon pumping. Depending upon pre-existing co-morbidity and the underlying etiology, LV assist devices may be needed as a bridge to transplantation or cardiac surgery. Cardiac re-synchronization therapy is now recommended for symptomatic chronic heart failure patients (NYHA III-IV) with poor LV ejection fraction (LVEF) and QRS prolongation [44], and implantable cardiac defibrillators for survivors of cardiac arrest and/or sustained ventricular arrhythmias and also for symptomatic chronic heart failure patients with impaired LVEF.

In patients with cardio-renal syndrome type 3 and 4, the clinical problem is often sodium and water retention. Prompt and adequate treatment of hypervolemia may help prevent cardiac decompensation. Uremic abnormalities and hyperkalemia may further contribute to secondary heart dysfunction and every effort should be made to avoid advanced disorders. Mediators of inflammation in renal ischemia [14] have also been suspected to play an important role in negative organ cross-talk with the heart. Strategies directed towards decreasing these mechanisms should be attempted in order to reduce the combination of multiple factors in the pathogenesis of heart dysfunction. Moreover, it is important to retard the progression of CKD, which may result in cardioprotective strategies. Early treatment of anemia, minimizing vascular calcification and vitamin D

receptor abnormalities may help to prevent progression of CKD and may help limit cardiovascular complications. Special measures, such as use of biocompatible materials, convective therapy and ultrapure dialysate, can also be implemented to reduce the incidence of cardiovascular complications in hemodialysis patients leading to reduced rates of type 4 cardio-renal syndrome.

Finally, in patients with cardio-renal syndrome type 5, treatment of the primary illness (diabetes mellitus, amyloidosis, sepsis, rhabdomyolysis, hemorrhagic shock, etc) generally improves both heart and kidney function.

Conclusion

The new definition and classification system for cardio-renal syndromes seems to represent an important advance and spur new interest in a collaborative nephrological-cardiological effort. The complexity of cardio-renal syndromes and the specificity of care necessary to offer best therapy to these patients demand a multidisciplinary approach, combining the expertise of cardiology, nephrology, and critical care medicine. This multidisciplinary effort should facilitate a better appreciation of the interaction between heart and kidneys during dysfunction of each or both organs with significant practical clinical implications. Epidemiological studies in different settings could be carried out classifying patients according to specific disorders or cardio-renal syndrome subtypes. Investigators can identify aspects of each single syndrome subtype that carry clear priorities for further research. It is true that patients may move from one subtype to another but this should not discourage categorization of a patient in a specific timeframe of his/her medical history. It may be difficult to distinguish between type 2 and type 4 cardio-renal syndrome in some cases but careful discussion about prevention and therapeutic priorities should anyway be made collegially between nephrologists and cardiologists. Hopefully, all these efforts will contribute to an increased awareness and physiological understanding leading to some innovative therapeutic approaches and possibly to improved clinical outcomes.

References

1. Ronco C (2008) Cardiorenal and renocardiac syndromes: clinical disorders in search of a systematic definition. Int J Artif Organs 31: 1–2
2. Ronco C, House AA, Haapio M (2008) Cardiorenal syndrome: refining the definition of a complex symbiosis gone wrong. Intensive Care Med 34: 957–962
3. Ronco C, Haapio M, House AA, Anavekar N, Bellomo R (2008) Cardiorenal syndrome. J Am Coll Cardiol 52: 1527–1539
4. Ronco C, McCullough P, Anker SD, et al (2010) Cardio-renal syndromes: report from the consensus conference of the acute dialysis quality initiative. Eur Heart J 31: 703–711
5. Adams KF Jr, Fonarow GC, Emerman CL, et al (2005) Characteristics and outcomes of patients hospitalized for heart failure in the United States: rationale, design, and preliminary observations from the first 100,000 cases in the Acute Decompensated Heart Failure National Registry (ADHERE). Am Heart J 149: 209–216
6. Liang KV, Williams AW, Greene EL, Redfield MM (2008) Acute decompensated heart failure and the cardiorenal syndrome. Crit Care Med 36 (Suppl 1): S75–88
7. Gottlieb SS, Abraham W, Butler J, et al (2002) The prognostic importance of different definitions of worsening renal function in congestive heart failure. J Card Fail 8: 136–141
8. Newsome BB, Warnock DG, McClellan WM, et al (2008) Long-term risk of mortality and end-stage renal disease among the elderly after small increases in serum creatinine level during hospitalization for acute myocardial infarction. Arch Intern Med 168: 609–616

9. Goldberg A, Hammerman H, Petcherski S, et al (2005) Inhospital and 1-year mortality of patients who develop worsening renal function following acute ST-elevation myocardial infarction. Am Heart J 150: 330 – 337
10. Cao Z, Cooper ME (2001) Role of angiotensin II in tubulointerstitial injury. Semin Nephrol 21: 554 – 562
11. Hillege HL, Nitsch D, Pfeffer MA, et al (2006) Renal function as a predictor of outcome in a broad spectrum of patients with heart failure. Circulation 113: 671 – 678
12. Heywood JT, Fonarow GC, Costanzo MR, et al (2007) High prevalence of renal dysfunction and its impact on outcome in 118,465 patients hospitalized with acute decompensated heart failure: a report from the ADHERE database. J Card Fail 13: 422 – 430
13. Meyer TW, Hostetter TH (2007) Uremia. N Engl J Med 357: 1316 – 1325
14. Kelly KJ (2006) Acute renal failure: much more than a kidney disease. Semin Nephrol 26: 105 – 113
15. McCullough PA, Jurkovitz CT, Pergola PE, et al (2007) Independent components of chronic kidney disease as a cardiovascular risk state: results from the Kidney Early Evaluation Program (KEEP). Arch Intern Med 167: 1122 – 1129
16. Go AS, Chertow GM, Fan D, et al (2004) Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med 351: 1296 – 1305
17. Gross ML, Ritz E (2008) Hypertrophy and fibrosis in the cardiomyopathy of uremia--beyond coronary heart disease. Semin Dial 21: 308 – 318
18. Remppis A, Ritz E (2008) Cardiac problems in the dialysis patient: beyond coronary disease. Semin Dial 21: 319 – 325
19. Cunningham PN, Dyanov HM, Park P, Wang J, Newell KA, Quigg RJ (2002) Acute renal failure in endotoxemia is caused by TNF acting directly on TNF receptor-1 in kidney. J Immunol 168: 5817 – 5823
20. Kumar A, Paladugu B, Mensing J, et al (2007) Nitric oxide-dependent and -independent mechanisms are involved in TNF-alpha -induced depression of cardiac myocyte contractility. Am J Physiol Regul Integr Comp Physiol 292: R1900 – 1906
21. Parikh SV, de Lemos JA (2006) Biomarkers in cardiovascular disease: integrating pathophysiology into clinical practice. Am J Med Sci 332: 186 – 197
22. Carr SJ, Bavanandan S, Fentum B, et al (2005) Prognostic potential of brain natriuretic peptide (BNP) in predialysis chronic kidney disease patients. Clin Sci (Lond) 109: 75 – 82
23. Howie-Esquivel J, White M (2008) Biomarkers in acute cardiovascular disease. J Cardiovasc Nurs 23: 124 – 131
24. Needham DM, Shufelt KA, Tomlinson G, Scholey JW, Newton GE (2004) Troponin I and T levels in renal failure patients without acute coronary syndrome: a systematic review of the literature. Can J Cardiol 20: 1212 – 1218
25. Cameron SJ, Sokoll LJ, Laterza OF, Shah S, Greene GB (2007) A multi-marker approach for the prediction of adverse events in patients with acute coronary syndromes. Clin Chim Acta 376: 168 – 173
26. Sommerer C, Beimler J, Schwenger V, et al (2007) Cardiac biomarkers and survival in haemodialysis patients. Eur J Clin Invest 37: 350 – 356
27. Austin WJ, Bhalla V, Hernandez-Arce I, et al (2006) Correlation and prognostic utility of B-type natriuretic peptide and its amino-terminal fragment in patients with chronic kidney disease. Am J Clin Pathol 126: 506 – 512
28. Hickman PE, McGill DA, Talaulikar G, et al (2009) Prognostic efficacy of cardiac biomarkers for mortality in dialysis patients. Intern Med J 39: 812 – 818
29. Hayashi T, Obi Y, Kimura T, et al (2008) Cardiac troponin T predicts occult coronary artery stenosis in patients with chronic kidney disease at the start of renal replacement therapy. Nephrol Dial Transplant 23: 2936 – 2942
30. Codognotto M, Piccoli A, Zaninotto M, et al (2010) Effect of a dialysis session on the prognostic values of NT-proBNP, troponins, endothelial damage and inflammation biomarkers. J Nephrol 23: 465 – 471
31. Wang AY, Lam CW, Yu CM, et al (2007) N-terminal pro-brain natriuretic peptide: an independent risk predictor of cardiovascular congestion, mortality, and adverse cardiovascular outcomes in chronic peritoneal dialysis patients. J Am Soc Nephrol 18: 321 – 330

32. Iwanaga Y, Miyazaki S (2010) Heart failure, chronic kidney disease, and biomarkers--an integrated viewpoint. Circ J 74: 1274 – 1282
33. Aghel A, Shrestha K, Mullens W, et al (2010) Serum neutrophil gelatinase-associated lipocalin (NGAL) in predicting worsening renal function in acute decompensated heart failure. J Card Fail 16: 49 – 54
34. Poniatowski B, Malyszko J, Bachorzewska-Gajewska H, et al (2009) Serum neutrophil gelatinase-associated lipocalin as a marker of renal function in patients with chronic heart failure and coronary artery disease. Kidney Blood Press Res 32: 77 – 80
35. Bolignano D, Basile G, Parisi P, et al (2009) Increased plasma neutrophil gelatinase-associated lipocalin levels predict mortality in elderly patients with chronic heart failure. Rejuvenation Res 12: 7 – 14
36. Ix JH, Shlipak MG, Chertow GM, et al (2007) Association of cystatin C with mortality, cardiovascular events, and incident heart failure among persons with coronary heart disease: data from the Heart and Soul Study. Circulation 115: 173 – 179
37. Patel PC, Ayers CR, Murphy SA, et al (2009) Association of cystatin C with left ventricular structure and function: the Dallas Heart Study. Circ Heart Fail 2: 98 – 104
38. Taglieri N, Fernandez-Berges DJ, Koenig W, et al (2010) Plasma cystatin C for prediction of 1-year cardiac events in Mediterranean patients with non-ST elevation acute coronary syndrome. Atherosclerosis 209: 300 – 305
39. Campbell CY, Clarke W, Park H, Haq N, Barone BB, Brotman DJ (2009) Usefulness of cystatin C and prognosis following admission for acute heart failure. Am J Cardiol 104: 389 – 392
40. Hemdahl AL, Gabrielsen A, Zhu C, et al (2006). Expression of neutrophil gelatinase-associated lipocalin in atherosclerosis and myocardial infarction. Arterioscler Thromb Vasc Biol 26: 136 – 142
41. Yndestad A, Landro L, Ueland T, et al (2009) Increased systemic and myocardial expression of neutrophil gelatinase-associated lipocalin in clinical and experimental heart failure. Eur Heart J 30: 1229 – 1236
42. Zografos T, Haliassos A, Korovesis S, et al (2009) Association of neutrophil gelatinase-associated lipocalin with the severity of coronary artery disease. Am J Cardiol 104: 917 – 920
43. Mori K, Nakao K (2007) Neutrophil gelatinase-associated lipocalin as the real-time indicator of active kidney damage. Kidney Int 71: 967 – 970
44. Dickstein K, Cohen-Solal A, Filippatos G, et al (2008) ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the diagnosis and treatment of acute and chronic heart failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). Eur J Heart Fail 10: 933 – 989
45. National Kidney Foundation (2002) K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis 39 (2 Suppl 1): S1 – 266
46. Taal M, Tomson C (2008) Clinical practice quidelines. Module 1. Chronic kidney disease. Available at: http://www.renal.org/Libraries/Old_Guidelines/Module_1_-_Chronic_Kidney_Disease_CKD_-_4th_Edition.sflb.ashx Accessed Nov 2010
47. Bangalore S, Messerli FH, Kostis JB, et al (2007) Cardiovascular protection using beta-blockers: a critical review of the evidence. J Am Coll Cardiol 50: 563 – 572
48. Pfeffer MA, Swedberg K, Granger CB, et al (2003) Effects of candesartan on mortality and morbidity in patients with chronic heart failure: the CHARM-Overall programme. Lancet 362: 759 – 766
49. Pitt B, Zannad F, Remme WJ, et al (1999) The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. N Engl J Med 341: 709 – 717
50. Hollenberg SM (2007) Vasodilators in acute heart failure. Heart Fail Rev 12: 143 – 147

Blood Purification in Sepsis and Acute Kidney Injury in Critically Ill Patients

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Introduction

Despite major advances in blood purification therapies, numerous questions remain. As a result, clinicians may still have some hesitation regarding the real efficacy of these techniques in sepsis as well as the best mode of hemofiltration therapy when treating patients with septic shock plus acute kidney injury (AKI) [1]. However, despite major recent therapeutic improvements, septic shock remains a leading cause of mortality in intensive care patients [2]. In addition, according to the latest available literature, it is of paramount importance to realize that the mortality rate of patients with septic AKI is much higher compared to that of patients with non-septic AKI [3, 4]. In the last decade, several milestone studies [5, 6] have shown that dose of therapy is important in terms of mortality, although recent so-called negative trials have challenged this concept. Nevertheless, a critical dose is still desirable and beyond that dose, mortality will be affected [7, 8]. We should not forget, however, that these studies carry some very important limitations [9, 10]. Regarding specifically rationale, it seems at least theoretically reasonable that effectively removing mediators from the tissue, where they are harmful, and transporting them to the central circulation must be effective. Effectiveness through only a passive transportation mechanism remains elusive. Indeed, the surface of the central blood compartment is about 30 m^2, which is much smaller than the surface of the capillary blood compartment, which is about 300 m^2 [11], so that passive transport between these two asymmetric compartments will not yield the same elimination rate on both sides. As a consequence, when a given technique is able to remove 40 % of the mediators from the central blood compartment, it will only represent 4 % of the removal into the capillary blood compartment if the removal is only a passive mechanism (**Fig. 1**). It is, therefore, easy to understand, that another, active transportation mechanism has to take place [11]. This chapter will review the most recent insights regarding rationale and especially the 'new active transportation between two asymmetric compartments' hypothesis [11] and will also review the strengths and the weaknesses of the so-called recent negative studies regarding dose of continuous renal replacement therapy (CRRT) in critically ill patients.

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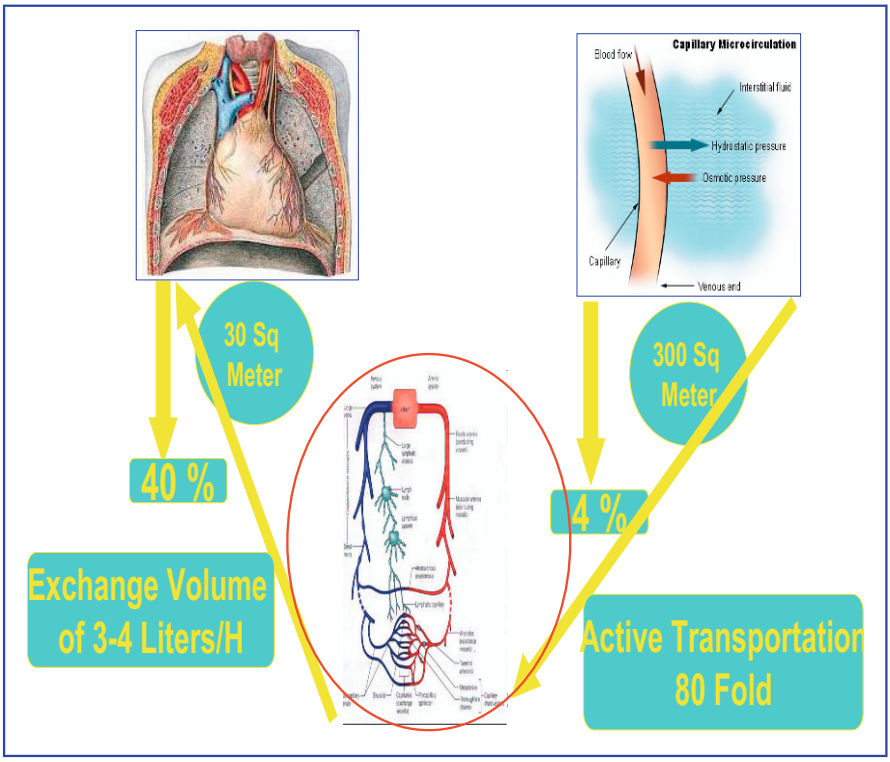

Fig. 1. The 'active transportation' hypothesis. From [15] with permission

'New Active Transportation between two Asymmetric Compartments' Hypothesis and New Insights into Rationale and Potential Mechanisms

Pro-mediators as well as mediators are removed at interstitial and tissue levels following removal from the blood compartment, until a so-called threshold point is reached at which some pathways and cascades are stopped [12]. At this level, the cascades are interrupted and no further harm can be done to the tissues. Until recently, this mechanism was believed to be a passive transportation pathway. As mentioned in the introduction, effectiveness through only a passive transportation mechanism remains elusive. Indeed, as discussed, passive transport between the asymmetric central and capillary blood compartments will not yield the same elimination rate on both sides [11]. The potential beneficial use of high volume hemofiltration (HVHF) and especially of high replacement volumes (3 to 5 liters/hour) has been emphasized in recent years [13, 14], but mainly for increasing immunomodulation of septic shock, most probably – although not proven – by increasing removal of middle and large molecules [13, 14]. It is only very recently that it has been shown that high replacement volumes (3 to 5 liters/hour) used during hemofiltration cannot only remove but can also displace mediators throughout the body [15, 16]. Indeed, this technique can induce a 20- to 80-fold increase in lymphatic flow [15–18]. This finding can result in a concomitant

substantial drag and displacement of mediators and cytokines to the blood compartment where they become available for removal. Thus, the use of high volumes of replacement fluid might be of great importance, not only for extraction but also to stimulate lymphatic transport between the interstitium and tissue compartments and the blood compartment although these are very asymmetric compartments. Once these mediators are in the lymphatic system, they will be available in the central blood compartment but inside the lymphatic compartment, they will also be available for removal by the liver and the reticulo-endothelial system which have an extremely large capacity of storage and may work as buffer storage. Indeed, these systems will be able to absorb huge quantity of mediators during a storm and releasing them during the aftermath in order to make them available somewhat later for further removal by hemofiltration [19]. Obviously, confirmation of this new working hypothesis requires several experiments (which are underway) and these should incorporate the latest technology, including nuclear imaging techniques, in order to effectively trace the mediators from the tissue, through the lymphatic circulation and inside the central blood compartment [20]. Another more invasive procedure would be to catheterize the thoracic duct in order to collect the lymph and to make direct measurements of mediators from time to time as was performed in the past when treating severe acute pancreatitis [21]. Another possibility would be to measure indirect markers of mediator activity at the tissue level. Indeed, markers of apoptosis and oxidative stress occurring in the tissue, especially inside the inflammatory cells, may be a good alternative in place of direct measurements [22]. In recent years, Kellum et al. have provided additional evidence [23]. These investigators induced sepsis in a rat model and randomly assigned the animals to hemofiltration or sham in order to assess the effect on liver production of mediators through nuclear factor-kappa B (NF-κB) production. Application of hemofiltration improved not only hemodynamics but also survival. These experiments also demonstrated for the first time that hemofiltration was able not only to reduce mediator blood levels but also mediator production in the liver. The exact mechanism of this upstream down-regulated effect remains to be elucidated. Nevertheless, measurement of NF-κB production might also be seen as an indirect tool to measure a reduction in pro-mediator production induced by the immunomodulation related to hemofiltration. Nonetheless, this technique would need the systematic realization of a liver biopsy which is still quite an invasive procedure in critically ill patients.

New Therapeutic Targets Defined by the Latest Findings

Timing of hemofiltration remains a crucial aspect, but recent investigations have clarified the issue somewhat. Indeed, a recently published study by Kellum and co-workers [23] shed new light on this controversial issue. These authors conducted a study (the so-called GenIMS Study for genetic and Inflammatory Markers of Sepsis) in nearly 2,000 patients hospitalized for community acquired pneumonia (CAP) [24]. They evaluated the pro- and anti-inflammatory balance in these patients by measuring the ratio of interleukin (IL)-6 (pro-inflammatory) to IL-10 (anti-inflammatory), and subsequently investigated whether a defined profile of this ratio could be a good predictor of the evolution of CAP into sepsis, septic shock and eventually death. In this study, 31 % of patients developed severe sepsis and 26 % exhibited high circulating levels of cytokines. The highest risk of

death was correlated with a high ratio of pro- and anti-inflammatory cytokine levels (p value < 0.001). As a consequence, a hemofiltration technique, which could lower the pro- and anti-inflammatory cytokine levels, would improve survival whenever the intervention was given (during the hyper-inflammatory phase or during the immuno-paralysis period) by reducing both levels in order to recover a better immune homeostasis [24]. Hence, the technique can be performed irrespective of the status of inflammation in patients during their stay in an intensive care unit (ICU) [11, 19].

Recent Positive Studies regarding Blood-Purification for Acute Kidney Injury in the ICU

The pioneer study on dosing blood purification in the ICU was set up by Ronco and co-workers in a study publish in the *Lancet* in the early 2000s [5]. This prospective randomized controlled study of 425 patients compared three doses of therapy: 20, 35 and 45 ml/kg/h in ICU patients with AKI. Survival in the 35 ml/kg/h and 45 ml/kg/h groups was significantly higher than in the 20 ml/kg/h group with a difference of nearly 20 % and p values of 0.0007 and 0.0013, respectively. In addition to this finding, the study also showed that in the 35 and 45 ml/kg/h groups, survivors had a significantly lower urea at start when compared to non-survivors, suggesting that timing was also important in that study [5, 11]. Moreover, with this study, the foundations for the high volume technique were also laid by Ronco who showed that in their subgroup of sepsis patients, increasing the volume of treatment from 35 to 45 ml/kg/h could improve outcome, thus suggesting that septic AKI should be handled differently [5, 25]. That study effectively demonstrated that hemofiltration could be considered as a viable medication in the ICU. The volume of treatment not only has to be adapted to body weight but also to the severity and type of illness of the ICU patient (septic or non-septic AKI). Finally, the authors also looked at renal recovery; the percentages of complete renal recovery were 95, 92 and 90 %, for the three doses respectively, suggesting also that dosing might affect renal recovery. The pivotal study was further confirmed by the trial by Saudan et al. [6]. In this prospective randomized study in ICU patients with AKI, the authors compared two doses of CRRT. The first group started with continuous veno-venous hemofiltration (CVVH) alone at a dose of 25 ml/kg/h and the second group started with CVVH at a dose of 25 ml/kg/h plus continuous veno-venous hemodiafiltration (CVVHDF) at 18 ml/kg/h, giving a total dose of 42 ml/kg/h, very comparable to the 35 ml/kg/h dose in the Ronco study. It was, therefore, not surprising to see that the survival rates at 28 days were 39 % (25 ml/kg/h group) and 59 % (42 ml/kg/h group) (p value < 0.03). Renal recovery was also assessed and was 71 and 78 %, respectively, suggesting again that a higher dose was correlated with a better renal recovery rate. In the same line, a study performed by Schiffl and colleagues [26] but this time evaluating the use of hemodialysis in a prospective randomized fashion in ICU patients with AKI and comparing extended daily dialysis versus every other day dialysis during four hours. The mortality rates at the end of dialysis treatment were 28 % for the daily dialysis group and 46 % for the every other day dialysis group. Renal recovery was also much quicker in the daily dialysis group suggesting that dosing, whatever the technique used, was of paramount importance for renal recovery [27]. As mentioned above, a number of observa-

tional studies [28–30], with higher fluid replacement in CVVH seem to demonstrate an additional beneficial effect of this strategy on survival, although methodological restrictions must be taken into consideration.

Recently, a South American team headed by Cornejo performed a similar observational study with a protocol of pulse HVHF (85 ml/kg/h for 6–8 hours) in 20 septic patients with multiple organ dysfunction syndrome and obtained comparable results [31]. They created an algorithm based on the international recommendations for sepsis treatment and incorporated intermittent HVHF (100 ml/kg/h for a single 12 hour period) as a salvage therapy for patients in refractory septic shock [31]. All these studies were only single center, non-randomized and uncontrolled, but they all showed the same results and proved at least that HVHF can be delivered safely.

Update on Very Recent Negative Trials in Critically ill Patients with AKI

Although all these studies were promising, larger studies and randomized controlled clinical trials were needed, especially regarding dosing and timing of RRT. The results from one such study, the so-called VA/NIH study were published in 2008 [7]. This was a very large and well conducted randomized study comparing two different doses of CRRT (20 versus 35 ml/kg/h) and two different intensities of intermittent RRT depending on the hemodynamic status of the patient. This study was not able to show that intensive renal support in critically ill patients with AKI resulted in decreased mortality, improved recovery of kidney function, or reduced rate of non-renal organ failure as compared with less-intensive therapy. Several criticisms have been formulated against this study [9, 10], notably related to the supposed 35 ml/kg/h dose of CVVH in the intensive treatment group. This group was split into an 18 ml/kg/h dose of dialysis (1500 ml/h) and a 17 ml/kg/h of convection rate, giving an actual dose of roughly 15 ml/kg/h (when taking into account the pre-dilution modality instead of full post-dilution). Additionally, the patients were enrolled in the study and treated relatively late in the course of the illness, as compared to other studies (after a mean of 7 days in the ICU and 10 days in hospital). Of note also, is the fact that more than 65 % of the patients received either intermittent hemodialysis or sustained low efficiency dialysis (SLED) treatment within 24 hours prior to the randomization.

More related to the timing of RRT, a Swedish study published a number of years ago, demonstrated the importance of the initial therapy on the renal recovery rate after AKI in ICU patients [32]. In the same vein, a recent review highlighted that in the recently published VA/NIH (ATN) trial [7], the delay in timing was most probably responsible for the high rate of dialysis dependency [33]. Recently, a multicenter French study evaluated the impact of early hemofiltration in 12 French ICUs [34]. The design was to evaluate the impact of hemofiltration on organ dysfunction, plasmatic cytokines and mortality. The study design was set up in the late 1990s before the Ronco study was published. Therefore, the dose of hemofiltration was fixed (2 liters per hour) regardless of the body weight of the patient. Of the 80 patients enrolled in the study, 76 were included in the study protocol. Patients with severe sepsis or septic shock were included within the first 24 hours following the initial organ failure. The included septic patients did not have any form of AKI when the hemofiltration was started. Randomization was

performed between hemofiltration on top of classical treatment of sepsis or classical treatment of sepsis alone. As the body weight was close to 80 kg, the final dose given was 25 ml/kg/hour and so still far from the 35 ml/kg/hour given in the Ronco study. The primary objective was to evaluate the number, the severity and the duration of organ failure at Day 14 using the SOFA (Sequential Organ Failure Assessment) score. The study had to be prematurely stopped because of an insufficient number of inclusions but also because of the fact that, in the hemofiltration group, the number and severity of organ failures was significantly higher compared to the control group. Nevertheless, no significant differences in mortality were seen at any time between the two groups although there was a trend in favor of the control group. The take home message of this study was that hemofiltration should not be started in classical hyperdynamic septic shock without any kidney injury unless the patient is in refractory septic shock, and the dose of 25 ml/kg/h was not able to improve mortality. Whether a dose of 35 ml/kg/h may improve survival remains to be investigated. Another very recent negative trial is the RENAL (Randomized Evaluation of Normal versus Augmented Level) study conducted by the Anzics investigators in Australia and New-Zealand [8]. In this study, 1508 critically ill patients with AKI were randomized to a dose of CVVHDF of 25 ml/kg/h or a dose of 40 ml/kg/h. The primary objective was to evaluate mortality at 90 days. No difference was observed between the two groups in terms of mortality. Although this trial was very well conducted, two criticisms can be made: First, as 50 % of the dose was given in diffusion, the dose in convection was only 20 ml in the higher intensity group and so a bit far from the 35 ml of the Ronco study. The second comment that can be made is that the study design was for global AKI including septic and non-septic AKI. The study was not really designed to evaluate the dose in septic AKI and even less in septic shock patients with AKI [35]. A take home message of this study was that for non-septic AKI, a dose of 25 ml/kg/h may be sufficient. Another interesting finding of this study when compared to the NIH trial [7] is the fact that because of quasi exclusive use of CRRT instead of intermittent therapies in the RENAL trial and certainly, also due to the early timing of this study, the rate of dialysis dependency was reduced by 50 % in the RENAL study compared to the NIH study [36].

Potential Impact of High Cut-off Membranes in Future Sepsis Trials

Already some years ago, a pilot trial looked at the performance of high cut-off membranes in septic patients with AKI [37]. Thirty patients were randomized into two groups, one with a high cut-off membrane (about 60 kDa) and another with a classical cut-off (about 35 kDa). This study showed that in the high cut-off group, norepinephrine dose was significantly less than in the classical cut-off group ($p < 0.0002$) and the clearance of IL-6 and IL-1 receptor antagonist (IL-1ra) was increased by more that ten fold ($p < 0.0001$).

The first results from a very recently completed randomized study, the so called HICOSS (High Cut-Off Sepsis) study were presented at the 10th WFSCICCM in Florence in 2009 [38]. The design forecast inclusion of 120 patients in septic shock plus AKI randomized to either a conventional membrane or a high cut-off membrane (60 kDa). These patients were treated for five consecutive days using a continuous veno-venous hemodialysis (CVVHD) mode. The primary objective was mortality at 28 days. The study was stopped prematurely because of a lack of

difference between groups after 81 patients had been included. Mortality at day 28 was similar (31 % for the high cut-off group versus 33 %) and there were no differences in terms of vasopressor use, duration of mechanical ventilation, or duration of ICU stay. The only positive finding of the study was a safety issue as there was no difference in albumin levels between groups and this high cut-off membrane is safe. It should be emphasized that the study was realized in CVVHD, a mode in which no synergy can be observed between HVHF and high permeability hemofiltration (HPHF). Indeed, CVVH would be much more efficient at removing mediators and cytokines as shown by another recent study [39]. In this *ex-vivo* study, blood from healthy volunteers was spiked with endotoxin and than randomized to a high cut-off filter of 100 kDa at a dose of 16.6 ml/kg/h or the same filter plus a dose of 80 ml/kg/h. Clearance of cytokines was nearly 10 fold higher in the mixed high cut-off and HVHF group demonstrating a synergy between HVHF and HPHF [39].

What Is the Future for Blood Purification?

Most of the large randomized trials investigating hemofiltration doses in AKI patients are now completed, but the results of one, comparing HVHF with standard CVVH in septic AKI, are still being collected and analyzed. The IVOIRE study (hIgh VOlume in Intensive caRE) compared treatment with CVVH for a period of 96 h at 35 versus 70 ml/kg/h in septic AKI [40, 41]. As reviews showed indirect evidence that early initiation of therapy could be associated with further improvement in mortality, it was decided to start therapy in septic shock at the injury level of the RIFLE classification [42]. The first patient was randomized at the end November 2005 but most centers joined only in mid-2006. The overall primary objective of this study was to assess the effects of early high-volume CVVH (70 ml/kg/h) on 28-day mortality in patients with septic shock complicated by acute renal insufficiency. The secondary objectives were to assess the consequences of hemofiltration on hemodynamic parameters, doses and duration of use of catecholamines, organ failure, duration of artificial ventilation and extravascular lung water, morbidity rate, duration of ICU stay and early mortality (96 h), and mortality after 60 and 90 days. IVOIRE was a randomized multicenter clinical trial. In all cases, patients were treated in accordance with current recommendations in the literature. This study was a superiority trial, aiming to detect a reduction of at least 15 % in mortality rate. An estimated sample size with 240 patients in each arm was calculated to give > 80 % power to detect such a difference at an α of 0.5. The team at the center coordinating the IVOIRE trial conducted two pilot studies to prepare for this trial [43, 44]. The choice of hemofiltration volume in the control group (35 ml/kg/h) was motivated by the latest recommendations in the literature applied to intensive care. The choice for the high-volume group (70 ml/kg/h) was made by consensus, taking into account intensive care practices using this latest technique and the opinion of investigators who were consulted at various congresses, and taking into account that, at present, there is no reference in the literature that allows a specific treatment volume to be selected. The duration of treatment (96 hours) was motivated by the experience of the team and the pilot studies, which were based on the same periods. This duration corresponds to the critical period of septic shock during which treatment has the greatest impact on survival. It is also the duration stipulated for other

sepsis treatments in large studies at present. Block randomization was used by means of a dedicated website. Data regarding losses of trace elements, vitamins, amino acids and other nutrients, apoptosis, oxidative stress, renal repair capacity index, cytokines and mediators and antibiotic pharmacokinetics are being collected as part of this study. By the end of December 2009, more than 140 patients had been randomized with more than 45 patients in the last year. The first interim analysis took place in January 2010. The expected mortality of the first 100 patients according to three severity scores (SOFA, SAPS II and logistic organ dysfunction [LOD]) was 68 % whereas the observed mortality at 28 days was 39 % and at day 90 only 48 %. Hence, the observed global mortality was much less than expected. This low mortality informs the medical community that HVHF is a very safe technique and that the early start (at injury level) may improve mortality. Ongoing analyses will tell us in the near future whether a higher dose of 70 ml is desirable in septic shock plus AKI plus three organ failures. Other details regarding the study can be found at the NCT website [40].

Two other recent studies need to be highlighted. The so-called EUPHAS (Early Use of Polymyxin B Hemoperfusion in Abdominal Sepsis) study tested the impact of polymyxin (PMX) B hemoperfusion on hemodynamics, SOFA score and mortality in 64 patients with abdominal sepsis requiring urgent laparotomy [45]. The patients were randomized into two groups: PMX and control. The PMX group showed a significant improvement in hemodynamics as well an improved mortality at 28 days after adjusting for the initial SOFA score. This very selected group of patients did not exhibit any signs of renal injury. The DO-RE-MI study (Dose Response Multicenter International Collaborative Initiative) was conducted in 30 ICUs in 8 countries [46]. The primary objective was to see the effect of dose of CRRT. Of 15,200 ICU patients, 553 had AKI and were treated with CRRT or intermittent renal replacement therapy (IRRT). There were no differences in mortality between the group treated with less than 35 ml/kg/h versus the group with more than 35 ml/kg/h. The only significant differences between the two groups were in ICU length of stay and duration of mechanical ventilation which were shorter in the group with a dose larger than 35 ml/kg/h. Nevertheless, the major finding of this study is that the delivered dose was significantly less than the prescribed dose. The difference was about 8 ml/kg/h suggesting that we should prescribe about 5 to 10 ml more than our target dose. The exact determination of timing regarding AKI [47] and a better delineation of the type of AKI [48] will represent major challenges in the future of blood purification. Moreover, a better understanding of the immunomodulatory effects of AKI has to be achieved in order to better define the best timing of CRRT [49].

Conclusions and Recommendations for the Clinician at the Bedside

Regarding the use of CRRT in ICU in 2011, it is safe to say that optimalization of delivered dose has a role to play: Therefore an ultrafiltration rate of around 35 ml/kg/h, with adjustment for predilution, can still be recommended for the septic patient with AKI. Recent studies, like the VA/NIH trial, did not have enough power to change this recommendation in view of its shortcomings. The RENAL study, which was conducted perfectly, was not designed to specifically assess the septic AKI population but rather the global critical care AKI population. Finally, the recommendation in septic AKI (and surely in septic shock

patients with AKI) is to keep going with a continuous technique, a pure CVVH mode and at a dose of 35 ml/kg/h while awaiting for the results of other studies, like IVOIRE, to be published. In non-septic AKI, 25 ml/kg/h should be a target dose as demonstrated in the RENAL study. Nonetheless, we have to consider the impact of the DO-RE-MI study suggesting that we should prescribe 5 to 10 ml higher and so perhaps a dose of 30 – 35 ml/kg/h to have a delivered dose of 25 ml/kg/h. In the meantime, we can say that the global results of IVOIRE show that HVHF is safe regarding mortality and that early intervention at the injury level may be warranted in terms of global survival. Further ongoing analyses will inform us in the near future whether a higher dose is better than 35 ml/kg/h in patients with septic shock plus AKI plus three organ failures. Better understanding of the immunomodulatory effects of AKI has to be achieved in order to better define the best timing of CRRT.

References

1. Cerda J, Ronco C (2009) Modalities of continuous renal replacement therapy: technical and clinical considerations. Semin Dial 22: 114 – 122
2. Vincent JL, Atalan HK (2008) Epidemiology of severe sepsis in the intensive care unit. Br J Hosp Med 69: 442 – 443
3. Parmar A, Langenberg C, Wan L, May CN, Bellomo R, Bagshaw SM (2009) Epidemiology of septic acute kidney injury. Curr Drug Targets 10: 1169 – 1178
4. Chvojka J, Sykora R, Karvunidis T, et al (2011) New developments in septic acute kidney injury. Physiol Res (in press)
5. Ronco C, Bellomo R, Homel P, et al (2000) Effect of different doses in continuous veno-venous haemofiltration on outcomes of acute renal failure: A prospective randomised trial. Lancet 356: 26 – 30
6. Saudan P, Niederberger M, de Seigneux S, et al (2006) Adding a dialysis dose to continuous hemofiltration increases survival in patients with acute renal failure. Kidney Int 70: 1312 – 1317
7. Palewsky PM, Zhang JH, O'Connor TZ, et al (2008) Intensity of renal support in critically ill patients with acute kidney injury. N Engl J Med 359: 7 – 20
8. Bellomo R, Cass A, Cole L, et al (2009) Intensity of continuous renal-replacement therapy in critically ill patients, N Engl J Med 361: 1627 – 1638
9. Ronco C, Cruz D, Oudemans van Straaten H, et al (2008) Dialysis dose in acute kidney injury: no time for therapeutic nihilism – a critical appraisal of the Acute Renal Failure Trial Network study. Crit Care 12:308
10. Ronco C, Honoré PM (2008) Renal support in critically ill patients with acute kidney injury. N Engl J Med 359: 1959 – 1962
11. Honoré PM, Joannes-Boyau O, Jacobs R, Solignac M (2010) Blood purification in sepsis: fiction or fact for the clinician. Reanimation 19: 7 – 12
12. Honoré PM, Zydney AL, Matson JR (2003) High volume and high permeability haemofiltration in sepsis. The evidences and the key issues. Care Crit Ill 3: 69 – 76
13. Ronco C, Bellomo R (2002) Acute renal failure and multiple organ dysfunction in the ICU: from renal replacement therapy (RRT) to multiple organ support therapy (MOST). Int J Artif Organs 25: 733 – 747
14. Matson J R, Zydney AR, Honoré PM (2004) Blood filtration: New opportunities and the implications on system biology. Crit Care Resusc 6: 209 – 218
15. Di Carlo JV, Alexander SR (2005) Hemofiltration for cytokine-driven illness: the mediator delivery hypothesis. Int J Artif Organs 28: 777 – 786
16. Olszewski WL (2003) The lymphatic system in body homeostasis : physiological conditions. Lymph Fat Res Biol 1: 11 – 21
17. Onarherim H, Missavage E, Gunther RA, Kramer GC, Reed RK, Laurent TC (1991) Marked increase of plasma hyaluronan after major thermal injury and infusion therapy. J Surg Res 50: 259 – 65

18. Wasserman K, Mayerson HS (1952) Dynamics of lymph and plasma protein and exchange. Cardiologia 21: 296 – 307
19. Honoré PM, Joannes-Boyau O, Boer W, Collin V (2009) High-volume hemofiltration in sepsis and SIRS: current concepts and future prospects. Blood Purif 28: 1 – 11
20. Honoré PM, Joannes-Boyau O (2004) High volume hemofiltration (HVHF) in sepsis : a comprehensive review of rationale, clinical applicability, potential indications and recommendations for future research. Int J Artif Organs 27: 1077 – 1082
21. Dugernier T, Reynaert MS, Deby-Dupont G, et al (1989) Prospective evaluation of thoracic-duct drainage in the treatment of respiratory failure complicating severe acute pancreatitis. Intensive Care Med 15: 372 – 378
22. Mariano F, Cantaluppi V, Stella M, et al (2008) Circulating plasma factors induce tubular and glomerular alterations in septic burn patients. Crit Care 12: R42
23. Kellum JA, Song M, Venkataraman R (2004) Hemoadsorption removes tumor necrosis factor, interleukin-6, and interleukin-10, reduces nuclear factor-kappaB DNA binding, and improves short-term survival in lethal endotoxemia. Crit Care Med 32: 801 – 805
24. Honoré PM, Joannes-Boyau O, Boer W, Collin V, Jennes S (2009) Continuous haemofiltration in 2009: What's new for clinicians regarding: Pathophysiology, technique to be privileged and dose to be recommended. Blood Purif 28: 135 – 143
25. Ronco C, Ricci Z, Bellomo R (2002) Importance of increased ultrafiltration volume and impact on mortality: sepsis and cytokine story and the role for CVVH. EDTNA ERCA J 2: 13 – 18
26. Schiffl H, Lang SM, Fisher R (2002) Daily hemodialysis and the outcome of acute renal failure. N Engl J Med 346: 305 – 310
27. Honoré PM, Joannes-Boyau O, Collin V, Boer W, Gressens B, Janvier G (2008) [Practical daily management of extra-renal continuous removal]. Reanimation 17: 472 – 478
28. Cole L, Bellomo R, Journois D, Davenport P, Baldwin I, Tipping P (2001) High-volume haemofiltration in human septic shock. Intensive Care Med 27: 978 – 986
29. Ratanarat R, Brendolan A, Piccinni P, et al (2005) Pulse-high volume haemofiltration for treatment of severe sepsis: effects on hemodynamics and survival. Crit Care 9: 294 – 302
30. Piccinni P, Dan M, Barbacini S, et al (2006) Early isovolaemic haemofiltration in oliguric patients with septic shock. Intensive Care Med 32: 80 – 86
31. Cornejo R, Downey P, Castro R, et al (2006) High-volume hemofiltration as salvage therapy in severe hyperdynamic septic shock. Intensive Care Med 32: 713 – 722
32. Bell M, SWING, Granath F, Schon S, Ekbom A, Martling CR (2007) Continuous renal replacement therapy is associated with less chronic renal failure than intermittent haemodialysis after acute renal failure. Intensive Care Med 33: 773 – 780
33. Ridel C, Balde MC, Rondeau E, Vinsonneau C (2009) Dose of dialysis in intensive care unit. Reanimation 18: 385 – 396
34. Payen D, Mateo J, Cavaillon JM, Fraisse F, Floriot C, Vicaut E (2009) Hemofiltration and Sepsis Group of the Collège National de Réanimation et de Médecine d'Urgence des Hôpitaux extra-Universitaires. Impact of continuous veno-venous hemofiltration on organ failure during the early phase of severe sepsis: A randomized controlled trial. Crit Care Med 37: 803 – 810
35. Joannes-Boyau O, Honoré PM, Boer W, Collin V (2009) Are the synergistic effects of high-volume haemofiltration and enhanced adsorption the missing key in sepsis modulation? Nephrol Dial transplant 24: 354 – 357
36. Prowle JR, Bellomo R (2010) Continuous renal replacement therapy: recent advances and future research. Nature Rev Nephrol 6: 521 – 529
37. Morgera S, Haase M, Kuss T, et al (2006) Pilot study on the effects of high cutoff hemofiltration on the need for norepinephrine in septic patients with acute renal failure. Crit Care Med 34: 2099 – 2104
38. Honoré PM (2009) Novel therapeutical concepts for extracorporeal treatment of hyperinflammation and sepsis: immunomodulation approach with a novel high cut-off membrane:The SepteX membrane. Proceedings of the 10th WFSCICCM, Florence, S10-S12 (abst)
39. Uchino S, Bellomo R, Goldsmith D, et al (2002) Super high flux hemofiltration : a new technique for cytokine removal. Intensive Care Med 28: 651 – 655
40. Joannes-Boyau O, Honoré PM (2010) Haemofiltration Study: IVOIRE (hIgh VOlume in

Intensive Care). Available at: http://clinicaltrials.gov/ct2/show/NCT00241228?term=ivoire&rank = 1. Accessed Nov 2010
41. Bellomo R, Palevsky P, Bagshaw S, et al (2010) Recent trials in critical care nephrology. Contrib Nephrol 166: 299 – 309
42. Bellomo R, Ronco C, Kellum J, Mehta R, Palevsky P, and the ADQI workgroup (2004) Acute renal failure – definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. Crit Care 8: 204 – 212
43. Honoré PM, Jamez J, Wauthier M, et al (2000) Prospective evaluation of short term high volume isovolemic haemofiltration on the haemodynamic course and outcome in patients with intractable circulatory failure resulting from septic shock. Crit Care Med 28: 3581 – 3587
44. Joannes-Boyau O, Rapaport S, Bazin R, Fleureau C, Janvier G (2004) Impact of high volume hemofiltration on hemodynamic disturbance and outcome during septic shock. ASAIO J 50: 102 – 109
45. Cruz DN, Antonelli M, Fumagalli R, et al (2009) Early use of polymyxin B hemoperfusion in abdominal septic shock: the EUPHAS randomized controlled trial JAMA 301: 2445 – 2452
46. Vesconi R, Cruz DN, Fumagalli R et al (2009) Delivered dose of renal replacement therapy and mortality in critically ill patients with acute kidney injury. Crit Care 13: R57
47. Honoré PM, Joannes-Boyau O, Boer W, Rose T (2010) Real time non-invasive follow-up of acid-base correction by the kidney: A step closer. Minerva Anestesiol 76: 307 – 309
48. Joannes-Boyau O, Honoré PM, Boer W, Rose T (2010) Septic acute kidney injury and inflammatory apoptosis: never a lone ranger. Intensive Care Med 36: 385 – 388
49. Honoré PM, Jacobs R, Boer W, Joannes-Boyau O (2011) Sepsis and AKI: more complex than just a simple question of Chicken and Egg. Intensive Care Med (in press)

VIII Fluids

The Lymphatic Vasculature as a Participant in Microvascular Exchange

J. Scallan and V.H. Huxley

Introduction

Optimal organ function requires the two-way movement of substrates and cell products between the circulatory system and the cells themselves. The common thought is that the circulatory system consists of arteries, arterioles, capillaries, venules and veins and that exchange occurs chiefly across capillaries and the venules. The capillaries, given their thin walls and large number, present a large surface area and are therefore perceived as the primary site for fluid and gas exchange. The venules, also thin walled and numerous, possess only minimal coverage by vascular smooth muscle and are seen as the primary site for the movement of larger solutes up to and including the white cells observed to roll along their walls. In fact, the exchange of solutes occurs across the walls of the arterioles, albeit at lower rates [1], especially in organs such as the heart where significant numbers of cardiac myocytes are far removed from capillaries or venules [2]. Essential elements omitted from the list of constituents of the cardiovascular system are the components of the lymphatic system residing within the organ. These include the blind-end initial lymph sacs, collecting lymphatics, and lymph nodes. As will be discussed further, for materials to move from the vascular and tissue compartments, the barriers must possess a finite permeability. In addition, unlike what is presented in the textbooks, all fluid that filters from the vascular space into the tissue space is not reabsorbed back across the same barrier [3]. Obviously, that fluid and accompanying solute must be transported back into the vascular space, otherwise edema occurs and tissue function is lost. It is known that the lymphatic vasculature plays a critical role in the uptake of these materials, but the exact mechanisms whereby this occurs remain to be elucidated more fully. This review provides an overview of recent studies of the contribution of the lymphatic vasculature to the attainment of fluid and solute homeostasis and concludes with consideration of a novel role the lymphatics may play in both health and disease.

Anatomy of the Lymphatic System

Solutes and fluids extravasated from the exchange vasculature form the interstitial fluid that percolates through the interstitial matrix where it enters blind-ended sacs composed of a single endothelial cell layer tethered to the matrix. These bulbous sacs, termed initial lymphatics (also known as terminal lymphatics or lymphatic capillaries), are 10–60 μm in diameter and possess overlapping

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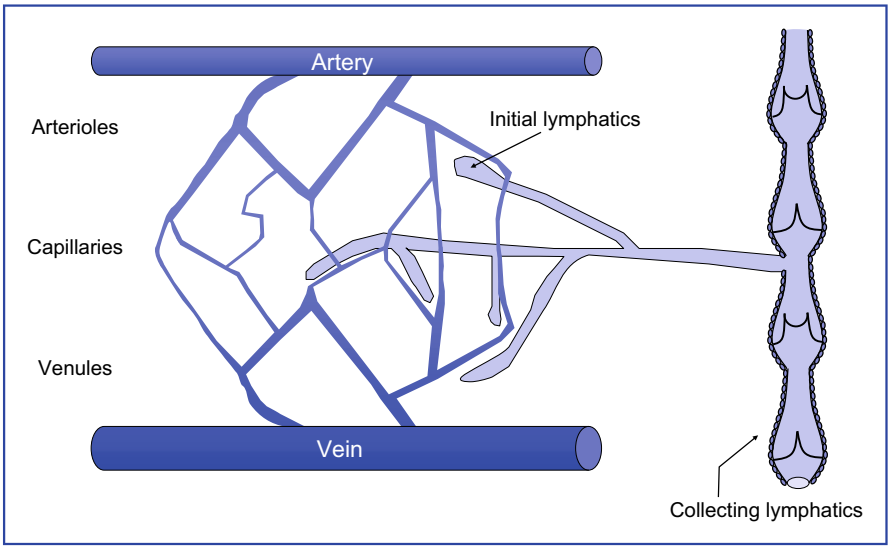

Fig. 1. Idealized schematic of the microvascular and lymphatic vascular anatomy and transport.

endothelial cells that behave collectively as a one-way valve allowing fluid, solute, and cell entry into the vessel lumen. The fluid, thereafter referred to as lymph, moves along vessels of a similar diameter that consist of an endothelial cell layer and basement membrane [3]. Lymph carried by these vessels empties into the larger collecting lymphatic vessels that are 50–200 μm in diameter and are composed of an endothelial cell layer, basement membrane, lymphatic muscle cells, pericytes, and endothelial valves that serve to prevent retrograde lymph flow [4]. Once lymph passes through lymph nodes and then the larger lymphatic ducts, it is finally propelled to the thoracic duct, which empties into the left subclavian vein (**Fig. 1**).

With a cursory glance this anatomy seems like that of the blood vessels, but the mammalian lymphatic vasculature possesses several unique features that enable its function. For instance, the junctional proteins inbetween the endothelial cell of the initial lymphatics are expressed in a punctate manner, unlike the junctional protein expression of the collecting lymphatics, which appear strikingly similar to that of the blood vessels despite their relatively lower expression [5]. This adaptation enables the absorption of fluid, macromolecules, and cells as large as 1–2 μm. The valves of the initial lymphatics also differ from those of the collecting lymphatics in that they consist of overlapping endothelial cells that allow the entry, but not exit, of fluid and solute while the valves of the collecting lymphatics are composed of two modified endothelial cell leaflets that project into the vessel lumen, not unlike valves of the larger mammalian veins. Finally, the lymphatic muscle layer of the collecting lymphatics is unique in that it possesses both tonic and phasic contractile activity [4]. Phasic contractions, also referred to as spontaneous contractions, aid in propelling lymph along the intervalvular segments of the lymphatic vessels, called lymphangions.

The particulars of the anatomical arrangement of the constituents of the lymphatic vessels can vary greatly between organs; therefore the reader is referred to two reviews for further details on this subject [4, 6].

Formation of Lymph

Lymph is the product of the interstitial fluid formed by the extravasation of fluid and solute from the blood microvascular exchange vessels once it has entered into the initial lymphatics. The mechanisms responsible for this process are poorly understood, but two main hypotheses were originally proposed. The first was that an osmotic gradient becomes established across the initial lymphatic wall through sieving of protein that then generates its own convective flow by pulling in protein-containing interstitial fluid *against* a concentration gradient [7]. Despite the appearance of this explanation over three decades ago, very little, if any, experimental support exists for this theory, which is in direct violation of the 2nd law of thermodynamics. Therefore, the ensuing discussion focuses on the 2nd hypothesis, that a hydrostatic pressure gradient is needed to fill the initial lymphatics.

As stated previously, the endothelial cells of the initial lymphatics overlap and are tethered to the surrounding extracellular matrix. This specialized structure minimizes the potential of the initial lymphatic lumen to collapse under a positive pressure difference (i.e., when the interstitial pressure exceeds the luminal pressure). Consequently, on hydration the tissue matrix swells and pulls endothelial cells apart to form ~1–2 μm diameter pores that act like a non-selective one-way valve, trapping fluid, solute, and cells passively [8]. The pores are a consequence of the 'button'-like pattern of endothelial junctional adhesion proteins mentioned earlier, in contrast to the contiguous expression of these molecules in blood vessel and collecting lymphatic endothelium [5]. Interstitial fluid is thus able to access the initial lymphatic lumen with greater ease during edematous states when tissue pressure becomes positive.

A logical conclusion, given the unique structure of the initial lymphatics, is that a pressure gradient across the interstitium is sufficient to drive fluid and solute into the lymphatic vasculature. From the few measurements of interstitial pressures, a gradient of 0.2 to 0.8 cmH_2O has been demonstrated [9, 10]. The magnitude of the pressure gradient appears at first glance to be small, yet a pressure head of only 0.12 cmH_2O has been calculated to be all that is required to drive the capillary filtrate into the low resistance initial lymphatics [11].

One foreseeable drawback to this hypothesis is that interstitial pressures, relative to atmospheric, are routinely measured to be negative which would cause water to flow out of any vessel into the interstitium [12, 13]. Depending on the composition of the fluid bathing the tissue and time after surgery, simultaneous measures of interstitial and initial lymphatic pressures are found to overlap significantly [12]. For the rat mesentery preparation, 30 minutes after exposure during superfusion with oil (to preserve natural tissue hydration) the interstitial and initial lymphatic pressures were -0.2 and -0.25 mmHg, respectively. Therefore, it is possible that a positive pressure gradient can facilitate fluid entry into the initial lymphatics even in the face of a negative interstitial pressure. More current support for this hypothesis has been reported [14].

The existence of a passive interstitial pressure gradient, while sufficient, does not provide a complete description of all the mechanisms contributing to lymph formation. One long-standing study [15] demonstrated that arterial pulsation aided in removal of an interstitial tracer and that when the arterial pressure was held constant, tracer movement ceased. In the conscious *in vivo* bat wing preparation, cyclical dilatation of the venules was found to provide a form of extrinsic

pumping that stimulated intrinsic spontaneous contractions of the collecting lymphatics [16]. Other mechanisms shown to increase local tissue pressure and facilitate lymph formation include respiration, muscle contraction (e.g., peristalsis, walking), elevation of capillary filtration (e.g., venous hypertension, increased capillary permeability), and massage. Opposite to an increase in interstitial pressure, a variant of the hydrostatic pressure hypothesis posits that spontaneously contractile collecting lymphatic lymphangions, during their relaxation phase, are able to generate a suction that draws interstitial fluid into the initial lymphatics [17]. Negative pressures produced by isolated bovine mesenteric collecting lymphatics under 'low filling' states have been reported [18], but direct evidence for transmission of this suction to the initial lymphatics is needed.

Thus, the present consensus is that initial lymphatics passively absorb particles, protein, cells, and fluid from the interstitium through large pores without regard for molecular size. Indeed it has been shown that the lymph protein concentration of initial lymphatics probably approximates the protein concentration of the interstitium [19, 20]. Consensus is replaced by controversy concerning the question of whether the protein concentration of lymph from collecting lymphatics equals that of interstitial fluid; i.e., whether collecting lymphatics possess the ability to concentrate solute along their length [19, 21, 22]. For this to occur, the wall of the collecting lymphatics would have to possess a finite permeability to fluids and solutes.

Microvascular Exchange

Microvessels carrying whole blood transport sugars, proteins, lipids and gases to and from the tissues to support life. To enable this transfer, the vessels participating in this exchange process must be porous – or permeable – to both solute and water. The movement of solutes and fluid from the vascular space is, at the very least, a function of the physiochemical properties (including size, charge, shape, surface area, solubility) of the solutes themselves, the endothelial cell surface glycocalyx, the basement membrane, the vascular mural cells, and the interstitium or ground substance. Permeability and hydraulic conductivity describe the velocity with which solutes and fluids move in response to gradients in concentration or pressure, respectively. Thus, contrary to terminology creeping into the current literature, vessels do not 'get permeability', instead they already possess a finite permeability.

From the strict view of mass transfer, permeability and hydraulic conductivity are constants. In the case of permeability, its maximum value is the free diffusion coefficient of the solute in water divided by the thickness of the exchange barrier. In reality, we know that permeability is not a constant in a living organism – in the extreme we know that permeability increases in response to inflammation and to injury [23]. Further, in recent years it has been shown that a number of vasoactive agents are capable of altering permeability from basal levels acutely [24] and chronically in adaptation to exercise training [25]. In addition it has been shown that amongst the agents that alter permeability, some reduce permeability from basal levels demonstrating that microvascular exchange elements possess a basal exchange 'tone' with the capacity to up- or downregulate solute passage thereby adapting exchange to the metabolic requirements of the tissue. A further implication of this work is that pathophysiology will result not only in the

condition of inflammation or injury, when barrier integrity is lost, but also in the state when permeability is reduced. In this state, tissue function is compromised by failure of substrates to reach the cells or for tissue products to leave and enter the vascular space.

The prior discussion has focused on the permeability characteristics of the exchange microvasculature without inclusion of the role of the lymphatics in the attainment and maintenance of tissue homeostasis. This reflects the lack of data on lymphatic vessel permeability.

Collecting Lymphatics as Exchange Vessels

In general, the anatomy of collecting lymphatic vessels appears similar to that of veins in that they are both low-pressure vessels vested with a muscle layer and intraluminal valves. In support of a theory of lymphatic development proposed by Sabin [26], one group has recently demonstrated that lymphatic endothelial cells are derived directly from the cardinal vein [27]. This finding spurred us to posit the hypothesis that if lymphatics and venules share a common embryologic origin, then they share common functions, e.g., exchange properties.

In fact, one structural similarity between vascular and lymphatic endothelium is the presence of numerous cytoplasmic vesicles [28–30]. To date, a role for these vesicles in solute uptake has not been elucidated fully. Further, whether lymphatic vessels possess other features similar to the vessels carrying whole blood – such as a glycocalyx or *bona fide* caveoli – has yet to be demonstrated. Nor is it known whether lymphatic vessels possess the same receptors to physiological agonists and antagonists as displayed by the blood vasculature. However, that these vessels both possess similar machinery for regulating their transvascular permeability to water and solute leads one to suspect that lymphatic vessels, either initial and/or collecting, are: 1) permeable to solute and water, and 2) able to regulate this permeability to achieve fluid homeostasis.

Some groups have attempted to answer the question of whether or not collecting lymphatic vessels possess a finite permeability to macromolecules. For instance, in the 1960s Mayerson et al. performed experiments in which canine leg lymphatic vessels were infused with radioactive albumin that was recovered at the thoracic duct [34]. The results of these experiments were that only low levels of the infused radioactive macromolecule were detected in blood, thus, it was concluded that lymphatic vessels are virtually impermeable to macromolecules. Perhaps as a consequence of this landmark study, many have now held the belief that lymphatic vessels are not permeable to solute (or fluid for that matter) because such a permeability might negate one of the primary functions of the lymphatic vasculature – to return extravasated fluid and solutes to the blood.

More recently, though, techniques developed for the assessment of microvascular permeability to proteins *in vivo* have been adapted to the study of collecting lymphatic vessels [31–33]. This enabled the examination of vessels isolated from their surrounding tissue or of *in situ* vessels with quantitative fluorescent approaches that are inherently more sensitive than radiometric measures. When isolated collecting lymphatics were assessed for their permeability to different sized molecules conjugated to fluorescent dyes, it was discovered that they were indeed permeable to solute and that the rate of solute movement from the vessel was dependent on the molecular size of the probe [35]. Using a different

approach [36], it was demonstrated that human lymphatic endothelial cells could be cultured in a type I collagen tube with which subsequent permeability assays could be performed. The advantage of this method was that absolute values of permeability were obtained which allows the comparison, through space and time, of the barrier properties for different vessels. Absolute values of permeability are also inherently more accurate than measures of solute flux because the former is a coefficient that takes into account hydrostatic pressure and concentration differences across the vascular wall, as well as the surface area of the vessel that is available for exchange. The permeability values obtained in that study [36] were on average 10-fold greater than those reported for similarly sized venules. The drawback of growing human lymphatic endothelial cells in a collagen tube is that other cell types and barrier components that make up an intact barrier and contribute to the regulation of permeability are missing, namely, pericytes and lymphatic muscle cells. Further, a basement membrane is not present. Therefore, the values reported from these experiments are likely more germane to the barrier properties of initial lymphatic vessels, which are composed of only an endothelial cell layer. A better answer of the relative permeability of lymphatic vessels to other blood microvessels can be gleaned from studies of collecting lymphatic vessels *in vivo*.

One report to date has quantified collecting lymphatic vessel permeability *in vivo* [32]. The hypothesis being tested was that collecting lymphatic permeability to the macromolecule, albumin, would not differ from that of venules of a similar size in the same tissue. Interestingly, it was discovered that collecting lymphatics had the same permeability to albumin as comparable venules (**Fig. 2**). In the same study, the smaller initial lymphatic vessels were also cannulated and perfused with the fluorescently labeled albumin to assess their permeability properties. In agreement with Price et al. [36], the permeability of these smaller lymphatic vessels was 10-fold greater than that of the venules. Thus, much like the blood microvascular network in which arterioles are less permeable than the venules, heterogeneity exists within the lymphatic vascular network in that initial lymphatics possess a higher permeability to solute than do collecting lymphatics.

For these results to make sense physiologically, the function of the lymphatic vasculature must be considered. Initial lymphatics should be more permeable to fluid and solute given that their barrier is much less pronounced. Without continuous junctional protein expression, a basement membrane, or muscle cell coverage, these specialized structures are able to absorb fluid, solutes, and even cells at

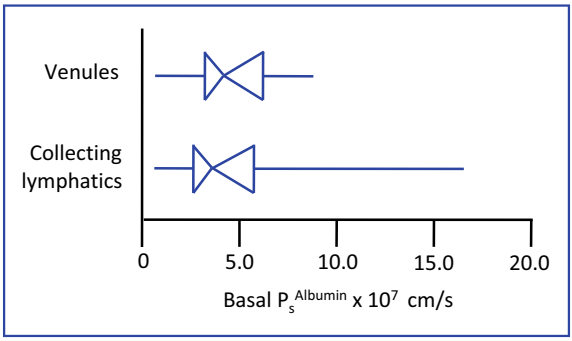

Fig. 2. Comparison of the basal permeability to albumin of venules and collecting lymphatic vessels.

a much faster rate than venules or collecting lymphatics, which possess endothelial cells, basement membrane, and muscle cell layers to impede solute and fluid transport. The collecting lymphatic vessels possess a lower permeability, which is aligned with their main role in transporting the absorbed tissue fluid to the bloodstream.

Yet, the fact remains that collecting lymphatics are as permeable as venules. So what does this mean in terms of where solute and fluid will be distributed? For venules, we know the hydrostatic and osmotic pressure differences across the vessel wall, and that these forces cause fluid and solute to escape and leak out into the tissue spaces. During the same experiments used to quantify collecting lymphatic vessel permeability [32], hydrostatic pressure was measured. Additionally, samples of lymph were obtained from which total protein and albumin concentrations were determined. From that information the direction of solute and fluid movement were calculated and found to travel from the vessel lumen towards the interstitium, just as for the blood vessels.

Collecting lymphatics and venules differ in many respects, but somehow maintain the same permeability setpoint. One chief difference is that collecting lymphatic vessels are spontaneously contractile, and possess fluctuating hydrostatic pressures, while venules possess a relatively steady pressure. This difference is of paramount importance when predicting the movement of water across the endothelial cell barrier. For microvessels, it has been demonstrated that at constant perfusion pressures, fluid cannot be continuously reabsorbed across the vessel wall [37]. In the face of a transient pressure change, however, fluid may be reabsorbed until such time as a steady state is achieved. Since collecting lymphatics are constantly changing their hydrostatic pressure, they possess the unique ability to reabsorb fluid from the tissues when their hydrostatic pressure is sufficiently low. Therefore, collecting lymphatic vessel permeability properties, in conjunction with their transmural pressure characteristics, enable the exchange of fluid and proteins with the surrounding tissue.

At first these results seem paradoxical. How can collecting lymphatic vessels leak fluid and solute into the tissue and at the same time prevent edema from occurring? The reason that edema does not occur is that the percentage of fluid filtering into the tissue space is small relative to the amount being transported away from the tissue. To integrate all that we know about lymphatic permeability into one theory, we should consider the initial lymphatics as absorptive sacs owing to their lower hydrostatic and osmotic pressures, while the collecting lymphatic vessels with higher pressures are capable of filtering or reabsorbing fluid from the tissue.

The implications of constitutive leakage of water and solute from the collecting lymphatics into the tissue space are that the lymphatic vasculature is able to participate in microvascular exchange and that in pathophysiological conditions this leakage may be augmented or diminished with consequences for water balance and organ function. For instance, if the net fluid loss across the vessel wall ever exceeds the net fluid transport along the vessel length (i.e., out of the tissue bed), then edema will likely ensue because any fluid that is absorbed by the initial lymphatics is rapidly lost right back into the tissue. Knowledge of the mediators that can cause such an increase in lymphatic vessel permeability is vital to understanding when and under what conditions edema will occur. As an example, one mediator that will elicit a 2-fold increase in collecting lymphatic vessel permeability is atrial natriuretic peptide, a cardiac hormone that is released in response to

atrial stretch as occurs during congestive heart failure [31]. At first glance this may seem puzzling, but during congestive heart failure the heart perceives, falsely, an increase in blood volume that the body attempts to reduce. While diuresis is one mechanism used, another is to displace water into the tissues (i.e., third spacing). An increase in collecting lymphatic permeability to water and/or solute would allow more of the capillary filtrate to be retained by the tissues since it would be unable to be returned to the bloodstream.

Control of lymphatic permeability is necessary not only for the regulation of water balance, but could also be a contributing factor in several other disease states. The lymphatic vasculature is known to be a major route for the dissemination of cancer cells to distant organs and it is conceivable that an increase in lymphatic permeability may allow a higher concentration of signaling molecules to escape into the peritumoral environment to instigate metastasis. Another outcome of an elevated lymphatic permeability, identified in a genetic mouse model heterozygous for the gene *Prox1*, has been shown to be adult-onset obesity [38]. An increased leakage of lymph from the lymphatic vessels in the peritoneal cavity was demonstrated as the culprit, especially since lymph itself was identified to contain an adipogenic factor.

VIII Conclusion

Failure to include consideration of the lymphatics in the regulation of fluid and solute distribution contributes to incomplete understanding of fluid and solute homeostasis. This partial understanding may not be detrimental in health but it likely contributes to our failure to adequately treat edema under a variety of conditions including post-surgery, congestive heart failure, sepsis, and eclampsia. Finally, it is likely that exercise conditioning, obesity, pregnancy, low gravity, and treatment with drugs that are known to alter vascular smooth muscle function likely also alter lymphatic function with respect to both pumping and permeability. Our current paradigms for the treatment of patients do not include consideration of the 'hidden circulation', with potentially grave consequences.

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References

1. Huxley VH, Williams DA (1996) Basal and adenosine-mediated protein flux from isolated coronary arterioles. Am J Physiol 271: H1099-H1108
2. Kaimovitz B, Huo Y, Lanir Y, Kassab GS (2008) Diameter asymmetry of porcine coronary arterial trees: structural and functional implications. Am J Physiol 294:H714-H723
3. Vainionpaa N, Butzow R, Hukkanen M, et al (2007) Basement membrane protein distribution in LYVE-1-immunoreactive lymphatic vessels of normal tissues and ovarian carcinomas. Cell Tissue Res 328: 317–328
4. von der Weid PY, Zawieja DC (2004) Lymphatic smooth muscle: the motor unit of lymph drainage. Int J Biochem Cell Biol 36: 1147–1153
5. Baluk P, Fuxe J, Hashizume H, et al (2007) Functionally specialized junctions between endothelial cells of lymphatic vessels. J Exp Med 204: 2349–2362
6. Aukland K, Reed RK (1993) Interstitial-lymphatic mechanisms in the control of extracellular fluid volume. Physiol Rev 73: 1–78

7. Casley-Smith JR (1975) A theoretical support for the transport of macro-molecules by osmotic flow across a leaky membrane against a concentration gradient. Microvasc Res 9: 43 – 48
8. Trzewik J, Mallipattu SK, Artmann GM, Delano FA, Schmid-Schonbein GW (2001) Evidence for a second valve system in lymphatics: endothelial microvalves. FASEB J 15: 1711 – 1717
9. Hogan RD (1981) Lymph Formation in the Bat Wing. University of New South Wales, Kensington
10. Wiig H, Reed RK, Aukland K (1987) Measurement of interstitial fluid pressure in dogs: evaluation of methods. Am J Physiol 253: H283-H290
11. Schmid-Schonbein GW (1990) Microlymphatics and lymph flow. Physiol Rev 70: 987 – 1028
12. Clough G, Smaje LH (1978) Simultaneous measurement of pressure in the interstitium and the terminal lymphatics of the cat mesentery. J Physiol 283: 457 – 468
13. Guyton AC, Granger HJ, Taylor AE (1971) Interstitial fluid pressure. Physiol Rev 51: 527 – 563
14. Negrini D, Fabbro MD (1999) Subatmospheric pressure in the rabbit pleural lymphatic network. J Physiol 520: 761 – 769
15. Parsons RJ, McMaster PD (1938) The effect on the pulse upon the formation and flow of lymph. J Exp Med 68: 353 – 376
16. Dongaonkar RM, Stewart RH, Laine GA, Davis MJ, Zawieja DC, Quick CM (2009) Venomotion modulates lymphatic pumping in the bat wing. Am J Physiol 296: H2015-H2021
17. Reddy NP, Krouskop TA, Newell PH Jr (1975) Biomechanics of a lymphatic vessel. Blood Vessels 12: 261 – 278
18. Gashev AA, Orlov RS, Zawieja DC (2001) [Contractions of the lymphangion under low filling conditions and the absence of stretching stimuli. The possibility of the sucking effect]. Ross Fiziol Zh Im I M Sechenova 87: 97 – 109
19. Taylor A, Gibson H (1975) Concentrating ability of lymphatic vessels. Lymphology 8: 43 – 49
20. Zawieja DC, Barber BJ (1987) Lymph protein concentration in initial and collecting lymphatics of the rat. Am J Physiol 252: G602-G606
21. Takahashi T, Shibata M, Kamiya A (1997) Mechanism of macromolecule concentration in collecting lymphatics in rat mesentery. Microvasc Res 54: 193 – 205
22. Jacobsson S, Kjellmer I (1964) Flow and protein content of lymph in resting and exercising skeletal muscle. Acta Physiol Scand 60: 278 – 285
23. Scallan JP, Huxley VH, Korthuis RJ (2010) Capillary Fluid Exchange: Regulation, Functions, and Pathology. Morgan-Claypool, New Jersey
24. Huxley VH, Rumbaut RE (2000) The microvasculature as a dynamic regulator of volume and solute exchange. Clin Exp Pharmacol Physiol 27: 847 – 854
25. Huxley VH, Wang JJ, Sarelius IH (2007) Adaptation of coronary microvascular exchange in arterioles and venules to exercise training and a role for sex in determining permeability responses. Am J Physiol 293: H1196-H1205
26. Sabin FR (1902) On the origin of the lymphatic system from the veins, and the development of the lymph hearts and thoracic duct in the pig. Am J Anat 1: 367 – 389
27. Srinivasan RS, Dillard ME, Lagutin OV, et al (2007) Lineage tracing demonstrates the venous origin of the mammalian lymphatic vasculature. Genes Dev 21: 2422 – 2432
28. Leak LV (1970) Electron microscopic observations on lymphatic capillaries and the structural components of the connective tissue-lymph interface. Microvasc Res 2: 361 – 391
29. Casley-Smith JR (1980) The fine structure and functioning of tissue channels and lymphatics. Lymphology 13: 177 – 183
30. O'Morchoe CC, Jones WR, 3rd, Jarosz HM, O'Morchoe PJ, Fox LM (1984) Temperature dependence of protein transport across lymphatic endothelium in vitro. J Cell Biol 98: 629 – 640
31. Scallan J (2010) Collecting Lymphatic Vessel Permeability to Albumin and its Modification by Natriuretic Peptides. Doctoral Dissertation, University of Missouri – Columbia
32. Scallan J, Huxley VH (2010) *In vivo* determination of collecting lymphatic vessel permeability to albumin: a role for lymphatics in exchange. J Physiol 588: 243 – 254

33. Scallan JP, Huxley VH (2010) Lymphatic vessels – absorptive sumps or leaky pumps? Physiology News 80: 18 – 20
34. Mayerson HS, Patterson RM, McKee A, LeBrie SJ, Mayerson P (1962) Permeability of lymphatic vessels. Am J Physiol 203: 98 – 106
35. Ono N, Mizuno R, Ohhashi T (2005) Effective permeability of hydrophilic substances through the walls of lymph vessels: roles of endothelial barrier. Am J Physiol 289: H1676-H1682
36. Price GM, Chrobak KM, Tien J (2008) Effect of cyclic AMP on barrier function of human lymphatic microvascular tubes. Microvasc Res 76: 46 – 51
37. Michel CC, Phillips ME (1987) Steady-state fluid filtration at different capillary pressures in perfused frog mesenteric capillaries. J Physiol 388: 421 – 435
38. Harvey NL, Srinivasan RS, Dillard ME, et al (2005) Lymphatic vascular defects promoted by Prox1 haploinsufficiency cause adult-onset obesity. Nat Genet 37: 1072 – 1081

The Interstitium and Lymphatics have an Important Role in Edema Generation during Sepsis

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Introduction

Increased fluid filtration is one of the hallmarks of inflammation. During systemic inflammatory response syndrome (SIRS) and sepsis, excessive fluid extravasation takes place. Restoring and maintaining an adequate intravascular fluid volume is, therefore, one of the most important goals in the clinical situation. There are two reasons for this: First, the increased fluid filtration results in edema, which may lead to organ dysfunction or failure. Importantly, the increased tissue water and edema may impede normal lung function. Furthermore, the increased amount of tissue fluid will lead to increased diffusion distance for nutrients and waste products. Second, the increased fluid filtration is a central element of septic pathophysiology, and may, combined with increased vasodilatation, lead to hypovolemic shock. Based on the prominent role of fluid filtration, it is no surprise that much of the discussion on sepsis pathophysiology is focused on the capillary wall. Here we will review recent data showing that the interstitium or the extracellular matrix outside the blood vessels has a central pathogenetic role in fluid extravasation and edema generation in sepsis. We will also discuss data on the potential role of the lymphatics in this context since they are crucial for maintaining a normal fluid balance in the tissues, and even more so for returning extravasated plasma proteins to the circulation. In doing so, we will briefly address normal transcapillary exchange and edema prevention while maintaining our focus on the extravascular compartment.

Normal Transcapillary Fluid Exchange

We owe many of our concepts on fluid filtration to the work of Starling, who formulated his hypothesis on fluid filtration in 1896 [1], showing that fluid could, as a result of osmotic forces, transverse the blood vessel walls, from the tissue into the plasma. He hypothesized, that fluid movement across the small blood vessels was determined by the balance between hydrostatic pressure inside the vessels where fluid is forced out from the capillaries, and osmotic pressure in plasma, tending to absorb fluid back from the connective tissues. During normal physiological conditions, there is net fluid filtration from plasma to the interstitium [2].

Starling's hypothesis was later formulated as an equation:

$$J_v = L_p S\,[(P_c - P_{if}) - \sigma\,(COP_c - COP_{if})] \qquad \text{(Eqn. 1)}$$

where J_v is fluid flux over the capillary wall, L_p is the hydraulic permeability of the capillaries, S is the surface area available for filtration, and σ is the capillary

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reflection coefficient. (P_c – P_{if}) is the hydrostatic pressure difference between plasma in the capillaries (c) and fluid in the interstitium (if) and (COP_c – COP_{if}) represents the corresponding difference in colloid osmotic pressures.

Autoregulation of J_v and Edema Formation

Normally, capillary filtration equals lymph drainage, thus resulting in an interstitial fluid steady state. Edema means swelling and the interstitial fluid volume (V_{if}) is increased; this can be the result of increased J_v, or lowered lymph flow. Increased V_{if}, as seen during inflammation and sepsis, is due to increased filtration that is not compensated for by a corresponding increase in lymph flow.

Changes in the parameters of the Starling equation alter fluid flux across the microvasculature. A tissue has an inherent ability to 'autoregulate' its volume and thereby counteract edema formation [3, 4] by the following mechanisms:

1. Increased interstitial fluid will increase P_{if} as a function of the tissue compliance (C; defined as $\Delta V_{if}/\Delta P_{if}$). Increased P_{if} results, according to Starling's equation, in reduced fluid extravasation over the vasculature.
2. Increased formation of interstitial fluid will dilute the protein concentration in the same fluid, and thereby reduce COP_{if}. As seen from Starling's equation, this leads to reduced fluid extravasation.
3. Increased interstitial fluid volume and P_{if} will increase lymph drainage.

As edema is a typical sign of sepsis, fluid filtration seems to overcome these autoregulatory mechanisms.

Fluid Exchange in Sepsis

When treating patients with sepsis, clinicians have indirect access to some of the parameters in the Starling equation. Pappenheimer and Soto-Rivera showed how P_c was dependent on arterial and venous pressures and their respective resistances [5]. Arterial and central venous pressures (CVP) are important parameters when deciding the therapeutic strategy in sepsis [6], although it is difficult to estimate the actual P_c. The relative precapillary (R_A) and postcapillary (R_V) resistances are important, and the former is normally ~4 times higher then the latter [7]. This fact explains why increasing CVP has a higher impact on the fluid filtration than increasing arterial pressure, and correlates much better to what is observed clinically: Heart failure or excessive fluid administration can lead to increased CVP and are associated with edema. An inflammatory condition will, if accompanied by vasodilation, result in a reduced R_A/R_V ratio, and thereby in increased capillary pressure, again leading to increased filtration and possibly edema development [7].

The inflammatory response will reduce the capillary reflection coefficient. Anti-inflammatory therapies could theoretically counteract such a reduction, tending to reduce the increased fluid (and protein) flux seen in sepsis. Because of the pathophysiological processes, but also as a result of treatment, both COP_{if} and P_{if} will be affected during this condition.

In a situation with increased filtration, the protein concentration in the interstitial fluid decreases as a result of increased fluid filtration ('wash-down'). Dur-

ing inflammation, however, such dilution is counteracted by increased capillary protein permeability resulting in a reduced capillary reflection coefficient, As the osmotic pressure difference is multiplied by the capillary reflection coefficient, this will contribute to raise filtration since the reabsorbing pressures diminish. In addition to these changes at the capillary wall, recent studies also support that the interstitial fluid pressure can have an 'active' role in generating edema in acute inflammation [8, 9] as discussed in more detail below.

The Interstitium and Interstitial Fluid Pressure

When considering transcapillary exchange and fluid balance, the connective tissue and properties of the interstitium are often forgotten, leading to the risk of overseeing important processes and therapeutic targets in sepsis. The following sections will emphasize some new aspects of the interstitial environment *per se* that are important determinants of fluid balance during systemic inflammation with a focus on sepsis. It should be remembered, however, and as recently reviewed by Reed and collaborators [8, 9], that the interstitium 'actively' contributes to enhance transcapillary fluid flux in several other inflammatory and trauma situations as well as tumors and pathologies involving fibrosis.

The interstitium may be defined as the space between capillaries and cells [3]. It is composed first of glycosaminoglycans, which may be associated with proteins (proteoglycans), constituting a hydrated gel phase, and, second, there are fibrous proteins of which collagens are the most abundant. Finally, the interstitial fluid contains plasma proteins in a concentration determined by the properties of the capillary wall and the capillary filtration rate. Recent data suggest that the hydrostatic pressure in the interstitial fluid, i.e., P_{if} (c.f. Eq. 1 above), may have a central role in edema generation in sepsis. In addition to influencing the J_v, P_{if} also represents the filling pressure for initial lymphatics and thus lymph formation discussed in the last part of this paper.

In pioneering studies using implanted plastic capsules in tissues, Guyton and co-workers demonstrated that the interstitial fluid pressure, P_{if}, was subatmospheric in normal skin [10]. Other authors later confirmed these findings, and Wiig and co-workers measured negative P_{if} in skin by using the micropipette method (reviewed in [4]). The first indication that P_{if} could represent a major pathogenetic factor in traumatic and inflammatory edema formation came from studies by Lund and co-workers [11]. They demonstrated that P_{if} became strongly negative during full thickness burn injury, leading to increased fluid flux and therefore represented a new mechanism for edema generation. Later, a decrease in P_{if}, although less extensive, was demonstrated to be a general feature of acute inflammatory conditions [4, 8]. In a series of studies it was shown that interactions between matrix molecules, notably collagen and integrins, could explain this modulation of P_{if}. We will therefore discuss integrins in more detail, and their role in modulating P_{if} and thereby fluid filtration.

Integrins

Integrins are heterodimeric membrane proteins functioning as adhesion receptors. They are composed of an α- and a β-subunit, both with an intra- and an

extra-cellular domain, and assemble into 24 distinct integrins in vertebrates [12]. Different integrins have different ligand specificity, which can be macromolecules in the extracellular matrix or membrane proteins on other cells. The intracellular part is linked to the cytoskeletal filaments [13]. The mechanisms for integrin activation are complex, and both conformation change (affinity regulation) [14] and clustering (avidity regulation) [15] have been emphasized.

There are four collagen-binding integrins: α1β1, α2β1, α10β1 and α11β1. The α1β1 and α2β1 integrins have in addition affinity for laminin [12]. The α1β1 integrin is often associated with basement membranes, and has higher affinity for type IV collagen than fibrillar type I collagen, in contrast to the α2β1 integrin, which has higher affinity for fibrillar collagen [16]. Both α1β1 and α2β1 are widely distributed, and are found in connective tissue, on some leukocytes and on endothelial cells. Although the α1β1 integrin is so widely expressed, $\alpha1^{-/-}$ mice are viable and fertile, showing no overt phenotype [17]. $\alpha2^{-/-}$ mice show a branching morphogenesis defect in mammary glands and a platelet defect [18, 19]. The α10β1 integrin is associated with cartilage and, similar to the α1β1 integrin, has higher affinity for network-forming collagens than fibrillar collagens. The α11β1 integrin is the most recently discovered [12] and, similar to the α2β1 integrin, its highest affinity is for fibrillar collagen [20].

The β3 subfamily of integrins is composed of the αIIbβ3 integrin, expressed on platelets and megakaryocytes, and the widely distributed αvβ3 integrin. These receptors recognize the tripeptide sequence RGD, which is found in molecules like vitronectin and fibronectin, but also in denatured, relaxed collagen triple helix [13, 21]. The αIIbβ3 integrin is important for normal platelet function, and blocking this receptor is used as an anticoagulating agent during ischemic heart disease. The αvβ3 integrin is associated with angiogenesis and vascular permeability [22, 23].

Because of their interactions with collagen, the integrins mentioned above are interesting for their potential role as modulators of tension in the extracellular matrix and thus of P_{if}. To address this issue in more detail, studies of the interaction between fibroblasts and collagen have been performed *in vitro*, i.e, measuring the compaction of collagen gels over time during different conditions, and in animal models *in vivo*.

P_{if} Regulation during Inflammation

To explore a potential role for integrins in the control of P_{if}, specific blocking antibodies have been injected in rat and mouse skin based on *in vitro* observations in the collagen contraction assay [24]. When adding anti-integrin β1 IgG concomitant with edema formation, P_{if} is lowered, suggesting that β1 integrins mediate cellular tension on the collagen/microfibrillar network during fluid homeostasis [25]. Experiments have shown an important role for the fibrillar collagen binding α2β1 integrin in this situation [26]. Recent studies also suggest that the α11β1 integrin is involved in fibroblast-collagen gel contraction [27] and P_{if} regulation [28]. During normal physiological conditions, P_{if} in mice lacking the α11β1 integrin was similar to that of wild type (WT) mice. During an acute anaphylactoid reaction, however, modulation of P_{if} was different in these animals, suggesting a role in regulation of tissue compaction, visible only during inflammatory conditions.

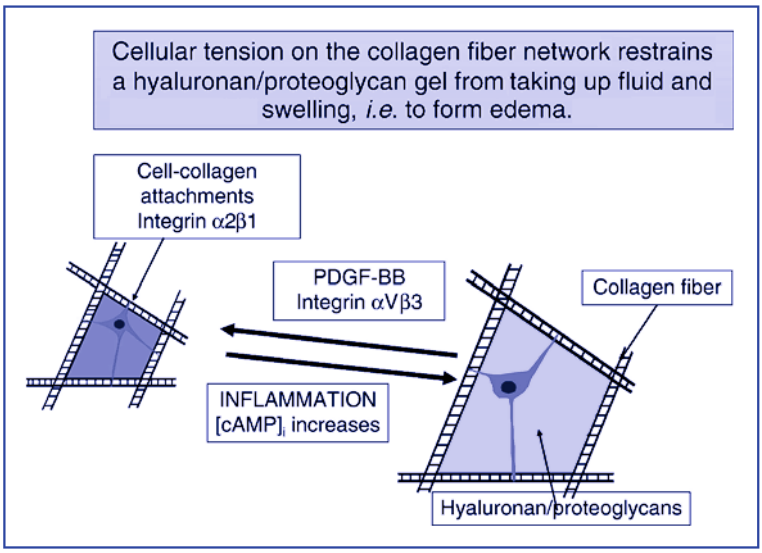

Fig. 1. Model for modulation of interstitial fluid pressure (P_{if}) during inflammation. The interstitium 'sucks' plasma from the microcirculation, as the collagen-fiber restrain becomes weaker. Platelet-derived growth factor (PDGF)-BB and insulin have been shown to counteract this process in an integrin αvβ3-dependent mechanism. From [8] with permission.

Although the exact mechanisms for collagen-binding integrin-mediated regulation of P_{if} are not known, a mechanism based on *in vitro* as well as *in vivo* experimental data has been proposed [8] (**Fig. 1**). A central element is reduced compaction of the connective tissue resulting from integrin-mediated tension between fibroblasts and collagen [8]. In this model, the fibroblasts mediate a tension on the collagen fibrils. During inflammation, this tension is diminished and the connective tissue expands due to its content of glycosaminoglucans, resulting in 'suction' of fluid from the capillaries into the interstitium.

The influence of platelet-derived growth factor (PDGF)-BB to attenuate and reverse a lowering of P_{if} [26] was demonstrated [26], rather surprisingly, not to be mediated by one of the collagen-binding integrins, whereas the widely distributed αvβ3 integrin was shown to be involved [29]. Experiments suggest that PDGF-BB stimulates fibronectin production by cells and that fibronectin can link the cells to the collagen via the αvβ3 integrins in cell-mediated collagen gel contraction [30]. Interactions between αvβ3 integrins and denatured collagen, which exhibits the RGD tripeptide sequence [13, 21], could theoretically also play a role. Jointly these observations demonstrate that P_{if} operates around a setpoint, with the α2β1-integrin normally mediating tension from the connective tissue cells to the fibers in the loose connective tissue. When this tension is released and P_{if} is lowered, this lowering can be attenuated by, amongst others, PDGF-BB and, in the case of PDGF-BB, tissue compaction is restored via the αvβ3-integrin [8, 9].

Sepsis, Insulin and P_{if}

Recently we have shown that insulin has a role in P_{if} control mediated via integrins [31, 32]. This observation is potentially relevant for the pathophysiology of sepsis due to the recent focus on glucose control. The management of blood glucose in the intensive care situation was greatly influenced by a seminal study published by Van den Berghe et al. [33] in which the investigators exerted strict blood glucose control in patients admitted to the intensive care unit (ICU) (over 60 % were cardiac surgery patients). Maintaining glucose values between 4.4 – 6.1 mmol/l by insulin infusions resulted in a more than 40 % risk reduction for mortality. The potentially beneficial effect was thought to be caused by the normalized blood glucose levels [34], but a direct anti-inflammatory effect of insulin has also been proposed [31, 35]. When trying to reproduce the results in a medical ICU, there was no decrease in mortality, although there were subgroups that benefited from strict blood glucose control [36]. In contrast, in a large multicenter study, including both medical and surgical ICU patients, an increased mortality was observed in the strict blood glucose control group [37]. Finally, another study was stopped because of the high incidence of hypoglycemia in the experimental group, and the results showed no decrease in mortality in the strict blood glucose control group [38].

Although the potentially beneficial effect of insulin in sepsis is questionable, the direct effect of insulin on P_{if} is interesting in this context. Nedrebø et al. showed a modulating effect of insulin on P_{if} in rat skin during sepsis [31], tending to counteract the initial fall in P_{if}, and consequently attenuate fluid filtration. Contraction of gels composed of C2C12 cells (lacking collagen-binding integrins) and collagen was stimulated by insulin, and the process was shown to be depen-

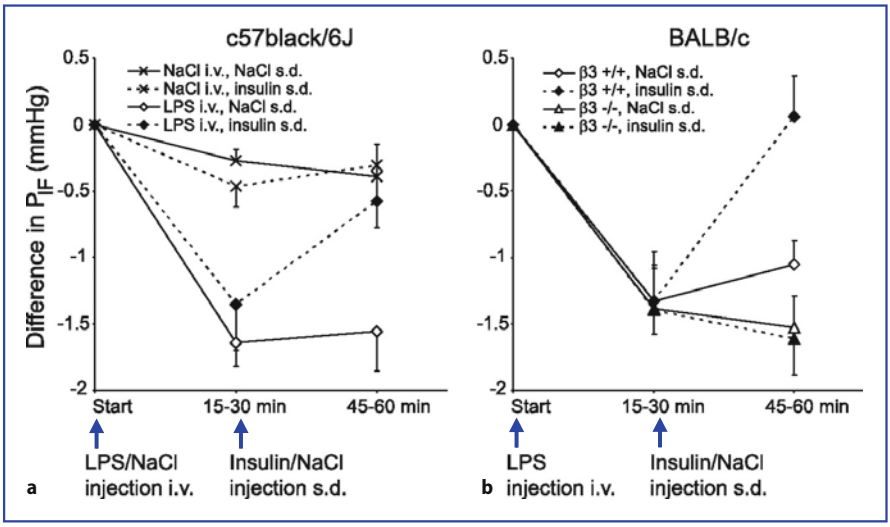

Fig. 2. Effect of insulin on interstitial fluid pressure (P_{if}) in inflammation. During lipopolysaccharide (LPS)-induced inflammation, P_{if} decreases in wild type c57black mice (left). Insulin restores P_{if}, when injected subdermally (black diamonds). However, this restoration is not seen in mice which lack β3-integrins (right, black triangles). From [32] with permission.

dent on the αvβ3 integrin [32]. Mice lacking the β3 integrins showed the previously observed lowering of P_{if} during induction of a septic condition. However, in contrast to wild type mice, P_{if} was not restored when injecting insulin in the dermis after the initial drop in P_{if} [32] (**Fig. 2**). These results suggest an effect of insulin on P_{if} during sepsis, mediated via the αvβ3 integrin. However, even though capillary recruitment and vasodilatation in the microcirculation associated with insulin administration [39] will increase the microvascular surface area available for extravasation (S in Starling's equation) and complicate the picture further, the attenuation of the lowering of P_{if} should nevertheless tend to reduce the fluid filtration.

Lymphatics and Lymph Formation

In the normal steady-state condition, fluid and protein extravasated across the microvascular wall are transported back to the cardiovascular system via lymph, and thus steady state is maintained. Fluid can be reabsorbed into the capillary, but for extravasated protein the only return path back to the circulation is via the lymphatics. Almost all organs have lymph vessels and, similar to blood vessels, lymph vessels are lined by an endothelium. The smallest vessels, called terminal or initial lymphatics, start blindly in the interstitium, and have discontinuous basal lamina. The composition of prenodal lymph may be considered to represent interstitial fluid [3], and the lymphatic fluid flow is driven in a one-way direction as a result of intraluminal valves. The extrinsic lymph pump, which refers to pressure generated from outside the lymph vessels (pulsations, contractions, movements, etc) and the intrinsic lymph pump (smooth muscle in the lymph vessel wall) are responsible for propulsion of the lymph. Postnodal lymph is drained into the subclavian veins via the thoracic and the right lymphatic duct.

Intestinal lymph flow increases as a function of increase in interstitial fluid volume during absorption [40]. It has been proposed that P_{if} is the main determinant for the initial lymph filling process [3]. Although P_{if} is decreased in the initial phase of inflammation, the ensuing increased fluid filtration will lead to a relatively higher P_{if} than during the control situation. This implies that lymph formation should speed up during edema development, counteracting the tissue swelling seen clinically.

During chronic inflammation, there is proliferation and remodeling of lymph and blood vessels [41], and there can be development of so-called tertiary lymphatic organs, showing similarities with lymph nodes, and lymphangiogenesis [42]. In other words, fluid from the chronically inflamed interstitium can be drained via newly formed lymph vessels. However, during acute inflammation like sepsis, the direct physiological impact on the interstitium and lymph vessels is more important for fluid homeostasis than the morphological changes over time.

Quantification of lymph flow in the septic patient is challenging, and studies on the function of lymphatics in sepsis are scarce. Interestingly, in a septic patient with a traumatic lymph fistula, increased lymph flow was reported in the septic phase when compared with the recovery phase [43]. These findings are also supported by experimental studies. In anesthetized and mechanically ventilated pigs, endotoxin increased thoracic duct lymph flow 2.5 times that of baseline [44]. These results are reinforced by data from sheep showing a 3 – 10 times increase in

intestinal lymph flow [45] and by our own experiments in a rat model where the spleen of lymph flow was shown to increase 9 times after systemic inflammation induced by lipopolysaccharide (LPS) injection [46]. Additional insight into the mechanism of lymph formation in sepsis was provided by a study in sheep by Elias et al. [45]. These authors were able to separate the effect of endotoxin on lymphatics *per se* from that of the increased fluid load that is a consequence of increased transcapillary filtration and thus lymphatic input, and found that endotoxin had a negative effect on contraction frequency as well as on lymph pumping. Their study suggested that the lymphatics needed a higher filling pressure to provide the same level of pumping, and thus that this lymphatic insufficiency contributed to the edema formation since a higher interstitial fluid volume was needed for transmural stimulation of the vessels. The combined effects will be that the blunted lymphatic response in this situation will contribute to maintain the edema, rather than contributing to reduce the interstitial volume as is normally the case.

In septic patients, additional negative effects are sedation and respirator treatment that implies little mobilization and reduces extrinsic lymph pump activity. Moreover, mechanical ventilation, positive end-expiratory pressure (PEEP) and increased CVP will tend to reduce lymph flow [47], and the negative influence on the intrinsic lymphatic pumping discussed above may add to this effect [45], mimicking the reduced heart contractility seen during this condition [48]. Actually, lymph contractions have similarities with the cardiac contraction cycles [49], and the transmural pressure-pumping curve may be shifted to the right as suggested by the experiments in sheep discussed above [45]. In addition, the lymphatic contractility is likely affected by hypovolemia in sepsis *per se* [49]. Collectively, these studies suggest that despite observations of increased lymph flow in sepsis, the lymphatic pumping and the role of lymphatics in maintaining fluid homeostasis is impaired in the septic patient compared to normal.

Conclusion

Normal fluid homeostasis is strongly affected during sepsis with increased capillary fluid filtration and enhanced capillary permeability, which may lead to hypovolemia combined with increased tissue edema. The previous focus on treating sepsis has mainly been on cardiovascular features in addition to treating the infection. The changes in parameters affecting fluid filtration during inflammation are, however, more complex, and the role of the interstitium in regulating fluid extravasation should also be considered. Here we have discussed some properties of connective tissue, notably P_{if}, which are affected by inflammation and thus influence edema formation. These may be potential targets when developing new strategies in sepsis treatment. The lymphatics are important contributors to normal fluid homeostasis, and may also be so in sepsis. Much is, however, unknown regarding the role of lymphatics during this inflammatory condition, a topic that should be addressed in future studies.

References

1. Starling EH (1896) On the absorption of fluids from the connective tissue spaces. J Physiol 19: 312–326
2. Levick JR, Michel CC (2010) Microvascular fluid exchange and the revised Starling principle. Cardiovasc Res 87: 198–210

3. Aukland K, Reed RK (1993) Interstitial-lymphatic mechanisms in the control of extracellular fluid volume. Physiol Rev 73: 1–78
4. Wiig H, Rubin K, Reed RK (2003) New and active role of the interstitium in control of interstitial fluid pressure: potential therapeutic consequences. Acta Anaesthesiol Scand 47: 111–121
5. Pappenheimer JR, Soto-Rivera A (1948) Effective osmotic pressure of the plasma proteins and other quantities associated with the capillary circulation in the hindlimbs of cats and dogs. Am J Physiol 152: 471–491
6. Rivers EP, Coba V, Whitmill M (2008) Early goal-directed therapy in severe sepsis and septic shock: a contemporary review of the literature. Curr Opin Anaesthesiol 21: 128–140
7. Levick JR (2003) An introduction to Cardiovascular Physiology, 4th edn. Arnold, London
8. Reed RK, Liden A, Rubin K (2010) Edema and fluid dynamics in connective tissue remodelling. J Mol Cell Cardiol 48: 518–523
9. Reed RK, Rubin K (2010) Transcapillary exchange: role and importance of the interstitial fluid pressure and the extracellular matrix. Cardiovasc Res 87: 211–217
10. Guyton AC, Armstrong GG, Crowell JW (1960) Negative pressure in the interstitial spaces. Physiologist 3: 70 (abst)
11. Lund T, Wiig H, Reed RK, et al (1987) A 'new' mechanism for oedema generation: strongly negative interstitial fluid pressure causes rapid fluid flow into thermally injured skin. Acta Physiol Scand 129: 433–435
12. Popova SN, Rodriguez-Sánchez B, Lidén A, et al (2004) The mesenchymal alpha11beta1 integrin attenuates PDGF-BB-stimulated chemotaxis of embryonic fibroblasts on collagens. Dev Biol 270: 427–442
13. Hynes RO (2002) Integrins: bidirectional, allosteric signaling machines. Cell 110: 673–687
14. Carman CV, Springer TA (2003) Integrin avidity regulation: are changes in affinity and conformation underemphasized? Curr Opin Cell Biol 15: 547–556
15. Bazzoni G, Hemler ME (1998) Are changes in integrin affinity and conformation overemphasized? Trends Biochem Sci 23: 30–34
16. Jokinen J, Dadu E, Nykvist P, et al (2004) Integrin-mediated cell adhesion to type I collagen fibrils. J Biol Chem 279: 31956–31963
17. Gardner H, Kreidberg J, Koteliansky V, et al (1996) Deletion of integrin alpha 1 by homologous recombination permits normal murine development but gives rise to a specific deficit in cell adhesion. Dev Biol 175: 301–313
18. Chen J, Diacovo TG, Grenache DG, et al (2002) The alpha(2) integrin subunit-deficient mouse: a multifaceted phenotype including defects of branching morphogenesis and hemostasis. Am J Pathol 161: 337–344
19. Holtkotter O, Nieswandt B, Smyth N, et al (2002) Integrin alpha 2-deficient mice develop normally, are fertile, but display partially defective platelet interaction with collagen. J Biol Chem 277: 10789–10794
20. Popova SN, Lundgren-Akerlund E, Wiig H, et al (2007) Physiology and pathology of collagen receptors. Acta Physiol (Oxf) 190: 179–187
21. Grundstrom G, Mosher DF, Sakai T, et al (2003) Integrin alphavbeta3 mediates platelet-derived growth factor-BB-stimulated collagen gel contraction in cells expressing signaling deficient integrin alpha2beta1. Exp Cell Res 291: 463–473
22. Brooks PC, Clark RA, and Cheresh DA (1994) Requirement of vascular integrin alpha v beta 3 for angiogenesis. Science 264: 569–571
23. Robinson SD, Reynolds LE, Wyder L, et al (2004) Beta3-integrin regulates vascular endothelial growth factor-A-dependent permeability. Arterioscler Thromb Vasc Biol 24: 2108–2114
24. Gullberg D, Tingstrom A, Thuresson AC, et al (1990) Beta 1 integrin-mediated collagen gel contraction is stimulated by PDGF. Exp Cell Res 186: 264–272
25. Reed RK, Rubin K, Wiig H, et al (1992) Blockade of beta 1-integrins in skin causes edema through lowering of interstitial fluid pressure. Circ Res 71: 978–983
26. Rodt SA, Ahlen K, Berg A, et al (1996) A novel physiological function for platelet-derived growth factor-BB in rat dermis. J Physiol 495 (Pt 1): 193–200
27. Barczyk MM, Olsen LH, da Franca P, et al (2009) A role for alpha11beta1 integrin in the human periodontal ligament. J Dent Res 88: 621–626

28. Svendsen OS, Barczyk MM, Popova SN, et al (2009) The {alpha}11{beta}1 Integrin Has a Mechanistic Role in Control of Interstitial Fluid Pressure and Edema Formation in Inflammation. Arterioscler Thromb Vasc Biol 29: 1864 – 1870
29. Liden A, Berg A, Nedrebo T, et al (2006) Platelet-derived growth factor BB-mediated normalization of dermal interstitial fluid pressure after mast cell degranulation depends on beta3 but not beta1 integrins. Circ Res 98: 635 – 641
30. Liden A, van Wieringen T, Lannergard J, et al (2008) A secreted collagen- and fibronectin-binding streptococcal protein modulates cell-mediated collagen gel contraction and interstitial fluid pressure. J Biol Chem 283: 1234 – 1242
31. Nedrebo T, Karlsen TV, Salvesen GS, et al (2004) A novel function of insulin in rat dermis. J Physiol 559: 583 – 591
32. Svendsen OS, Liden A, Nedrebo T, et al (2008) Integrin alphavbeta3 acts downstream of insulin in normalization of interstitial fluid pressure in sepsis and in cell-mediated collagen gel contraction. Am J Physiol Heart Circ Physiol 295: H555 – 560
33. Van den Berghe G, Wouters P, Weekers F, et al (2001) Intensive insulin therapy in the critically ill patients. N Engl J Med 345: 1359 – 1367
34. Van den Berghe G, Wouters PJ, Bouillon R, et al (2003) Outcome benefit of intensive insulin therapy in the critically ill: Insulin dose versus glycemic control. Crit Care Med 31: 359 – 366
35. Das UN (2001) Is insulin an antiinflammatory molecule? Nutrition 17: 409 – 413
36. Van den Berghe G, Wilmer A, Hermans G, et al (2006) Intensive insulin therapy in the medical ICU. N Engl J Med 354: 449 – 461
37. Finfer S, Chittock DR, Su SY, et al (2009) Intensive versus conventional glucose control in critically ill patients. N Engl J Med 360: 1283 – 1297
38. Preiser JC, Devos P, Ruiz-Santana S, et al (2009) A prospective randomised multi-centre controlled trial on tight glucose control by intensive insulin therapy in adult intensive care units: the Glucontrol study. Intensive Care Med 35: 1738 – 1748
39. Serne EH, RG IJ, Gans RO, et al (2002) Direct evidence for insulin-induced capillary recruitment in skin of healthy subjects during physiological hyperinsulinemia. Diabetes 51: 1515 – 1522
40. Granger DN, Mortillaro NA, Kvietys PR, et al (1980) Role of the interstitial matrix during intestinal volume absorption. Am J Physiol Gastrointest Liver Physiol 238: G183 – 189
41. Baluk P, Yao LC, Feng J, et al (2009) TNF-alpha drives remodeling of blood vessels and lymphatics in sustained airway inflammation in mice. J Clin Invest 119: 2954 – 2964
42. Mounzer RH, Svendsen OS, Baluk P, et al (2010) Lymphotoxin alpha contributes to lymphangiogenesis. Blood 116: 2173 – 2182
43. Groeneveld AB, Teule GJ, Bronsveld W, et al (1987) Increased systemic microvascular albumin flux in septic shock. Intensive Care Med 13: 140 – 142
44. Lattuada M, Hedenstierna G (2006) Abdominal lymph flow in an endotoxin sepsis model: influence of spontaneous breathing and mechanical ventilation. Crit Care Med 34: 2792 – 2798
45. Elias RM, Johnston MG, Hayashi A, et al (1987) Decreased lymphatic pumping after intravenous endotoxin administration in sheep. Am J Physiol 253: H1349 – 1357
46. Semaeva E, Tenstad O, Skavland J, et al (2010) Access to the spleen microenvironment through lymph shows local cytokine production, increased cell flux, and altered signaling of immune cells during lipopolysaccharide-induced acute inflammation. J Immunol 184: 4547 – 4556
47. Hedenstierna G, Lattuada M (2008) Lymphatics and lymph in acute lung injury. Curr Opin Crit Care 14: 31 – 36
48. Flynn A, Chokkalingam Mani B, Mather PJ (2010) Sepsis-induced cardiomyopathy: a review of pathophysiologic mechanisms. Heart Fail Rev 15: 605 – 611
49. Li B, Silver I, Szalai JP, et al (1998) Pressure-volume relationships in sheep mesenteric lymphatic vessels in situ: response to hypovolemia. Microvasc Res 56: 127 – 138

Fluid is a Drug that can be Overdosed in the ICU

S.L. Goldstein

Introduction

Recent and important advances in acute kidney injury (AKI) research have focused primarily on: (1) Deriving and validating multi-dimensional AKI definitions and classification systems (e.g., RIFLE [Risk of renal dysfunction, Injury to the kidney, Failure of kidney function, Loss of kidney function and End-stage kidney disease] [1], pediatric [p]RIFLE [2] or the Acute Kidney Injury Network [AKIN] [3] definitions); (2) demonstrating that even small serum creatinine increases (e.g., > 0.3 mg/dl) can be associated with increased patient mortality [4–5]; and (3) discovering and validating novel urinary biomarkers [6–7] to detect AKI earlier than serum creatinine changes with the hope that earlier detection may provide clinicians with the opportunity to intervene to prevent or at least mitigate the effects of AKI. Although these advances will undoubtedly lead to improved patient care by prompting clinicians to be vigilant for early AKI development, they may provide little benefit once patients have already developed AKI.

Care for the critically ill patient with sepsis and AKI is further complicated by the need to manage multiorgan system failure, often requiring complex supportive measures of fluid resuscitation, vasoactive medication administration and decisions as to timing of renal replacement therapy [8–9]. Clinical research in adults with sepsis and acute respiratory distress syndrome (ARDS) has also primarily focused on the benefits of early and aggressive goal-directed fluid resuscitation to restore end-organ provision [10], with some recent attention paid to conservative late fluid management strategies to limit fluid administration [11, 12]. However, many pediatric studies and more recent adult studies have examined the concept of fluid accumulation in the critically ill patient with AKI [13–16]. The purpose of this article is to introduce the concept of 'fluid overdose' in the critically ill patient with AKI.

Can Fluid Be a Medication with Toxic Effects?

All physicians are taught about fluid and electrolyte homeostasis in medical school and early in postgraduate training, with an emphasis on how to respond to pathological homeostatic disorders, such as the syndrome of inappropriate anti-diuretic hormone secretion or diabetes insipidus. In these instances, physicians become quite adept at managing fluid composition and volume rates to correct or minimize the electrolyte derangements that accompany these syn-

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dromes. In fact, much controversy has arisen recently regarding the potential dangers of prescribing hypotonic solutions to any hospitalized patient [17–20], and not solely those with diagnosed syndromes. So, the concept that certain fluid compositions in particular settings may be toxic is certainly not new. Furthermore, limiting the rate of administration in a number of clinical situations, such as acute diabetic ketoacidosis or hyponatremia, to prevent central nervous system effects of overly rapid correction has also become standard teaching in fluid management.

In the setting of AKI, physicians are very cognizant to limit the dose of potentially harmful electrolytes (potassium, phosphorus) provided in exogenous fluids, but the concept of a fluid volume dose has been limited for the most part to an acute dose to treat hypotension (e.g., 10 ml/kg of normal saline). Yet, the concept of a deleterious degree of positive fluid accumulation, or *fluid overdose*, has received no systematic evaluation and certainly has not been defined. Neither of the two most recent, comprehensive, important randomized controlled trials comparing small solute dose of renal replacement therapy (RRT) have even reported to date the positive fluid balance in their patient cohorts at the time of RRT initiation [21, 22]. Given that these patients had oligoanuric AKI, and disordered fluid homeostasis is a primary indication to initiate RRT, our collective ignorance regarding the impact of fluid balance status and the definition of critical degrees of fluid overload in patients with AKI is perplexing.

Why has cumulative fluid balance received such short shrift? I suggest that physicians caring for the critically ill have assumed that patients are getting the amount of fluid they need (maybe too little, but rarely too much). Since prescribed fluid is usually of a relatively isotonic composition (e.g., normal saline or Ringer's lactate) and can be removed by RRT, may we have assumed that it cannot really be overdosed. However, recent lessons from the critical care literature challenge these assumptions.

Lessons from the Pediatric Intensive Care Unit

The lessons from pediatric nephrologists and intensivists emanate from two practice perspectives ingrained into pediatricians: (1) Disease prevention, and (2) medication dosing based on patient size. I am not suggesting that these perspectives are unique to pediatrics and absent in internal medicine, but they are more common in our training and everyday practice. In the area of pediatric AKI and RRT, concepts of relative fluid accumulation (percent fluid overload) based on ICU admission weight, and timing of RRT based on percent fluid overload (instead of BUN concentration) have driven extensive research in the past decade.

Critically ill patients often require aggressive fluid and inotropic support to maintain adequate perfusion. In fact, recent guidelines provide a clear algorithm for early fluid provision and vasoactive medication prescription to reverse shock in children [23]. An important aspect of these guidelines includes early initiation of continuous RRT (CRRT) or extracorporeal membrane oxygenation (ECMO) in children with unreversed shock after 60–80 ml/kg fluid resuscitation and initiation of inotropes. The guidelines do not recommend continuation of indiscriminate fluid boluses for prolonged hypotension *in lieu* of pressors and extracorporeal therapies. Substantial single-center and multicenter pediatric studies over the past decade demonstrate that increasing degrees of relative fluid accumulation, or

Table 1. Fluid overload and outcomes in pediatric continuous renal replacement therapy patients

Author [ref]	Cohort (n)	Outcome	p
Goldstein [25]	Single center (22)	Survivors 16 % fluid overload Non-survivors 34 % fluid overload	0.03
Gillespie [24]	Single center (77)	% fluid overload > 10 % with OR death 3.02	0.002
Foland [15]	Single center (113)	3 organ MODS patients Survivors 9 % fluid overload Non-Survivors 16 % fluid overload 1.78 OR death for each 10 % fluid overload increase	0.01
Goldstein [14]	Multicenter (116)	2+ organ MODS patients Survivors 14 % fluid overload Non-survivors 25 % fluid overload < 20 % fluid overload: 58 % survival > 20 % fluid overload: 40 % survival	0.002
Hayes [26]	Single center (76)	Survivors 7 % fluid overload Non-Survivors 22 % fluid overload OR death 6.1 > 20 % fluid overload	0.001
Sutherland [13]	Multicenter (340)	< 10 % fluid overload: 70.6 % survival 10 – 20 % fluid overload: 56.9 % survival > 20 % fluid overload: 34.4 % survival	0.001

MODS: multiple organ dysfunction syndrome; OR: odds ratio

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percent fluid overload at the time of RRT initiation in children with AKI is independently associated with mortality (**Table 1**) [14, 15, 24 – 26]. Percent fluid overload in the majority of these studies was calculated by totaling fluid volumes from ICU admission to RRT initiation using the following equation:

%FO = [(Fluid Input (l) – Fluid Output (l)) / Patient ICU admission weight (kg)]

In all these studies, estimated glomerular filtration rate (eGFR), patient age and size, urine output, diuretic use, and severity of illness did not differ between survivors and non-survivors. Analysis of different percent thresholds from these studies suggest mortality increases from 40 to 60 % in children with > 10 – 20 % fluid overload at CRRT initiation, independent of patient severity of illness (**Table 1**). Thus, the pediatric community now has data from over 600 children in six studies that consistently show a potential fluid overdose threshold at > 20 % positive accumulation from ICU admission to CRRT initiation.

The most extensive of these analyses was conducted by The Prospective Pediatric Continuous Renal Replacement Therapy (ppCRRT) Registry Group in which its entire 340 patient cohort used a tripartite classification for percent fluid overload at CRRT initiation: < 10 % fluid overload, 10 – 20 % fluid overload and > 20 % fluid overload [13]. In this analysis, patient severity of illness was no different between the 10 – 20 % fluid overload and > 20 % fluid overload groups, yet patient mortality increased from 40 to 60 %. One could still potentially argue that the patients actually 'needed' the fluids they received. However, in a previous multicenter study from the ppCRRT group, the mean central venous pressure (CVP) for survivors was 16.5 ± 6.1 mmH_2O versus 21.2 ± 6.6 mmH_2O for non-

survivors [14]. Current recommendations for early goal-directed fluid resuscitation advocate fluid administration until a CVP of 8 mmH_2O [10, 12, 23]. Since the mean CVP in both survivors and non-survivors was 2 to 3 fold above target recommendations, it is difficult to support the notion that patients received only the fluid volumes they needed; in fact, these patients may have been fluid overdosed.

Are Adults Different or are they Just Large Children?

Children comprise an informative population for study of critical illness, since they do not possess many of the common and often multiple comorbidities seen in adults, such as atherosclerotic heart disease, diabetes, chronic kidney disease, tobacco or illicit drug use. In addition, children manifest acute critical illness more often as primary respiratory decompensation compared to the cardiac compromise exhibited by adults. Thus, it is conceivable that fluid accumulation may lead to different outcomes in critically ill adults versus children. Recent data suggest that fluid accumulation is also independently associated with mortality in adults.

Bouchard and colleagues assessed cumulative fluid accumulation and outcomes in the 610 adult patients enrolled on the prospective Program to Improve Care for Acute Renal Diseases (PICARD) cohort [16]. Cumulative fluid accumulation from hospital admission to any time point during hospital course of > 10 % of admission hospital weight was classified as fluid overload. Patients with AKI and fluid overload had significantly higher mortality (48 % *vs.* 35 %). In addition, fluid accumulation in patients who received some form of RRT was significantly higher for non-survivors than survivors (14.2 % vs. 8.8 %). Payen and colleagues performed a secondary analysis of the Sepsis Occurrence in Acutely ill Patients (SOAP) trial and found that the 7-day cumulative fluid balance was significantly worse in AKI non-survivors versus survivors and mortality was lower in AKI patients who received earlier initiation of RRT [27]. Prospective and retrospective studies of fluid administration strategies have revealed the importance of standardizing and limiting fluid administration once a patient has been acutely resuscitated from shock. The ARDSnet trial assessed a liberal versus conservative fluid management strategy in 1000 patients with acute lung injury (ALI) [11]. Patients who received the conservative fluid management strategy had shorter mechanical ventilation duration and ICU stay. Murphy and colleagues assessed outcomes in 200 patients with septic shock who received adequate initial fluid resuscitation (defined as initial fluid bolus of ≥ 20 ml/kg prior to onset of vasopressor therapy and achievement of a CVP of ≥ 8 mmHg within 6 h after the onset of vasopressor therapy), conservative late fluid management (defined as even-to-negative fluid balance measured on at least 2 consecutive days during the first 7 days after septic shock onset), neither or both [12]. Data from this study showed that patients who received both adequate initial fluid resuscitation and conservative late fluid management demonstrated significantly better survival (81.7 %) compared to any of the other three groups. Of note, patients who received conservative late fluid management only demonstrated significantly better survival than those who received adequate initial fluid resuscitation only (58.2 % *vs.* 45.6 %), suggesting that conservative late fluid management and hence prevention of fluid overdose may be a key to optimizing chances for patient survival.

Conclusion

The studies discussed above, while mostly observational, generate some potentially provocative hypotheses to explain possible associations between fluid accumulation and mortality. For instance, in pediatric practice, almost all medications are prescribed according to patient size, in terms of body weight or surface area. One can imagine a scenario in which a child with Gram-negative sepsis treated with a 3rd generation cephalosporin dosed on ICU admission weight or historical dry weight is actually under dosed as a result of a severely increased volume of drug distribution from excessive fluid accumulation. In this example, it is possible that the antibiotic concentration is below the pharmacodynamic profile to eradicate the organism. Another obvious potential hypothesis would posit an association between excessive fluid accumulation and impaired oxygenation or other pulmonary mechanics, especially in patients with capillary leak syndromes such as sepsis. The purpose of this article was to promote a concept of fluid overdose in the critically ill child with AKI. Inherent in this concept is the importance of regarding fluid as a medication with respect to both composition and volume (dose). Future investigation will require prospective evaluation of different fluid dosing strategies beyond the initial resuscitation effort to optimize care for all critically ill patients.

References

1. Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P (2004) Acute renal failure – definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. Crit Care 8: R204 – 212
2. Akcan-Arikan A, Zappitelli M, Loftis LL, Washburn KK, Jefferson LS, Goldstein SL (2007) Modified RIFLE criteria in critically ill children with acute kidney injury. Kidney Int 71: 1028 – 1035
3. Mehta RL, Kellum JA, Shah SV, et al (2007) Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. Crit Care 11: R31
4. Chertow GM, Burdick E, Honour M, Bonventre JV, Bates DW (2005) Acute kidney injury, mortality, length of stay, and costs in hospitalized patients. J Am Soc Nephrol 16: 3365 – 3370
5. Price JF, Mott AR, Dickerson HA, et al (2008) Worsening renal function in children hospitalized with decompensated heart failure: evidence for a pediatric cardiorenal syndrome? Pediatr Crit Care Med 9: 279 – 284
6. Mishra J, Dent C, Tarabishi R, et al (2005) Neutrophil gelatinase-associated lipocalin (NGAL) as a biomarker for acute renal injury after cardiac surgery. Lancet 365: 1231 – 1238
7. Waikar SS, Bonventre JV (2007) Biomarkers for the diagnosis of acute kidney injury. Curr Opin Nephrol Hypertens 16: 557 – 564
8. Hui-Stickle S, Brewer ED, Goldstein SL (2005) Pediatric ARF epidemiology at a teritary care center from 1999 to 2001. Am J Kidney Dis 45: 96 – 101
9. Symons JM, Chua AN, Somers MJ, et al (2007) Demographic characteristics of pediatric continuous renal replacement therapy: a report of the prospective pediatric continuous renal replacement therapy registry. Clin J Am Soc Nephrol 2: 732 – 738
10. Rivers E, Nguyen B, Havstad S, et al (2001) Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med 345: 1368 – 1377
11. Wiedemann HP, Wheeler AP, Bernard GR, et al (2006) Comparison of two fluid-management strategies in acute lung injury. N Engl J Med 354: 2564 – 2575
12. Murphy CV, Schramm GE, Doherty JA, et al (2009) The importance of fluid management in acute lung injury secondary to septic shock. Chest 136: 102 – 109

13. Sutherland SM, Zappitelli M, Alexander SR, et al (2010) Fluid overload and mortality in children receiving continuous renal replacement therapy: the prospective pediatric continuous renal replacement therapy registry. Am J Kidney Dis 55: 316 – 325
14. Goldstein SL, Somers MJ, Baum MA, et al (2005) Pediatric patients with multi-organ dysfunction syndrome receiving continuous renal replacement therapy. Kidney Int 67: 653 – 658
15. Foland JA, Fortenberry JD, Warshaw BL, et al (2004) Fluid overload before continuous hemofiltration and survival in critically ill children: a retrospective analysis. Crit Care Med 32: 1771 – 1776
16. Bouchard J, Soroko SB, Chertow GM, et al (2009) Fluid accumulation, survival and recovery of kidney function in critically ill patients with acute kidney injury. Kidney Int 76: 422 – 427
17. Ayus JC, Arieff AI (1997) Postoperative hyponatremia. Ann Intern Med 126: 1005 – 1006
18. Moritz ML, Ayus JC (2003) Prevention of hospital-acquired hyponatremia: a case for using isotonic saline. Pediatrics 111: 227 – 230
19. Moritz ML, Ayus JC (2004) Hospital-acquired hyponatremia: why are there still deaths? Pediatrics 113: 1395 – 1396
20. Moritz ML, Ayus JC (2005) Hospital-induced hyponatremia. J Pediatr 147: 273 – 274
21. Palevsky PM, Zhang JH, O'Connor TZ, et al (2008) Intensity of renal support in critically ill patients with acute kidney injury. N Engl J Med 359: 7 – 20
22. Bellomo R, Cass A, Cole L, et al (2009) Intensity of continuous renal-replacement therapy in critically ill patients. N Engl J Med 361: 1627 – 1638
23. Brierley J, Carcillo JA, Choong K, et al (2009) Clinical practice parameters for hemodynamic support of pediatric and neonatal septic shock: 2007 update from the American College of Critical Care Medicine. Crit Care Med 37: 666 – 688
24. Gillespie RS, Seidel K, Symons JM (2004) Effect of fluid overload and dose of replacement fluid on survival in hemofiltration. Pediatr Nephrol 19: 1394 – 1399
25. Goldstein SL, Currier H, Graf C, Cosio CC, Brewer ED, Sachdeva R (2001) Outcome in children receiving continuous venovenous hemofiltration. Pediatrics 107: 1309 – 1312
26. Hayes LW, Oster RA, Tofil NM, Tolwani AJ (2009) Outcomes of critically ill children requiring continuous renal replacement therapy. J Crit Care 24: 394 – 400
27. Payen D, de Pont AC, Sakr Y, Spies C, Reinhart K, Vincent JL (2008) A positive fluid balance is associated with a worse outcome in patients with acute renal failure. Crit Care 12: R74

Crystalloid or Colloid Fluids: A Matter of Volumes?

R.J. Trof and A.B.J. Groeneveld

Introduction

Fluid infusion is a key element in the treatment of critically ill patients with hypovolemia and shock. The debate on the relative merits and detriments of (isotonic) crystalloid versus (roughly isooncotic) colloid fluids is ongoing. Large clinical trials and systemic reviews suggest that the use of one fluid type over the other does not affect overall mortality, but this similarity does not exclude heterogeneity of effects on hemodynamics, adverse effects and outcome among patient populations, so that benefits may be offset by detriments in some but not in other patient populations [1–7]. In the Saline versus Albumin Fluid Evaluation (SAFE) study, for instance, albumin 4 % versus saline loading may have improved survival of septic patients but not of those with traumatic brain injury [1].

This narrative review of the available literature on the topic is meant to summarize current knowledge on the hemodynamic differences, if any, between the fluid types, governed by heart function and underlying condition on the one hand and infusion volume on the other, since, in contrast to standard textbook statements, review papers, guidelines and common beliefs [4, 5, 8], the volume of crystalloid required may not be 3 to 4 times the volume of colloid in the treatment of hypovolemia and shock [1, 3, 6, 7]. This is an important issue in an era where fluid restriction policies to avoid harmful fluid overloading are increasingly propagated, taking the relative, dose-dependent adverse effects of fluid types into account [3, 4, 6].

First, we will review the mechanisms of a cardiac output increase with fluid loading. Second, we will review the clinical data regarding the crystalloid-colloid volume ratio in determining hemodynamic effects, excluding hypertonic or hyperoncotic solutions and animal studies. We will not address the issue of balanced versus unbalanced solutions.

How Does Fluid Loading Increase Cardiac Output?

The response of the heart to fluid loading is far more complex than usually assumed. It is commonly believed that fluid infusion increases cardiac output by increasing plasma volume. However, this relationship may not be straightforward when infused fluids are differently partitioned in stressed and unstressed plasma volume compartments and thereby variably increase end-diastolic volume, as demonstrated for instance in cardiac surgery patients [9, 10]. **Figure 1** shows the relation between plasma volume changes calculated from hemoglobin/hematocrit

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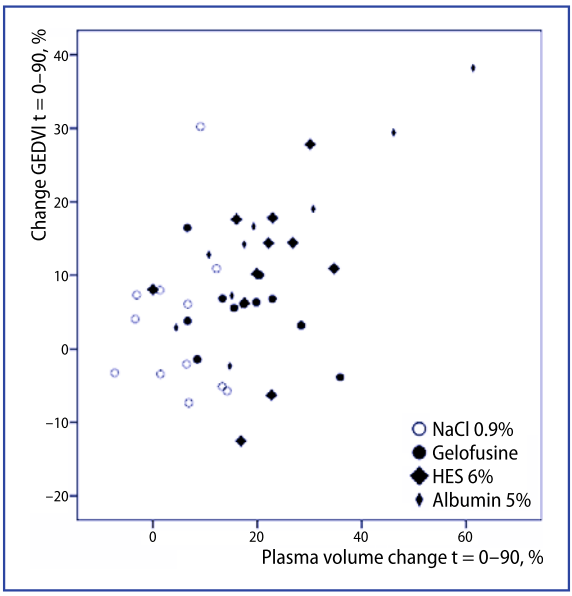

Fig. 1. Loose correlation between the change in plasma volume and the change in global end-diastolic volume index (GEDVI) after 90 minutes of fluid loading in septic and non-septic patients, according to fluid type. $r = 0.51$, $P < 0.001$. Data from [11]

changes, which may have shortcomings, and changes in global end-diastolic volume (GEDV) during crystalloid or colloid loading in septic and non-septic patients, who do not differ in this respect in spite of septic myocardial depression (unpublished data from [11]). This relatively loose relationship confirms earlier findings and suggests that the relationship between plasma volume and cardiac filling and output, apart from measurement difficulties, is not straightforward [9, 11, 12]. Although end-diastolic volume of the ventricles (preload) is an important determinant of cardiac output, fluid loading may also affect blood viscosity and may (thereby) lower cardiac afterload and increase contractility, both in healthy volunteers and in critically ill septic or non-septic patients, so that changes in cardiac output upon fluid loading are not solely determined by changes in preload [9–11, 13–15]. Finally, baseline loading and function of both ventricles and their interaction may affect the (mechanisms of the) cardiac output increase with fluid loading [16]. Indeed, fluid responsiveness, i.e., the increase in stroke volume or cardiac output upon fluid loading, is not only a matter of (type and volume of) fluid infused but also of baseline biventricular filling and (systolic and diastolic) function, which may differ among patients, conditions, and stages of disease. Conversely, the imperfect and sometimes controversial value of parameters thought to help predict fluid responsiveness is partly related to the complexity of effects of fluid loading on the heart and differences herein among patients and conditions. Otherwise, the increase in cardiac output with fluid loading mostly outweighs concomitant hemodilution, so that oxygen delivery (DO_2) is increased, but a potential difference in hemodynamic effects of fluid types may not translate into a difference in tissue oxygenation, when a greater increase in cardiac output is offset by greater hemodilution (with colloids) [10, 11, 17–19].

More Saline than Colloid Needed?

One of the arguments used in favor of colloids is that their infusion increases plasma volume and cardiac preload more (rapidly) than that of crystalloids [4, 12]. If colloids are capable of expanding the plasma volume to a greater extent than crystalloids, then the same volume of colloids would have greater effects on hemodynamics than crystalloids. The volume ratio of crystalloid to colloid relative to hemodynamic effectiveness depends on the rate and fate of the infused fluids and the hemodynamic monitoring tool and endpoint utilized. The hemodynamic endpoint of resuscitation varies from one study to the other from clinical judgment, arterial and central venous pressures, to pulmonary artery occlusion pressures and cardiac output and variables obtained by transpulmonary thermodilution. The variety is likely responsible, in part, for the widely varied volume ratios during resuscitation that are reported in the literature. In the SAFE study (comparing albumin with saline), for instance, the volume and rate of fluid administration was determined by the treating clinicians according to each patient's clinical status and response to treatment, without using a specific fluid loading protocol [1]. This resulted in an albumin to saline volume ratio of 1.4 to 1, but also in higher central venous pressures (CVPs) in the albumin group, suggesting dissimilar resuscitation. Conversely, judging the difference in hemodynamic effects during fixed and similar volume infusions depends on the parameter that is monitored to judge that response and how well the parameter reflects (changes in) plasma volume, which is only rarely (and certainly not routinely) measured [9–12, 17, 18, 20–23]. For instance, in a fluid non-responsive state, in the presence of severe cardiac dysfunction, the type of fluid infused would not translate into hemodynamic differences upon infusion, irrespective of plasma volume changes. We now elaborate on the theoretical and the practical differences in hemodynamic effects and volume ratios of (isotonic/isooncotic) crystalloid and colloid fluids that are reported in the literature.

Theory: Fluid Properties

In theory, crystalloid solutions expand the plasma volume by about 200 ml per liter infused, concomitantly lowering, by diluting circulating proteins, plasma colloid osmotic pressure (COP), as indeed demonstrated in patients [4, 10–12, 21, 24–26]. Depending on the rate of infusion, the equilibration rate of crystalloid with the interstitial space is rapid (minutes) even in patients with hypovolemia or shock, thereby resulting in potentially harmful interstitial overhydration [4, 17–19, 26–29]. In theory, crystalloids thus need to be administered at volumes approximately 3 to 5-fold greater than those of (isooncotic) colloids, which are largely maintained in the plasma compartment because of maintenance of COP, in order to achieve comparable plasma volumes and resuscitation endpoints [4, 8, 10, 11, 24–26, 30]. Conversely, the intravascular COP after colloid infusion is influenced by baseline COP, the degree of hemodilution and the COP of the infused volume and its plasma retention, determined by the molecular weight distribution. Albumin solutions are monodisperse (molecular weight of 69 kDa). Gelatins are polydisperse and in excess of 75 % of the molecules are thought to be smaller than the renal threshold of 30 kDa. The large number of small molecules exerts a powerful initial COP effect making gelatins good for short-term volume expansion, but molecules with a molecular weight less than 15 kDa have a similar

clearance to that of creatinine and will be filtered by the glomerulus. They are thus rapidly cleared from the intravascular space, with a half-life of 3.5–4 hours [8]. Hydroxyethyl starch (HES) solutions are very polydisperse, defined by degree of substitution (via partial hydrolysis) and by molecular weight, both of which affect pharmacokinetics [8, 30]. The greater the degree of substitution, the greater the resistance to degradation, which, therefore, prolongs the effectiveness of HES as a plasma expander. After substitution, the starch is refined into the final product by hydrolysis to the required molecular weight. The molecular weight distribution can be described using the COP50/COP10 ratio [8, 30]. This is the ratio of measured COPs across two different membranes, with a 50-kDa and a 10-kDa pore size, respectively, and reflects the relative proportion of molecules retained by filters with those pore sizes. Colloids with a low COP50/COP10 ratio will be lost more rapidly from the intravascular space. Small particles with a low molecular weight exert a greater COP effect and, for a given number of molecules, will have a lower viscosity than larger molecules. Thus, the concentration and molecular weight of colloid molecules and hence the COP, determine the initial degree of volume expansion, whereas both the molecular weight and surface charge characteristics determine the rate of loss through the capillary endothelial barrier and loss into the urine by glomerular filtration. Therefore, the intravascular retention and half time of colloids amount to hours, dependent on dispersion and weight of molecules. Conversely, plasma volume expansion differences with crystalloid fluid infusions may depend on time [19]. In addition, (endothelial) properties of the vessel wall and overlying luminal glycocalyx, which may change in disease states, may ultimately affect permeability (for proteins and colloids) and hydraulic conductance (to plasma water) [4]. Due to its electrostatic properties, albumin penetrates and binds to the endothelial surface glycocalyx and influences its barrier function. The resulting sealing effect may attenuate fluid extravasation independently of the COP by albumin. Similarly, large HES molecules have been claimed to 'seal pores' but the clinical significance of this effect has not yet been convincingly demonstrated. During conditions with increased vasopermeability, as in septic shock, albumin or starch administration may help in ameliorating the permeability defect on the one hand but may increasingly filtrate into the interstitium on the other, thereby attenuating the potential superiority of colloids in increasing plasma volume [17, 22, 21, 31, 32]. Finally, hypovolemia and shock are likely to lower capillary hydrostatic filtration pressure and promote resorption of interstitial fluids, so that intravascular retention of infused fluids may differ from that in normal individuals, without negating potential differences between fluid types [29, 33]. We will now summarize the evidence obtained in clinical practice for the volume differences between fluid types.

Practice

Volunteers

A recent study in healthy volunteers demonstrated that for the same volume of administered fluids, saline was a less effective plasma volume expander than gelatin 4 % and HES 6 %, which did not differ in this respect up to 6 h after starting infusion [34]. After infusion, 68 %, 21 % and 16 % of the infused volumes of saline, gelatin, and starch, respectively, had escaped from the intra- to the extravascular space, as estimated from hematocrit/hemoglobin changes. This observation indeed concords with a 3-fold greater (and prolonged) effectiveness, for a

given volume infused, of colloids than of crystalloids in plasma volume expansion [26].

Iso- or normovolemic hemodilution
Anesthetized patients undergoing hemodilution and receiving 3 times the volume of crystalloid for each unit of blood removed, or the same volume of (icooncotic) colloid fluid for the volume of blood removed achieved similar hemodynamic endpoints [35]. In volunteers receiving equal volumes of crystalloid or colloid for a given volume of withdrawn blood, the latter had better restoration of hemodynamics, unless twice the volume of crystalloid was given [27, 33].

Perioperative states and trauma
Following spinal anesthesia, colloid fluid requirements were higher than during crystalloid-based regimens, resulting in higher cardiac outputs in patients treated with the former [36]. The increase in plasma volume for a given fluid infusion volume, was about 5x greater with albumin 5 % than with crystalloid after cardiac surgery [9, 18]. Older studies had already suggested that colloid resuscitation required about twice less volume than crystalloid resuscitation to reach similar hemodynamic endpoints during and after (cardiovascular) surgery thereby avoiding some postoperative complications of fluid overload [21, 24, 25, 29, 37–44]. During emergency resuscitation from trauma and hemorrhage, colloid regimens were more (rapidly) effective in restoring the circulation than crystalloid regimens, at volume ratios of about 1 to 3 [45, 46]. More recently, Lang et al. again demonstrated that to reach the same CVP in patients after major abdominal surgery, 2-fold higher volumes of Ringer's lactate than HES 6 % were required [47]. Verheij et al. showed that 4–6 % colloid fluid loading (for 90 min) according to changes in filling pressures after cardiac or major vascular surgery resulted in a 4-fold greater increase in preload-recruitable stroke work fluid loading with saline, because of a greater plasma volume expansion following an increase in plasma COP, whereas about 15 % less colloid than crystalloid was administered (volume ratio about 1.2:1) [10]. A recent study in postoperative patients with hypovolemia showed that the administration of different types (but similar volumes) of colloid was associated with greater increases in cardiac filling, output and DO_2 than occurred with administration of Ringer's lactate [19].

Sepsis
Ernest et al. suggested that 5 % albumin infusion results in greater fluid extravasation in septic than in non-septic patients, but the (5-fold) superiority over saline in expanding the plasma versus interstitial volumes, per fluid volume administered, was maintained [17]. Hence, twice the volume of saline was needed to reach the same hemodynamic endpoints as with 5 % albumin loading. Nevertheless, Marx et al. suggested that severe septic shock accompanied by clinical evidence of a capillary leak syndrome was associated with shorter and less intravascular retention of intravenously administered 20 % albumin than in controls [22]. The VISEP trial documented that target values of CVP in severe sepsis were reached faster with 10 % HES loading than with Ringer's lactate, at an averaged volume ratio of 1:1.3, but mortality did not differ [3]. The CVP and central venous oxygen saturation ($ScvO_2$) in the HES group were somewhat higher than in the Ringer's lactate group, perhaps suggesting underestimation of saline requirements or overinfusion of starch. Trof et al., however, demonstrated, in per-

haps less severely ill patients, that 90 min fluid loading with 4–6 % colloids resulted in greater linear increase in cardiac filling, output and left ventricular stroke work than did saline loading both in septic and non-septic patients, probably due to a larger plasma volume following increased COP with the former and in spite of the characteristic myocardial depression of sepsis (**Fig. 1**) [11]. The effectiveness of colloids was 3-fold greater than that of saline, regardless of underlying condition, even though about 17 % more crystalloid was infused (volume ratio 1.2:1 see electronic supplement to ref. 11), confirming older data suggesting 2 to 5-fold greater fluid requirements with crystalloids in hypovolemic and septic shock aiming at similar hemodynamic endpoints [28, 48]. In children with Dengue shock syndrome, Ringer's lactate administration resulted in higher hematocrits, lower arterial (pulse) pressures and cardiac outputs, and slower shock reversal than did administration of (similar volumes of) colloids [2, 32]. In children with septic shock, up to 67 % more saline than gelatin (volume ratio 1.7:1) was required to reach similar plasma volume and hemodynamic targets [23].

General critical illness conditions

In patients with respiratory insufficiency and hemodynamic instability from sepsis or non-sepsis, Ringer's lactate was compared to 5 % albumin infusions to maintain hemodynamic 'stability' [49]. To attain similar hemodynamics, 1.8 volume of crystalloid for 1 volume of colloid had to be infused, although the difference did not reach statistical significance [49]. As mentioned, the SAFE study compared 4 % albumin with saline, guided by clinical parameters, and the volume ratio was about 1:1.4 [1].

Conclusion

Although a mortality benefit has not been documented, the use of (isooncotic) colloids results in more (rapid) plasma volume expansion and hemodynamic optimization than resuscitation with (isotonic) crystalloids in a variety of conditions, even when accompanied by presumed increased vasopermeability. Although recently suggested otherwise, the volume ratio for similar hemodynamic endpoints is approximately 1 colloid to 3 crystalloid. The factor is maintained when multiplying lower ratios, when applied, with the difference in hemodynamic endpoints attained. In randomized trials comparing colloids with crystalloids for fluid resuscitation and deviating from the ratio, the accurateness of hemodynamic monitoring and guiding of fluid therapy should be evaluated. Indeed, potential dissimilar resuscitation among groups may confound interpretation of relative benefits and detriments of solution types and future meta-analyses should take that disparity into account.

References

1. Finfer S, Bellomo R, Boyce N, et al for the SAFE Study Investigators (2004) A comparison of albumin and saline for fluid ressucitation in the intensive care unit. N Engl J Med 350: 2247–2256
2. Wills BA, Nguyen MD, Ha TL, et al (2005) Comparison of three fluid solutions for resuscitation in dengue shock syndrome. N Engl J Med 353: 877–889
3. Brunkhorst FM, Engel C, Bloos F, et al (2008) Intensive insulin therapy and pentastarch resuscitation in severe sepsis. N Engl J Med 358: 125–139

4. Chappell D, Jacob M, Hofmann-Kiefer K, Conzen P, Rehm M (2008) A rational approach to perioperative fluid management. Anesthesiology 109: 723 – 740
5. Dellinger RP, Levy MM, Carlet JM, et al (2008) International Surviving Sepsis Campaign Guidelines Committee. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock. Crit Care Med 36: 296 – 327
6. Hartog C, Reinhart K (2009) CONTRA: Hydroxyethyl starch solutions are unsafe in critically ill patients. Intensive Care Med 35: 1337 – 1342
7. Perel P, Roberts I (2007) Colloids versus crystalloids for fluid resuscitation in critically ill patients. Cochrane Database Syst Rev: CD000567.
8. Vercueil A, Grocott MP, Mythen MG (2005) Physiology, pharmacology, and rationale for colloid administration for the maintenance of effective hemodynamic stability in critically ill patients. Transfus Med Rev 19: 93 – 109
9. Salinas FV, Liu SS, Sueda LA, McDonald SB, Bernards CM (2006) Concurrent expansion of plasma volume and left ventricular end-diastolic volume in patients after rapid infusion of 5 % albumin and lactated Ringer's solution. J Clin Anesth 18: 510 – 514
10. Verheij J, van Lingen A, Beishuizen A, et al (2006) Cardiac response is greater for colloid than saline fluid loading after cardiac or vascular surgery. Intensive Care Med 32: 1030 – 1038
11. Trof RJ, Sukul SP, Twisk JW, Girbes AR, Groeneveld AB (2010) Greater cardiac response of colloid than saline fluid loading in septic and non-septic critically ill patients with clinical hypovolaemia. Intensive Care Med 36: 697 – 701
12. Shippy CR, Appel PL, Shoemaker WC (1984) Reliability of clinical monitoring to assess blood volume in critically ill patients. Crit Care Med 12: 107 – 112
13. Mangano DT, Van Dyke DC, Ellis RJ (1980) The effect of increasing preload on ventricular output and ejection in man. Limitations of the Frank-Starling mechanism. Circulation 62: 535 – 541
14. Kumar A, Anel R, Bunnell E, et al (2004) Effect of large volume infusion on left ventricular volumes, performance and contractility parameters in normmal volunteers. Intensive Care Med 30: 1361 – 1369
15. Hartemink KJ, Twisk JW, Groeneveld AB (2011) High circulating N-terminal pro-B-type natriuretic peptide is associated with greater systolic cardiac dysfunction and nonresponsiveness to fluids in septic vs nonseptic critically ill patients. J Crit Care (in press)
16. Schneider AJ, Teule GJ, Groeneveld AB, Nauta J, Heidendal GA, Thijs LG (1988) Biventricular performance during volume loading in patients with early septic shock, with emphasis on the right ventricle: a combined hemodynamic and radionuclide study. Am Heart J 116: 103 – 112
17. Ernest D, Belzberg AS, Dodek PM (1999) Distribution of normal saline and 5 % albumin infusions in septic patients. Crit Care Med 27: 46 – 50
18. Ernest D, Belzberg AS, Dodek PM (2001) Distribution of normal saline and 5 % albumin infusions in cardiac surgical patients. Crit Care Med 29: 2299 – 2302
19. Gondos T, Marjanek Z, Ulakcsai Z, et al (2010) Short-term effectiveness of different volume replacement therapies in postoperative hypovolaemic patients. Eur J Anaesthesiol 27: 794 – 800
20. Skillman JJ, Restall DS, Salzman EW (1975) Randomized trial of albumin vs. electrolyte solutions during abdominal aortic operations. Surgery 78: 291 – 303
21. Lamke LO, Liljadahl J-O (1976) Plasma volume changes after infusion of various plasma expanders. Resuscitation 5: 93 – 102
22. Marx G, Vangerow B, Burczyk C, et al (2000) Evaluation of noninvasive determinants for capillary leakage syndrome in septic shock patients. Intensive Care Med 26: 1252 – 1258
23. Upadhyay M, Singhi S, Murlidharan J, Kaur N, Majumdar S (2005) Randomized evaluation of fluid resuscitation with crystalloid (saline) and colloid (polymer from degraded gelatin in saline) in pediatric septic shock. Indian Pediatr 42: 223 – 231
24. Virgilio RW, Rice CL, Smith DE, et al (1979) Crystalloid vs. colloid resuscitation: is one better? Surgery 85: 129 – 139
25. Zetterström H (1981) Albumin treatment following major surgery.II. Effects on postoperative lung function and circulatory adaptation. Acta Anaesthesiol Scand 25: 133 – 141
26. Berg S, Golster M, Lisander B (2002) Albumin extravasation and tissue washout of hyalu-

ronan after plasma volume expansion with crystalloid or hypooncotic colloid solutions. Acta Anaesthesiol Scand 46: 166–172
27. McIlroy DR, Kharasch ED (2003) Acute intravascular volume expansion with rapidly administered crystalloid or colloid in the setting of moderate hypovolemia. Anesth Analg 96: 1572–1577
28. Rackow EC, Falk JL, Fein IA, et al (1983) Fluid resuscitation in circulatory shock: a comparison of the cardiorespiratory effects of albumin, hetastarch, and saline solutions in patients with hypovolemic and septic shock. Crit Care Med 11: 839–850
29. Tatara T, Tsunetoh T, Tashiro C (2007) Crystalloid infusion rate during fluid resuscitation from acute haemorrhage. Br J Anaesth 999: 212–217
30. Lange M, Ertmer C, Van Aken H, Westphal M (2011) Intravascular volume therapy with colloids in cardiac surgery. J Cardiothorac Vasc Anesth (in press)
31. Marx G (2003) Fluid therapy in sepsis with capillary leakage. Eur J Anaesthesiol 20: 429–442
32. Dung NM, Day NP, Tam DT, et al (1999) Fluid replacement in dengue shock syndrome: a randomized, double-blind comparison of four intravenous-fluid regimens. Clin Infect Dis 29: 787–794
33. Riddez L, Hahn RG, Brismar B, Strandberg A, Svensen C, Hedenstierna G (1997) Central and regional hemodynamics during acute hypovolemia and volume substitution in volunteers. Crit Care Med 25: 635–640
34. Lobo DN, Stanga Z, Aloysius MM, et al (2010) Effect of volume loading with 1 liter intravenous infusions of 0.9 % saline, 4 % succinylated gelatin (Gelofusine) and 6 % hydroxyethyl starch (Voluven) on blood volume and endocrine responses: a randomized, three-way crossover study in healthy volunteers. Crit Care Med 38: 464–470
35. Jones SB, Whitten CW, Monk TG (2004) Influence of crystalloid and colloid replacement solutions on hemodynamic variables during acute normovolemic hemodilution. J Clin Anesth 16: 11–17
36. Riemeier A, Schellhaass A, Boldt J, Suttner S (2009) Crystalloid/colloid versus crystalloid intravascular volume administration before spinal anesthesia in elderly patients: the influence on cardiac output and stroke volume. Anesth Analg 108: 650–654
37. Shires GT 3rd, Peitzman AB, Albert SA, et al (1983) Response of extravascular lung water to intraoperative fluids. Ann Surg 197: 515–519
38. Karanko MS, Klossner JA, Laaksonen VO (1987) Restoration of volume by crystalloid versus colloid after coronary artery bypass: hemodynamics, lung water, oxygenation, and outcome. Crit Care Med 15: 559–566
39. Hankeln K, Rädel C, Beez M, Laniewski P, Bohmert F (1989) Comparison of hydroxyethyl starch and lactate Ringer's solution on hemodynamics and oxygen transport of critically ill patients in prospective crossover studies. Crit Care Med 17: 133–135
40. Ley SJ, Miller K, Skow P, Preisig P (1990) Crystalloid versus colloid fluid therapy after cardiac surgery. Heart Lung 19: 31–40
41. Dawidson IJ, Willms CD, Sandor ZF, Coorpender LL, Reisch JS, Fry WJ (1991) Ringer's lactate with or without 3 % dextran-60 as volume expanders during abdominal aortic surgery. Crit Care Med 19: 36–42
42. Wahba A, Sendtner E, Strotzer M, Birnbaum DE (1996) Fluid therapy with Ringers solution versus Haemaccel following coronary artery bypass surgery. Acta Anaesthesiol Scand 40: 1227–1233
43. Marik PE, Iglesias J, Maini B (1997) Gastric intramucosal pH changes after volume replacement with hydroxyethyl starch or crystalloid in patients undergoing elective abdominal aortic aneurysm repair. J Crit Care 12: 51–55
44. Moretti EW, Robertson KM, El-Moalem H, Gan TJ (2003) Intraoperative colloid administration reduces postoperative nausea and vomiting and improves postoperative outcomes compared with crystalloid administration. Anesth Analg 96: 611–617
45. Shoemaker WC, Schluchter M, Hopkins JA, Appel PL, Schwartz S, Chang PC (1981) Comparison of the relative effectiveness of colloids and crystalloids in emergency resuscitation. Am J Surg 142: 73–84
46. Modig J (1983) Advantages of dextran 70 over Ringer acetate solution in shock treatment and in prevention of adult respiratory distress syndrome. A randomized study in man after traumatic-haemorrhagic shock. Resuscitation 10: 219–226

47. Lang K, Boldt J, Suttner S, Haisch G (2001) Colloids versus crystalloids and tissue oxygen tension in patients undergoing major abdominal surgery. Anesth Analg 93: 405 – 409
48. Allardyce DB (1974) Parenteral fluid therapy in septic shock: an evaluation of crystalloid and colloid. Am Surg 40: 542 – 547
49. Metildi LA, Shackford SR, Virgilio RW, Peters RM (1984) Crystalloid versus colloid in fluid resuscitation of patients with severe pulmonary insufficiency. Surg Gynecol Obstet 158: 207 – 212

Meaning of Pulse Pressure Variation during ARDS

J.-L. Teboul and X. Monnet

Introduction

Fluid management is a crucial issue during acute respiratory distress syndrome (ARDS). On the one hand, fluid administration is important to reverse adverse hemodynamic effects of mechanical ventilation with positive end-expiratory pressure (PEEP) or to restore adequate cardiovascular conditions in case of associated sepsis. On the other hand, since ARDS is characterized by the development of increased lung capillary permeability, fluid administration can result in lung fluid overload and hence in worsening of hypoxemia and further alteration of lung mechanics. Maintaining fluid balance is considered a major goal in the management of critically ill patients [1–3]. In comparison with a liberal strategy, a conservative strategy of fluid management in patients with acute lung injury (ALI) has been shown to shorten the duration of mechanical ventilation and intensive care without increasing non-pulmonary organ failure [3]. Accurate identification of patients who will not benefit from fluid administration in terms of hemodynamics ('preload unresponsive' patients) will enable unnecessary fluid loading to be avoided. In those identified as 'preload responders', the benefit/risk ratio of fluid administration should be assessed carefully before infusing fluid and must take into account not only indices of preload responsiveness but also markers of the severity of circulatory failure versus respiratory failure.

Functional hemodynamic parameters such as arterial pressure variation have gained wide popularity as predictors of the cardiovascular response to fluid administration in mechanically ventilated patients [4]. In the present chapter, we review the rationale, the practical use, and the limitations of measuring pulse pressure variation (PPV) in patients with ARDS.

Why use PPV?

The Concept of Preload Responsiveness

The relationship between ventricular preload and stroke volume (Frank-Starling relationship), is curvilinear: If the ventricle is operating on the steep part of the curve, an increase in preload must induce an increase in stroke volume (preload responsiveness). In contrast, if the ventricle is operating on the flat portion of the curve, increasing preload will not induce any significant increase in stroke volume (preload unresponsiveness). Thus, the patient is considered as a 'preload responder' only if both ventricles are operating on the steep part of the Frank-Starling curve.

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The Cyclic Effects of Mechanical Ventilation on Hemodynamics

Biventricular preload responsiveness can be determined by analyzing the cyclic consequences of mechanical ventilation on hemodynamics. Schematically, mechanical insufflation decreases preload and increases afterload of the right ventricle. The right ventricular preload reduction is due to the decrease in the venous return pressure gradient related to the inspiratory increase in intrathoracic pressure. The increase in right ventricular afterload is related to the inspiratory increase in transpulmonary pressure (alveolar minus intrathoracic pressure) [5]. The reduction in right ventricular preload and the increase in right ventricular afterload both lead to a decrease in right ventricular stroke volume, which is therefore minimal at the end of the inspiratory period [6]. The inspiratory decrease in venous return is the main mechanism of the inspiratory reduction of right ventricular stroke volume [7], which leads to a decrease in left ventricular filling after a phase lag of 2–4 heart beats because of the long pulmonary blood transit time. When conventional mechanical ventilation is applied, the decrease in left ventricular filling thus occurs during expiration. Finally, the left ventricular preload reduction may induce a decrease in left ventricular stroke volume, which is thus minimal during the expiratory period [6].

Interestingly, the cyclic changes in right ventricular preload induced by mechanical ventilation should result in greater cyclic changes in right ventricular stroke volume when the right ventricle operates on the steep rather than on the flat portion of the Frank-Starling curve [6]. The cyclic changes in right ventricular stroke volume – and hence in left ventricular preload – should also result in greater cyclic changes in left ventricular stroke volume when the left ventricle operates on the ascending and steep portion of the Frank-Starling curve [6]. Thus, the magnitude of the respiratory changes in left ventricular stroke volume should be an indicator of biventricular preload responsiveness [6].

PPV and Preload Responsiveness

At the aortic level, the pulse pressure (systolic minus diastolic pressure) is directly related to left ventricular stroke volume and inversely related to aortic compliance. Assuming that aortic compliance does not change during the respiratory cycle, the magnitude of cyclic changes in pulse pressure induced by mechanical ventilation (PPV) has been proposed to detect biventricular preload responsiveness in mechanically ventilated patients [8].

The PPV is calculated as the difference between the maximal (PPmax) and the minimal (PPmin) value of arterial pulse pressure over a single respiratory cycle (**Fig. 1**), divided by the mean of the two values, and expressed as a percentage:

$$PPV\ (\%) = (PPmax - PPmin) / [(PPmax + PPmin) / 2] \times 100.$$

PPV as a marker of fluid responsiveness

Numerous studies in various clinical settings have emphasized the usefulness of PPV in determining fluid responsiveness in mechanically ventilated patients [8–31]. Threshold predictive PPV values ranging between 9 and 17 % have been reported, although a cut-off value of 12 % has been more frequently reported [32, 33]. In the majority of the studies, areas under the receiver operating characteristics (ROC) curve greater than 0.90 have been reported, confirming the good predictive value of PPV [33]. Interestingly, PPV was demonstrated to be more accurate than static

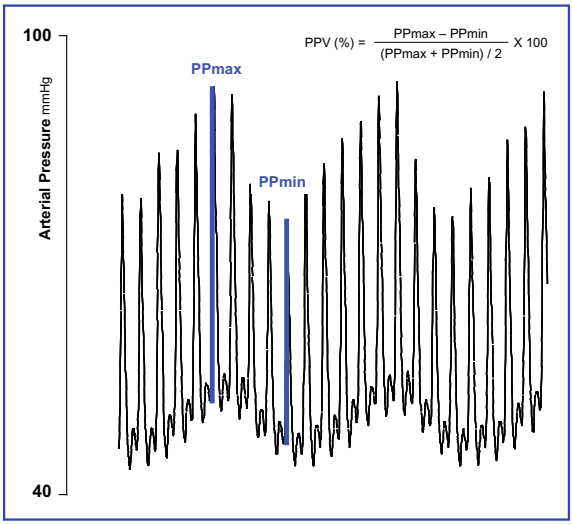

Fig. 1. Arterial pressure tracing in a mechanically ventilated patient. Pulse pressure variation (PPV) can be calculated as the difference between the maximal value of pulse pressure (PPmax) and the minimal value of pulse pressure (PPmin) divided by their averaged value and expressed as a percentage.

markers of preload in predicting fluid responsiveness [8, 10, 16–22, 33]. In addition, PPV can be used not only to predict fluid responsiveness but also to assess the actual changes in cardiac output following volume expansion. Indeed, a good correlation was found between the fluid-induced decrease in PPV and the increase in cardiac output (or stroke volume) following fluid administration [8, 34, 35].

PPV as a marker of the hemodynamic effects of PEEP

PPV can also be used to predict and assess the hemodynamic effects of PEEP in patients with ARDS. PEEP is frequently used with the aim of improving pulmonary gas exchange; however it may also decrease cardiac output and thus offset the expected benefits in terms of oxygen delivery. The adverse hemodynamic effects of PEEP are not easily predictable in clinical practice. It has been hypothesized that PPV could accurately predict the effects of PEEP on cardiac output [35]. Indeed, the PEEP-induced decrease in cardiac output and the decrease in right ventricular output induced by mechanical insufflation share the same mechanisms, i.e., the negative effects of the increased intrathoracic pressure on right ventricular filling and of the increased transpulmonary pressure on right ventricular ejection. Thus, it was hypothesized that the PEEP-induced decrease in cardiac output would correlate with the magnitude of the inspiratory decrease in right ventricular stroke volume and of the expiratory decrease in left ventricular stroke volume and hence with the magnitude of PPV [35]. In patients ventilated for ALI, a very close relationship was reported between PPV prior to the application of PEEP and the PEEP-induced decrease in cardiac output [35]. This finding strongly suggested that PPV before applying PEEP could predict the hemodynamic effects of PEEP [35]. Moreover, PEEP increased PPV such that the PEEP-induced decrease in cardiac index also correlated with the PEEP-induced increase in PPV [35]. Thus, the comparison of PPV prior to and after the application of PEEP may help to assess the hemodynamic effects of PEEP. In a study in cardiac surgery patients, a significant negative correlation was also found between PEEP-induced changes in cardiac output and PPV before PEEP application [34].

Practical Use of PPV in Patients with ARDS

The PPV is usually calculated from the arterial pressure waveform obtained with an arterial fluid-filled catheter (either radial or femoral artery). The calculation of PPV can be made either manually or automatically (**Fig. 1**). Manual determination of PPV can be obtained after freezing the screen of the hemodynamic monitor. Recent arterial pressure waveform-derived cardiac output monitors, such as PiCCO™ and LidCO™, allow automatic calculation of PPV. The PPV value can be displayed on the screen of the monitor and periodically updated.

As mentioned earlier, fluid management is a critical issue during ARDS since fluid resuscitation, which is often required because of the coexistence of sepsis and of PEEP application, can enhance pulmonary edema accumulation because of the presence of increased lung permeability. In this context, where a conservative fluid strategy is rather recommended [3], one may speculate that knowledge of PPV could be particularly useful for limiting the amount of fluid administered to the patient. Indeed, in the presence of low PPV (< 10 %), no beneficial hemodynamic effect of fluid administration is expected to occur and the clinician may judiciously choose to avoid volume resuscitation and might even adopt a fluid depletion strategy in some cases until the appearance of a significant increase in PPV [36]. In the presence of high PPV (above 12 – 15 %), the clinician has the knowledge that a positive hemodynamic response to volume infusion would occur if fluid were administered. The decision whether or not to infuse fluid will then depend on the expected benefit/risk ratio and thus on the degree of severity of other conditions such as circulatory failure, renal insufficiency or hypoxemia. If available, quantitative markers of lung tolerance, such as extravascular lung water (EVLW) measured using a PiCCO™ monitor or pulmonary artery occlusion pressure (PAOP) using a pulmonary artery catheter can also be helpful in the decision-making process.

PPV can also serve as a marker of the hemodynamic effects of PEEP in ARDS patients. A high PPV before applying PEEP indicates that application of around 10 cmH_2O of PEEP would significantly decrease the cardiac output [35]. Moreover, a significant increase in PPV after applying PEEP would confirm that the cardiac output has actually decreased [35]. Thus, determination of PPV could avoid the use of a sophisticated monitoring device with the only aim of assessing the hemodynamic consequences of PEEP application. From a practical point of view, it can be recommended that a trial at the initially desired level of PEEP is conducted. If there is a large increase in PPV during the trial, the clinician may then choose to infuse fluid or to reduce the level of PEEP, depending on other criteria, such as the degree of PEEP-induced improvement in lung mechanics and gas exchange and the severity of circulatory failure. In either case, the appropriate interpretation of PPV requires perfect synchronization of the patient with the ventilator (see below).

Limitations of the Use of PPV during ARDS

Although the usefulness of heart-lung interaction indices – such as PPV – to detect preload responsiveness, is now well established, a number of limitations must be remembered.

- **Persistence of Spontaneous Breathing Activity**

PPV cannot be used in patients with spontaneous breathing activity as has been demonstrated in at least three studies in critically ill patients [18, 37, 38]. This limitation is important since a large proportion of patients with ARDS may trigger their ventilator.

- **Cardiac Arrhythmias**

In cases of cardiac arrhythmias, the pulse pressure may vary for obvious reasons independent of mechanical ventilation, such that the PPV cannot be interpreted reliably [18].

- **Low Tidal Volume Ventilation**

The influence of tidal volume is a matter of debate. Obviously, for a given volume status, increasing tidal volume by increasing both transpulmonary pressure and intrathoracic pressure must increase PPV and *vice versa*. This has been confirmed in experimental as well as in clinical studies [39–42]. However, at the same time, increasing tidal volume can also decrease cardiac output mainly through a decrease in systemic venous return related to increased intrathoracic pressure. In this regard, increasing tidal volume can make preload responsive a patient who was not preload responsive [43]. Therefore, it is quite possible that PPV keeps its significance as a preload responsiveness index in case of increase in tidal volume [43]. Conversely, decreasing tidal volume should increase venous return and cardiac output [44] and potentially make preload unresponsive a patient who was previously preload responsive. Therefore, it is theoretically possible that PPV keeps its significance as a preload responsiveness index in case of decrease in tidal volume.

In almost all the studies examining the predictive value of PPV, patients were ventilated with tidal volumes ranging from 8 to 10 ml/kg. In a limited series of patients suffering from various critical illnesses, it has been reported that PPV was less predictive of volume responsiveness when tidal volume was < 8 ml/kg than when tidal volume was ≥ 8 ml/kg [14]. In addition, the threshold predictive value of PPV was lower in the case of tidal volume < 8 ml/kg (8 % *vs.* 12.8 %) [14]. Similar results were reported in another series of critically ill patients [45]. It must be stressed however, that low tidal volumes (around 6 ml/kg) are not generally applied to subjects with normal lungs but rather applied to patients with ARDS who exhibit high plateau pressure and reduced lung compliance. Consequently, during low tidal volume ventilation in patients with ARDS, respiratory changes in transpulmonary pressure should remain greater than normal and in spite of reduced lung compliance, cyclic changes in intrathoracic pressure may still be high enough for PPV to predict volume responsiveness [46]. Moreover, in ARDS patients ventilated with low tidal volume ventilation, application of relatively high levels of PEEP (between 10 and 15 cmH_2O) is now recommended [47]. This will result in increases in both transpulmonary pressure and intrathoracic pressure and hence in PPV [35]. Interestingly, in a study performed in patients with severe ARDS (mean PaO_2/FiO_2 96, mean static compliance 26 ml/kg) ventilated with low tidal volume (mean value 6.4 ml/kg), and high PEEP (mean value 14 cmH_2O), PPV was better than static markers of preload, such as cardiac filling

pressures, to predict fluid responsiveness and a 12 % threshold value was found [28]. Additional studies in severe ARDS patients are, however, necessary to investigate whether or not PPV could be used in cases of low tidal volume ventilation and high PEEP application.

Attempts have been made to improve the interpretation of PPV in cases of low tidal volume. For example, it was proposed that PPV be normalized to transalveolar pressure (plateau pressure minus PEEP) [45]. Unfortunately, with low tidal volume ventilation (< 8 ml/kg), the PPV/transalveolar pressure ratio did not perform better than PPV alone in predicting fluid responsiveness in a series of critically ill patients including only a few ARDS patients.

• High-frequency Ventilation

The hypothesis that PPV is a marker of preload responsiveness is based on the assumption that the decrease in left ventricular filling secondary to the insufflation-induced decrease in right ventricular stroke volume occurs 2–4 heart beats later owing to the long pulmonary transit time. This occurs during expiration when conventional mechanical ventilation is used. In case of high frequency ventilation, it may be possible for the two events (decrease in right ventricular output and decrease in left ventricular filling) to occur at the same period of the respiratory cycle (i.e., insufflation). Therefore, only minimal changes in stroke volume would occur during mechanical ventilation resulting in low PPV even in cases of biventricular preload responsiveness. De Backer et al. [48] recently addressed this issue in a series of 17 fluid responsive patients. PPV was measured at a low respiratory rate (14–16 breaths/min) and at the highest respiratory rate (30 or 40 breaths/min) achievable without altering tidal volume or inspiratory/expiratory ratio. Increase in heart rate resulted in a decrease in PPV from 21 % to 4 % and in respiratory variation in aortic flow from 23 % to 6 % [48]. The authors considered that PPV could be interpreted reliably when the heart rate/respiratory rate is higher than 3.6, a condition that is frequently encountered in ARDS patients, in whom tachycardia is frequently present, especially when they are fluid responsive.

• Right Ventricular Dysfunction

Another potential limitation of PPV in ARDS is related to the fact that, in some patients with marked right ventricular dysfunction (or with acute cor pulmonale), a significant PPV could result from a marked increase in right ventricular afterload during insufflation and thus could reflect preload responsiveness of the left ventricle but not of the right ventricle [49]. In this hypothesis, a high PPV could be observed in cases of fluid unresponsiveness (false positive cases). In a study performed in a series of 35 critically ill patients including a majority of surgical patients, the authors reported 34 % of false positive cases [50]. They attributed this finding to a predominant effect of transpulmonary pressure on the right ventricular afterload in presence of right ventricular dysfunction. However, it is hard to be totally convinced by such a hypothesis since the transpulmonary pressure was not very high as attested by the quite low plateau pressure and the presence of right ventricular dysfunction was probably overestimated with the tools used by the authors to detect it. It has to be stressed that few ARDS patients and no patients suffering from chronic right ventricular disease were included in this study. In other studies performed in septic and/or ARDS patients, a far lower

incidence of false positives was reported [8, 9, 14, 18, 21, 28] and the infusion of fluid in patients with high PPV resulted in a decrease in PPV accompanying the increase in cardiac output, even in cases of severe ARDS [35]. Interestingly, in patients ventilated with tidal volumes ≥ 8 ml/kg the PPV/transalveolar pressure ratio was reported to perform better than PPV in predicting fluid responsiveness by diminishing the number of false positive cases, presumably in relation to a right ventricular 'afterload effect' [45].

Clearly, other markers of fluid responsiveness are thus required in cases of spontaneous breathing activity, cardiac arrhythmias, high-frequency ventilation. They may also be helpful in some dubious cases, for example, when a low PPV is measured in case of low tidal volume, or when a high PPV is measured in presence of severe right ventricular dysfunction. In all these conditions, a passive leg raising (PLR) test has been proposed [50] to assess preload responsiveness. In this short test, lifting the legs passively from the horizontal position induces a gravitational transfer of blood from the lower limbs and from the abdominal compartment toward the intrathoracic compartment, and thus may act as a reversible 'self volume challenge' [51]. The real-time hemodynamic response to PLR measured by ultrasonography or arterial pressure waveform-derived cardiac output monitor has been demonstrated to accurately detect fluid responsiveness in spontaneously breathing patients [18, 52 – 57]. Alternatively, an end-expiratory occlusion test has been proposed in patients who are mechanically ventilated but have conditions where PPV may potentially be unreliable [57]. An increase in pulse contour cardiac output during a short end-expiratory occlusion was reported to identify fluid responsive patients with a good accuracy [56].

Finally, it must be stressed that preload responsiveness is a physiological phenomenon related to a normal cardiac preload reserve, since both ventricles of healthy subjects operate on the steep portion of the preload/stroke volume relationship. Therefore, detecting volume responsiveness cannot systematically lead to the decision to infuse fluid. Such a decision must be based on the presence of signs of cardiovascular compromise and must be balanced with the potential risk of enhancing pulmonary edema development and/or worsening gas exchange.

Conclusion

In mechanically ventilated patients, PPV has been demonstrated to be a more accurate marker of preload responsiveness than static measures of preload. Calculation of PPV can be helpful in the management of ARDS patients in terms of fluid and PEEP titration. However, appropriate use of PPV requires perfect synchronization of the patient with the ventilator and the presence of a regular cardiac rhythm. Further studies are required to investigate whether PPV and other heart-lung interaction indices can be appropriately used as predictors of preload responsiveness in severe ARDS patients ventilated with low tidal volumes.

References

1. Vincent JL, Sakr Y, Sprung CL, et al (2006) Sepsis Occurrence in Acutely Ill Patients Investigators. Sepsis in European intensive care units: results of the SOAP study. Crit Care Med 34: 344 – 353
2. Mitchell JP, Schuller D, Calandrino FS, Schuster DP (1992) Improved outcome based on fluid management in critically ill patients requiring pulmonary artery catheterization. Am Rev Respir Dis 145: 990 – 998
3. Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network (2006) Comparison of two fluid-management strategies in acute lung injury. N Engl J Med 354: 2564 – 2575
4. Michard F, Teboul JL (2002) Predicting fluid responsiveness in ICU patients. A critical analysis of the evidence. Chest 121: 2000 – 2008
5. Vieillard-Baron A, Loubieres Y, Schmitt JM, et al (1999) Cyclic changes in right ventricular output impedance during mechanical ventilation. J Appl Physiol 87: 1644 – 1650
6. Michard F, Teboul JL (2000) Using heart-lung interactions to assess fluid responsiveness during mechanical ventilation. Crit Care 4: 282 – 289
7. Vieillard-Baron A, Augarde R, Prin S, Page B, Beauchet A, Jardin F (2001) Influence of superior vena cava zone condition on cyclic changes in right ventricular outflow during respiratory support. Anesthesiology 95: 1083 – 1088
8. Michard F, Boussat S, Chemla D, et al (2000) Relation between respiratory changes in arterial pulse pressure and fluid responsiveness in septic patients with acute circulatory failure. Am J Respir Crit Care Med 162: 134 – 138
9. Vieillard-Baron A, Chergui K, Rabiller A, et al (2004) Superior vena cava collapsibility as a gauge of volume status in ventilated septic patients. Intensive Care Med 30: 1734 – 1739
10. Kramer A, Zygun D, Hawes H, Easton P, Ferland A (2004) Pulse pressure variation predicts fluid responsiveness following coronary artery bypass surgery. Chest 126: 1563 – 1568
11. Preisman S, Kogan S, Berkenstadt H, Perel A (2005) Predicting fluid responsiveness in patients undergoing cardiac surgery: functional haemodynamic parameters including the Respiratory Systolic Variation Test and static preload indicators. Br J Anaesth 95: 746 – 755
12. Hofer CK, Muller SM, Furrer L, Klaghofer R, Genoni M, Zollinger A (2005) Stroke volume and pulse pressure variation for prediction of fluid responsiveness in patients undergoing off–pump coronary artery bypass grafting. Chest 128: 848 – 854
13. Feissel M, Badie J, Merlani P, Faller JP, Bendjelid K (2005) Pre-ejection period variations predict the fluid responsiveness of septic ventilated patients. Crit Care Med 33: 2534 – 2539
14. De Backer D, Heenen S, Piagnerelli M, Koch M, Vincent JL (2005) Pulse pressure variations to predict fluid responsiveness: influence of tidal volume. Intensive Care Med 31: 517 – 523
15. Solus-Biguenet H, Fleyfel M, Tavernier B, et al (2006) Non-invasive prediction of fluid responsiveness during major hepatic surgery. Br J Anaesth 97: 808 – 816
16. Natalini G, Rosano A, Taranto M, Faggian B, Vittorielli E, Bernardini A (2006) Arterial versus plethysmographic dynamic indices to test responsiveness for testing fluid administration in hypotensive patients: a clinical trial. Anesth Analg 103: 1478 – 1484
17. Cannesson M, Slieker J, Desebbe O, Farhat F, Bastien O, Lehot JJ (2006) Prediction of fluid responsiveness using respiratory variations in left ventricular stroke area by transoesophageal echocardiographic automated border detection in mechanically ventilated patients. Crit Care 10: R171
18. Monnet X, Rienzo M, Osman D, et al (2006) Passive leg raising predicts fluid responsiveness in the critically ill. Crit Care Med 34: 1402 – 1407
19. Lafanechere A, Pene F, Goulenok C, et al (2006) Changes in aortic blood flow induced by passive leg raising predict fluid responsiveness in critically ill patients. Crit Care 10: R132
20. Cannesson M, Attof Y, Rosamel P, et al (2007) Variations in pulse oximetry plethysmographic waveform amplitude to predict fluid responsiveness in the operating room. Anesthesiology 106: 1105 – 1111
21. Feissel M, Teboul JL, Merlani P, Badie J, Faller JP, Bendjelid K (2007) Plethysmographic dynamic indices predict fluid responsiveness in septic ventilated patients. Intensive Care Med 33: 993 – 999

22. Wyffels PA, Durnez PJ, Helderweirt J, Stockman WM, De Kegel D (2007) Ventilation-induced plethysmographic variations predict fluid responsiveness in ventilated postoperative cardiac surgery patients. Anesth Analg 105: 448–452
23. Lee JH, Kim JT, Yoon SZ, et al (2007) Evaluation of corrected flow time in oesophageal Doppler as a predictor of fluid responsiveness. Br J Anaesth 99: 343–348
24. Biais M, Nouette-Gaulain K, Cottenceau V, Revel P, Sztark F (2008) Uncalibrated pulse contour-derived stroke volume variation predicts fluid responsiveness in mechanically ventilated patients undergoing liver transplantation. Br J Anaesth 101: 761–768
25. Cannesson M, Desebbe O, Rosamel P, et al (2008) Pleth variability index to monitor the respiratory variations in the pulse oximeter plethysmographic waveform amplitude and predict fluid responsiveness in the operating theatre. Br J Anaesth 101: 200–206
26. Cannesson M, Slieker J, Desebbe O, et al (2008) The ability of a novel algorithm for automatic estimation of the respiratory variations in arterial pulse pressure to monitor fluid responsiveness in the operating room. Anesth Analg 106: 1195–2000
27. Auler JO Jr, Galas F, Hajjar L, Santos L, Carvalho T, Michard F (2008) Online monitoring of pulse pressure variation to guide fluid therapy after cardiac surgery. Anesth Analg 106: 1201–1206
28. Huang CC, Fu JY, Hu HC, et al (2008) Prediction of fluid responsiveness in acute respiratory distress syndrome patients ventilated with low tidal volume and high positive end-expiratory pressure. Crit Care Med 36: 2810–2816
29. Cannesson M, Musard H, Desebbe O, et al (2009) The ability of stroke volume variations obtained with Vigileo/FloTrac system to monitor fluid responsiveness in mechanically ventilated patients. Anesth Analg 108: 513–517
30. Derichard A, Robin E, Tavernier B, et al (2009) Automated pulse pressure and stroke volume variations from radial artery: evaluation during major abdominal surgery. Br J Anaest 103: 678–684
31. Biais M, Bernard O, Ha JC, Degryse C, Sztark F (2010) Abilities of pulse pressure variations and stroke volume variations to predict fluid responsiveness in prone position during scoliosis surgery. Br J Anaesth 104: 407–413
32. Monnet X, Teboul JL (2007) Volume responsiveness. Curr Opin Crit Care 13: 549–553
33. Marik PE, Cavallazzi R, Vasu T, Hirani A (2009) Dynamic changes in arterial waveform derived variables and fluid responsiveness in mechanically ventilated patients: a systematic review of the literature. Crit Care Med 37: 2642–2647
34. Bendjelid K, Suter PM, Romand JA (2004) The respiratory change in preejection period: a new method to predict fluid responsiveness. J Appl Physiol 96: 337–342
35. Michard F, Chemla D, Richard C, et al (1999) Clinical use of respiratory changes in arterial pressure to monitor the hemodynamic effects of PEEP. Am J Respir Crit Care Med 159: 935–939
36. Teboul JL, Monnet X (2009) Detecting volume responsiveness and unresponsiveness in intensive care unit patients: two different problems, only one solution. Crit Care 13: 175
37. Heenen S, De Backer D, Vincent JL (2006) How can the response to volume expansion in patients with spontaneous respiratory movements be predicted? Crit Care 10: R102
38. Soubrier S, Saulnier F, Hubert H, et al (2007) Can dynamic indicators help the prediction of fluid responsiveness in spontaneously breathing critically ill patients? Intensive Care Med 33: 1117–1124
39. Kim HK, Pinsky MR (2008) Effect of tidal volume, sampling duration, and cardiac contractility on pulse pressure and stroke volume variation during positive-pressure ventilation. Crit Care Med 36: 2858–2862
40. Wiklund CU, Morel DR, Orbring-Wiklund H, et al (2010) Influence of tidal volume on pulse pressure variations in hypovolemic ventilated pigs with acute respiratory distress-like syndrome. Anesthesiology 113: 630–638
41. Reuter DA, Bayerlein J, Goepfert MS, et al (2003) Influence of tidal volume on left ventricular stroke volume variation measured by pulse contour analysis in mechanically ventilated patients. Intensive Care Med 29: 476–480
42. Charron C, Fessenmeyer C, Cosson C, et al (2006) The influence of tidal volume on the dynamic variables of fluid responsiveness in critically ill patients. Anesth Analg 102: 1511–1517

43. Michard F, Teboul JL, Richard C (2003) Influence of tidal volume on stroke volume variation. Does it really matter? Intensive Care Med 29: 1613
44. Kiiski R, Takala J, Kari A, Milic-Emili J (1992) Effect of tidal volume on gas exchange and oxygen transport in the adult respiratory distress syndrome. Am Rev Respir Dis 146: 1131 – 1135
45. Vallée F, Richard JC, Mari A, et al (2009) Pulse pressure variations adjusted by alveolar driving pressure to assess fluid responsiveness. Intensive Care Med 35: 1004 – 1010
46. Teboul Jl, Vieillard-Baron A (2005) Clinical value of pulse pressure variations in variations in ARDS. Still an unresolved issue? Intensive Care Med 31: 499 – 500
47. Briel M, Meade M, Mercat A, et al (2010) Higher vs lower positive end-expiratory pressure in patients with acute lung injury and acute respiratory distress syndrome: systematic review and meta-analysis. JAMA 303: 865 – 873
48. De Backer D, Taccone FS, Holsten R, Ibrahimi F, Vincent JL (2009) Influence of respiratory rate on stroke volume variation in mechanically ventilated patients. Anesthesiology 110: 1092 – 1097
49. Jardin F (2004) Cyclic changes in arterial pressure during mechanical ventilation. Intensive Care Med 30: 1047 – 1050
50. Antonelli M, Levy M, Andrews PJ, et al (2007) Hemodynamic monitoring in shock and implications for management. International Consensus Conference, Paris, France, 27 – 28 April 2006. Intensive Care Med 2007 33: 575 – 590
51. Monnet X, Teboul JL (2008) Passive leg raising. Intensive Care Med 34: 659 – 663
52. Lamia B, Ochagavia A, Monnet X, Chemla D, Richard C, Teboul JL (2007) Echocardiographic prediction of volume responsiveness in critically ill patients with spontaneous breathing activity. Intensive Care Med 33: 1125 – 1132
53. Maizel J, Airapetian N, Lorne E, Tribouilloy C, Massy Z, Slama M (2007) Diagnosis of central hypovolemia by using passive leg raising. Intensive Care Med 33: 1133 – 1138
54. Biais M, Vidil L, Sarrabay P, Cottenceau V, Revel P, Sztark F (2009) Changes in stroke volume induced by passive leg raising in spontaneously breathing patients: comparison between echocardiography and Vigileo/FloTrac device. Crit Care 13: R195
55. Thiel SW, Kollef MH, Isakow W (2009) Non-invasive stroke volume measurement and passive leg raising predict volume responsiveness in medical ICU patients: an observational cohort study. Crit Care 13: R111
56. Préau S, Saulnier F, Dewavrin F, Durocher A, Chagnon JL (2010) Passive leg raising is predictive of fluid responsiveness in spontaneously breathing patients with severe sepsis or acute pancreatitis. Crit Care Med 38: 819 – 825
57. Monnet X, Osman D, Ridel C, Lamia B, Richard C, Teboul JL (2009) Predicting volume responsiveness by using the end-expiratory occlusion in mechanically ventilated intensive care unit patients. Crit Care Med 37: 951 – 956

The Fluid Challenge

M. Cecconi, B. Singer, and A. Rhodes

Introduction

It is very hard to find a precise definition for what is one of the most commonly carried out interventions on intensive care units (ICUs) around the world. A fluid challenge is commonly understood to be a diagnostic intervention designed to give an indication of whether a patient with hemodynamic compromise will benefit from further fluid replacement. The principle is to administer a pre-determined volume of intravenous fluid over a short period of time while measuring a change in the patient's cardiovascular parameters. The aim is to differentiate hypovolemia, or relative hypovolemia, which might improve with further fluid, from cardiac failure or a full intravascular volume in which case further fluid will not improve things and may cause deterioration.

Patient Selection

A fluid challenge is usually indicated where there is clinical suspicion of hypovolemia or organ hypoperfusion as evidenced by changes in a patient's cardiovascular parameters. Causes of a low circulating volume are manifold. Some may be obvious, such as external losses in external hemorrhage, gastrointestinal losses, high urinary losses and burns. Others may be less obvious such as internal hemorrhage or distributive changes, e.g., in sepsis, inflammation or cardiac failure [1]. In Michard and Teboul's review of fluid challenges carried out in ICUs, the indications used by various authors to suspect a low circulating volume and a potential benefit of further fluid were the following [2]:

- Cardiac index < 2.5–3.5 l/min/m^2
- Systolic BP < 90 mmHg
- Heart rate > 120 bpm
- Oliguria (urine output < 25–30 ml/h)
- Lactic acidosis
- Oxygen delivery < 600 ml/min/m^2
- Cool extremities
- The need for vasoactive drugs
- Pulmonary artery occlusive pressure (PAOP) < 18 mmHg

Probably the most important indication cited was a clinical impression that cardiac output was inadequate and would respond to volume loading [2]. This is because none of the above signs and parameter changes is on its own specific;

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however, an overall assessment of the patient's presenting history combined with their clinical signs allows a physician to make an impression as to the likelihood of hypovolemia being present.

It is important to recognize the difference, however, between a patient who obviously needs fluids (the risk/benefit balance is in favor of immediate resuscitation) and one where the balance is more delicate. Therefore, a patient who is in hemorrhagic shock should obviously be resuscitated, whereas in a patient with septic shock who also has acute respiratory distress syndrome (ARDS) the situation is not so clear and they should undergo a fluid challenge rather than just blind intravenous volume administration.

Principle Behind the Fluid Challenge

Cardiac output is determined by a combination of stroke volume and heart rate. Stroke volume is a further product of afterload, ventricular contractility and preload. In a fluid challenge it is preload that is the variable that we are looking to affect.

Cardiac output can also be defined by a cardiac function and a venous return curve. A fluid challenge is initially aiming to affect the return function. Preload is the result of the return function and is governed by venous return, itself determined by a combination of vascular resistance to venous return and the gradient between mean systemic filling pressure and right atrial pressure. By giving a bolus of fluid in a fluid challenge you hope to increase circulating volume. This distends venous blood vessels, reducing resistance and increasing mean systemic pressure and, therefore, the gradient between mean systemic pressure and right atrial pressure, both leading to an increase in venous return and therefore preload [3] (**Fig. 1**).

The Frank-Starling mechanism explains how an increase in preload can lead to an increased force of ventricular contraction and, therefore, an increased stroke volume – a length-tension relationship. To understand how the Frank-Starling mechanism works we have to look at the physiology of the basic unit of a muscle fiber, the sarcomere. The length at which a muscle fiber develops greatest isometric active tension is defined as the optimum length [4]. In skeletal muscle, the resting sarcomere length is already approximately at the optimal length and further stretching reduces tension and contraction. However, in cardiac muscle, resting sarcomere length is less than the optimal length and lies on the rising part of a curve (**Fig. 2**). A further stretch of the sarcomere (e.g., by increased preload) causes an increase in length to a value nearer the optimum length and contraction is increased. This was initially thought to be due to the number of actin-myosin crossbridge overlaps increasing as the optimum length is approached, however the actual mechanism appears to be an increase in the sensitivity of troponin binding for calcium as length increases [5]. The length-tension curve levels out and even starts to dip as the sarcomere is stretched past its optimum length. This is explained by the reduction in the number of overlapping actin and myosin filaments able to form cross-bridges. Translating this into the physiology of a fluid challenge involves a starting hypothesis that the patient's current preload lies on the rising part of the length-tension relationship curve due to a sub-optimal filling volume. By giving a quick volume bolus you will increase the preload, and shift up the curve to a more optimal stretch length and, therefore, an

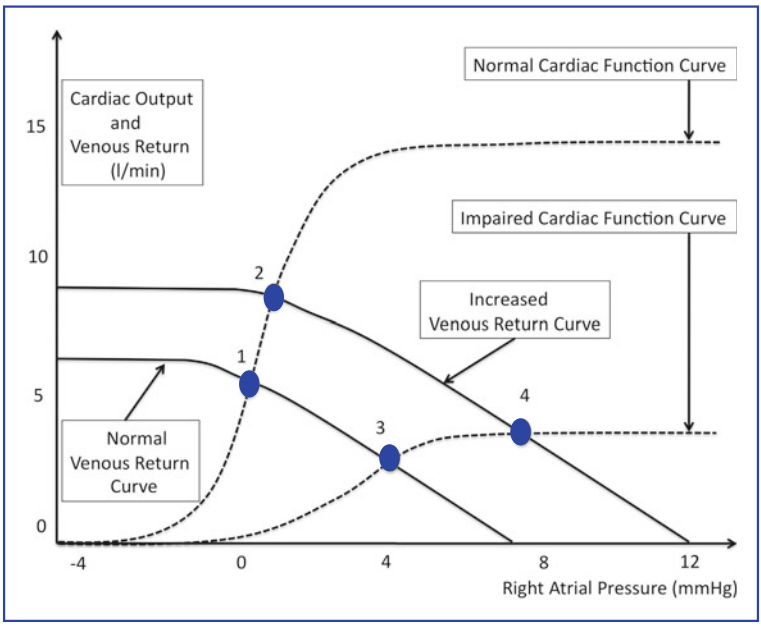

Fig. 1. This graph adapted from Guyton demonstrates two venous return curves intersecting two cardiac function curves. The normal venous return is zero at the intersection with the x-axis (right atrial pressure of about 8 mmHg). This is because in this example the mean systemic pressure (MSP) (the mean pressure pushing blood back towards the heart) is 8 mmHg before a fluid challenge and when the right atrial pressure equals the MSP there is no gradient and therefore no flow into the heart. Venous return increases as right atrial pressure falls and the gradient for venous return increases until a point where the right atrial pressure becomes negative and this negative pressure causes thoracic veins to collapse limiting the volume of venous return. Cardiac output occurs at the intersection with the normal cardiac function curve at point 1. Increasing blood volume by a fluid challenge in a heart with a suboptimal preload increases the MSP therefore increasing the gradient for venous return to occur, and increases the diameter of venous vessels reducing resistance to return and shifting the venous return curve up and to the right. This gives the increased venous return curve which intersects the normal cardiac function curve at a higher cardiac output at point 2 demonstrating the benefit of a fluid challenge in this situation. Also, as stroke volume increases with the increased preload, right atrial pressure hardly increases at all as the extra volume is ejected by the ventricle. In a failing heart, as demonstrated by the impaired cardiac function curve, the normal venous return curve intersects at a higher right atrial pressure giving a lower cardiac output (point 3). As the heart function is impaired, giving a fluid challenge fails to improve the cardiac output significantly as the preload and stretch is already likely to be towards the top of the Frank-Starling curve, and this is confirmed with the intersection with the increased venous return curve (point 4) demonstrating an insignificant improvement in cardiac output with a bigger increase in right atrial pressure likely due to the inability of the failing heart to deal with the extra return volume.

increased contraction and stroke volume. However, if for whatever reason preload is already adequate and stretch is already at the optimum length, a fluid challenge will not lead to any increases in stroke volume and may serve as a warning that if further fluid is given the heart will not be able to pump this extra volume and it will accumulate as peripheral and pulmonary edema.

The main principle that sits behind the fluid challenge is the fact that this is a ‘stress’ test. Increased intravascular volume, will lead to an increased right ven-

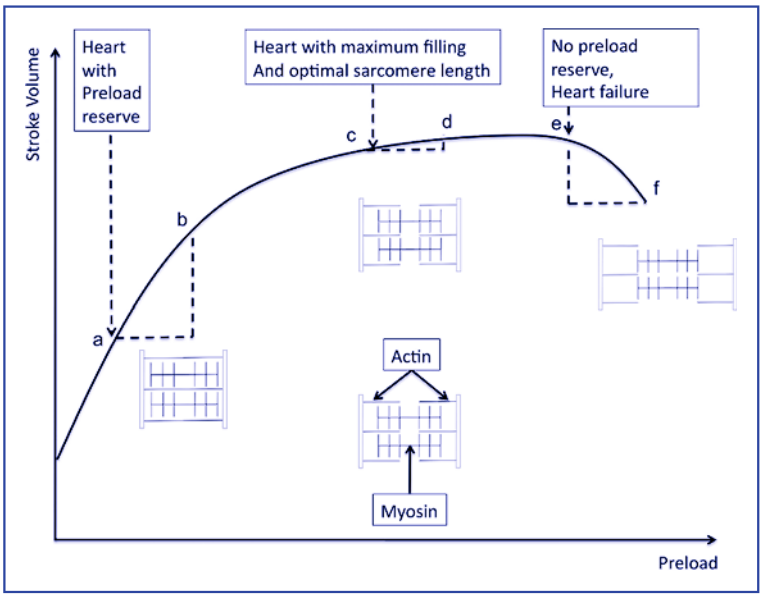

Fig. 2. Varying response to stoke volume with increasing preload as per the Frank-Starling mechanism. In a fluid challenge with the patient with a suboptimal preload stroke volume should increase by > 10 % (a-b). Once preload is optimized, stroke volume will no longer significantly increase (c-d) and if the heart is failing, theoretically you could see a decrease in stoke volume with further fluid and increased preload (e-f) although this has never been demonstrated *in vivo*.

tricular preload and then the test is to see how the heart reacts to this challenge. It should, therefore, be evident that it is vitally important for the test to 'challenge' the right ventricle. Insufficient fluid will lead to a negative response, not necessarily because the heart is not preload responsive but because the right ventricular preload was not increased (and then by Starling's law it should be obvious that contraction will not change).

Application of the Fluid Challenge

Before starting a fluid challenge, the first decision is what form of fluid resuscitation to use. The choices are colloid or crystalloid. Both have advantages and disadvantages, with a hyperosmotic colloid infusion likely to have a bigger hemodynamic impact than the same volume of isotonic crystalloid, but with colloids having small risks of interactions with clotting function and anaphylaxis. In a recent analysis of 406 fluid challenges in ICUs, 62 % of the challenges used colloid, 38 % crystalloid [2]. Recent evidence from the Saline versus Albumin Fluid Evaluation (SAFE) trial seems to suggest that either is as a safe as the other, so probably it makes little difference which fluid is used [6]. The next choice is how much volume to infuse. Some studies into fluid challenges do not infuse a pre-determined amount but instead give volume until a hemodynamic threshold is reached (e.g., until PAOP increases by 3 mmHg) [7]. However, the vast majority of fluid challenges give a set volume. The Surviving Sepsis resuscitation bundle recommends

1000 ml of crystalloid or 300–500 ml of colloid over 30 minutes [8]; however, a commonly used fluid challenge in intensive care would be 250 ml of colloid run in stat over 5–10 minutes.

One way of ensuring that enough fluid has been given in order to challenge the ventricle is to look at the filling pressures. Central venous pressure (CVP) can be used as a target for appropriate 'challenging' of the ventricle. If the CVP has increased by 2 mmHg, then the right ventricular end-diastolic volume will almost certainly have increased and this stretch should be sufficient to challenge the heart. Some authors would, therefore, advocate giving enough fluid over a quick period of time to increase the CVP by 2 mmHg. Remember, however, that this is only the guide to doing the challenge, the important variable is then the change in response of stroke volume.

The most important decision is to define how the impact of the fluid challenge will be measured and what will determine a successful or unsuccessful challenge. If cardiac filling pressures were a reliable indication of ventricular preload then CVP and PAOP (as an indication of left atrial filling pressure) would be ideal for determining any responsiveness to a fluid challenge, the theory being that small or no increases in filling pressures would indicate the heart was increasing the stroke volume in response to increased filling (coping with the extra volume) and as cardiac output was improving, preload was not optimal. If there was a significant rise in CVP or PAOP with fluid it would demonstrate that the heart was not able to deal with the increased blood volume and pressure was 'backing up' and more fluid would be detrimental. Unfortunately, despite this dynamic use of CVP and PAOP making physiological sense, it has never been properly investigated. CVP and PAOP have been looked at in different ways and there is strong evidence that neither baseline nor changes in CVP or PAOP are reliable predictors of fluid responsiveness. There are also studies that show no correlation between CVP level and actual blood volume, i.e., a patient with a high CVP is as likely to have a low circulating blood volume as a patient with a low CVP [9, 10]. This inability of CVP and PAOP to predict fluid challenge responders may be because preload is not only determined by the filling pressures, but also by afterload and perhaps most importantly by ventricular compliance, which is likely to be affected in critical illness.

CVP and PAOP can still be useful measurements in a fluid challenge by using dynamic rises as a guide that further fluid risks overloading that patient. A significant increase in CVP or PAOP immediately after a fluid challenge without any improvement in indicators of cardiac output may indicate right or left ventricular dysfunction with a risk of systemic or pulmonary edema. These parameters can, therefore, act as a safety net although they should not be used to help predict whether a patient will be fluid responsive [8]. We provide an example of a protocol evolved from Weil and Henning's work in the 1970s [11] and adapted from Venn et al. [12], which serves as a guide to interpreting increases in CVP and PAOP during and after a fluid challenge that might indicate that optimal cardiac filling pressures have been exceeded (**Table 1**)

Interestingly there is no gold standard used in the literature of what should be measured and to what degree increase in this variable should be seen as a positive response. The optimal parameter to decide whether a fluid challenge is successful is probably stroke volume. In most studies, a successful fluid challenge is defined by an increase in stroke volume of 10–20 % [2]. Measuring cardiac output either invasively or non-invasively is another outcome parameter commonly

Table 1. An example of a safety protocol using monitoring of central venous pressure (CVP) or pulmonary artery occlusion pressure (PAOP) during a fluid challenge (modified from [12])

	CVP	PAOP	Action
During fluid challenge	Increases > 5 mmHg	Increases > 7 mmHg	Stop infusion, WAIT and reassess
Following fluid challenge	Increases 3 – 5 mmHg	Increases 3 – 7 mmHg	WAIT and reassess
Following fluid challenge	Increases < 3 mmHg	Increases < 3 mmHg	Safe to repeat fluid bolus if indicated

Table 2. An example of one successful and two unsuccessful fluid challenges using a central venous pressure (CVP) safety protocol from **Table 1** and using 250 ml colloid given over 5 – 10 minutes with a cardiac index increase of > 15 % indicating a successful outcome (adapted from [1]). In Example 1, there is an increase of > 15 % in cardiac index with a fluid challenge indicating that the patient's cardiac filling pressures were suboptimal and the patient has responded to fluid. CVP has stayed within safety limits. In Example 2, there has been no increase in cardiac index and CVP has increased by 4 mmHg indicating that the patient has not responded to fluid and the CVP rise may indicate increased filling pressures and that further fluid will not be of benefit. In Example 3, the CVP has risen by 6 mmHg, a significant rise in filling pressure with a corresponding fall in cardiac index. As indicated in our safety protocol, the fluid challenge should be stopped as soon as the CVP increases by more than 5 mmHg as this CVP increase suggests optimal filling pressure have been exceeded and with no increase in cardiac index further fluid risks overload and pulmonary edema.

	Example 1		Example 2		Example 3	
Time	Baseline	5 – 10 mins	Baseline	5 – 10 mins	Baseline	5 – 10 mins
Cardiac index	2.7	3.4	3.2	3.2	2.9	2.7
CVP	9	10	8	12	12	18
Outcome	Successful	Repeat	Unsuccessful	Wait and reassess	Unsuccessful	Stop challenge and reassess

used; however cardiac output will also be affected by changes in heart rate. Other parameters that can be used depending on the patient and facilities available include mean arterial pressure (MAP), mixed venous saturations, lactate, heart rate, urine output, stroke volume variation, or even right end diastolic volume index. The most important thing is to decide on the parameter before starting the challenge, to measure the parameter dynamically if possible, and to clearly define what will be judged as a significant increase in that parameter. We present an example of a fluid challenge protocol using cardiac index as a measured outcome modified from Vincent and Weil [1] (**Table 2**). It is important to reduce any variables that may influence the outcome of the fluid challenge to a minimum. This involves avoiding changes in patient position or changes in infusions of inotrope or vasoactive drugs during the challenge.

It is important to mention that while a positive fluid challenge in a hemodynamically unstable patient may indicate that they will increase their cardiac output with further volume, this does not necessarily mean the patient should be given more fluid. This is a more clinical question and should be determined by an

overall assessment of the specific patient's needs. A negative fluid challenge indicates that further volume will not be beneficial and the challenge should not be repeated unless there is a change in the patient's underlying status or hemodynamic variables. Critical illness and intensive care therapy are dynamic processes with changes in cardiovascular tone or administration of inotropic or vasoactive drugs potentially making a non-responder a responder and *vice versa*.

Maximal Stroke Volume

Many authors describe the concept of maximal stroke volume [12–14]. This is where multiple fluid challenges are used in order to identify the flat part of the left ventricular function curve, or the 'maximal stroke volume'. This is an important concept to understand as it has been shown to improve outcomes in the perioperative period [12, 14]. The important point to understand is that although the term 'maximal' is used, it is not really what the investigators were doing. In reality, the challenges were being performed to achieve an increase in stroke volume of at least 10 %. This will probably put the patient still onto the rising part of the function curve and most definitely not reside within the flat part. If we use a lower level of increase in stroke volume, then two consequences may occur. One is that detecting the change many not have suitable precision for this small variation [15] and second that, especially in a young patient with a normally functioning heart, excess fluids may be given which will lead to very high filling pressures and tissue (and pulmonary) edema.

Risks

A fluid challenge is generally a very safe intervention. The main risk is of fluid overload, either systemic leading to peripheral edema or in the pulmonary circulation leading to pulmonary edema and worsening gas exchange. This risk is somewhat tempered by the fact that you are administrating a small amount of fluid as a diagnostic procedure that should indicate if a patient is not fluid responsive and potentially prevent greater amounts of fluid being given inappropriately. Therefore, the risks of fluid overload should if anything be reduced by a correctly performed fluid challenge. There remain potential risks of raised intracranial pressure in brain injured patients. The risks of fluid overload with fluid challenges in patients in renal failure are now reduced due to the increased availability of hemofiltration on ICUs [1].

Conclusion

As long as the indications for a fluid challenge as well as the potential successful and unsuccessful outcomes are defined and understood, it is a safe, simple and reproducible tool for the assessment and optimization of fluid replacement in hemodynamically unstable critical care patients.

References

1. Vincent JL, Weil MH (2006) Fluid challenge revisited. Crit Care Med 34: 1333 – 1337
2. Michard F, Teboul JL (2002) Predicting fluid responsiveness in ICU patients: a critical analysis of the evidence. Chest 121: 2000 – 2008
3. Guyton AC, Hall JE (2009) The Circulation. In: Guyton AC, Hall JE (eds) Textbook of Medical Physiology. Saunders, Philadelphia, pp: 229 – 240.
4. Widmaier EP, Raff H, Strang K (2008) Vander's Human Physiology: The Mechanisms of Body Function. McGraw-Hill, New York
5. Allen DG, Kurihara S (1982) The effects of muscle length on intracellular calcium transients in mammalian cardiac muscle. J Physiol 327: 79 – 94
6. Finfer S, Bellomo R, Boyce N, et al (2004) A comparison of albumin and saline for fluid resuscitation in the intensive care unit. N Engl J Med 350: 2247 – 2256
7. Wagner JG, Leatherman JW (1998) Right ventricular end-diastolic volume as a predictor of the hemodynamic response to a fluid challenge. Chest 113: 1048 – 1054
8. Dellinger RP, Levy MM, Carlet JM, et al (2008) Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. Intensive Care Med 34: 17 – 60
9. Osman D, Ridel C, Ray P, et al (2007) Cardiac filling pressures are not appropriate to predict hemodynamic response to volume challenge. Crit Care Med 35: 64 – 68
10. Marik PE, Baram M, Vahid B (2008) Does central venous pressure predict fluid responsiveness? A systematic review of the literature and the tale of seven mares. Chest 134: 172 – 178
11. Weil MH, Henning RJ (1979) New concepts in the diagnosis and fluid treatment of circulatory shock. Anesth Analg 58: 124 – 132
12. Venn R, Steele A, Richardson P, Poloniecki J, Grounds M, Newman P (2002) Randomized controlled trial to investigate influence of the fluid challenge on duration of hospital stay and perioperative morbidity in patients with hip fractures. Br J Anaesth 88: 65 – 71
13. Gan TJ, Soppitt A, Maroof M, et al (2002) Goal-directed intraoperative fluid administration reduces length of hospital stay after major surgery. Anesthesiology 97: 820 – 826
14. Pearse R, Dawson D, Fawcett J, Rhodes A, Grounds RM, Bennett ED (2005) Early goal-directed therapy after major surgery reduces complications and duration of hospital stay. A randomised, controlled trial [ISRCTN38797445]. Crit Care 9: R687 – 693
15. Cecconi M, Rhodes A, Poloniecki J, Della Rocca G, Grounds RM (2009) Bench-to-bedside review: the importance of the precision of the reference technique in method comparison studies--with specific reference to the measurement of cardiac output. Crit Care 13:201

Facing the Challenge: A Rational Strategy for Fluid and Volume Management

K. Heckel, M.S. Strunden, and D.A. Reuter

Introduction

Perioperative fluid and volume therapy is an important aspect relevant to outcome in the treatment of patients undergoing surgery and on the intensive care unit (ICU). New findings concerning the endothelial surface layer, its physiological functions and its role under pathological conditions, have led not only to a new understanding of the vascular barrier function, but also to challenges to traditional strategies for volume replacement in the operating room (OR) and in the ICU. The various studies comparing restrictive versus liberal fluid management are not directly comparable and are in most instances neither related to the physiological basis of perioperative fluid loss, nor do they differ between colloid and crystalloid administration for volume resuscitation.

Numerous different aspects contributing to perioperative volume resuscitation and fluid substitution have been the focus of basic and clinical research during recent years. Basically, three questions are intrinsically tied to infusion management:

1. What happens to intravascular fluid and why?
2. Which solutions should be used for fluid or volume replacement?
3. Can we deduce a rational strategy for infusion management?

During recent years, basic research has opened up new insights into the function of the endothelial vascular barrier and, in particular, into its functional changes during inflammation or other pathophysiological circumstances. Furthermore, experimental and clinical trials investigating the effects of crystalloid and colloid solutions – and their natural and artificial representatives – have shown quite conflicting results. The same accounts for the mainly clinical studies that have primarily focused on clinical goals to guide infusion therapy. However, all those aspects cannot be separated from each other when defining a rational strategy for infusion management.

Thus, we here first summarize current knowledge about the function and dysfunction of the endothelial vascular barrier and the effects of the different volume solutions in order to enable a rational concept of volume and fluid management to be developed based on current research regarding these topics.

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The Physiological Basis: What Happens to Intravascular Fluids and Why?

Why Does Fluid Stay Within the Vasculature? The Vascular Barrier!

Two-thirds of human body fluid is located in the intracellular compartment. The remaining extracellular space is divided into blood plasma and the interstitial space. Both compartments communicate across the vascular barrier to enable exchange of electrolytes and nutriments as the basis for cell metabolism. The positive intravascular pressure continuously forces blood towards the interstitial space. Under physiological conditions, large molecules, such as proteins and colloids, cannot cross the barrier in relevant amounts, which is a necessity for regular function of the circulation; otherwise the intravascular hydrostatic pressure would lead to uncontrollable loss of fluid towards the interstitial space and disseminated tissue edema [1]. Already in 1896, Ernest Starling suggested an interstitial colloid osmotic pressure (COP) far below the intravascular pressure. The concentration gradient across the vascular barrier generates a flow, which is directed into the vasculature. It opposes the hydrostatic pressure and results in a low filtration per unit of time. According to the Starling principle, only the endothelial cell line is responsible for providing vascular barrier function [2]. However, this classic concept cannot be completely sustained. Recent findings actually demonstrate similar protein concentrations in the intravascular and the interstitial spaces without causing vascular barrier dysfunction. In a rat mesenteric microvessel model, interstitial COP was nearly 70 % of intravascular osmotic pressure, which suggests, in contrast to the classical Starling concept, an only minor role for the interstitial protein concentration [3]. According to this theory, the endothelial cell line cannot be the only structure securing the transendothelial fluid balance [3]. Traditionally not recognized, the endothelial glycocalyx plays a pivotal role in this context. Healthy vascular endothelium is coated by transmembrane syndecans and membrane-bound glypicans containing heparan sulfate and chondroitin sulfate side chains, which together constitute the endothelial glycocalyx [4, 5]. Bound plasma proteins, soluble glycosaminoglycans and hyaluronan attach the glycocalyx to the endothelial surface layer, which is subject to periodic constitution and degradation. The endothelial surface layer has a thickness of around 1 μm, in large arterial vessels even 4 μm, and is therefore slightly thicker than the endothelial cell itself [4]. Under physiological conditions, the endothelial surface layer binds around 800 ml blood plasma, so the plasma volume can be divided into a circulating and non-circulating part [6]. Accordingly, the glycocalyx seems to act as a molecular filter retaining proteins and increasing the oncotic pressure within the endothelial surface layer. A small space between the anatomical vessel wall and the endothelial surface layer remains nearly protein-free [3]. Fluid loss across the vascular barrier seems to be limited by an oncotic pressure gradient within the endothelial surface layer, not across the whole anatomical vessel wall [7]. Starling's classical principle was, therefore, modified to the 'double-barrier-concept' in which not only the endothelial cell line but primarily the endothelial surface layer, formed by the glycocalyx and plasma proteins, constitutes the vascular barrier [7]. Therefore, an intact endothelial surface layer is a necessity for a regular circulation of blood. Under physiological conditions, the endothelial surface layer also provides a certain distance between blood cells and the anatomical vessel wall even in the smallest capillary vessels. In the past this effect was described as the physical 'Fahraeus-Lindqvist-

Effect' [8]. Not surprisingly, destruction of the glycocalyx by heparinase, an enzyme shedding heparin sulfate from the glycocalyx, selectively increased the physiologically lower capillary hematocrit nearly to levels of major blood vessels [9]. Thus, the 'Fahraeus-Lindqvist-Effect' cannot be the only mechanism explaining the distance between blood cells and vessel walls.

Degradation of the Vascular Barrier: Reasons and Consequences

The endothelial surface layer constitutes the first contact surface between blood and tissue and, therefore, seems to be involved in many processes concerning not only vascular barrier function, but also inflammation and the coagulation system.

A number of studies have identified various agents and pathophysiological situations that impair the endothelial surface layer thickness and the glycocalyx scaffolding. These experimental data could be confirmed by a clinical investigation showing increased plasma levels of syndecan-1 and heparan sulfate in patients with global or regional ischemia undergoing major vascular surgery. The dimension of glycocalyx degradation was proportional to the duration of ischemia in this study [10]. In addition to ischemia/reperfusion injury, several circulating mediators are known to initiate degradation of the glycocalyx. Tumor necrosis factor (TNF)-α, oxidized lipoproteins and cytokines, proteases and heparanase from activated mast cells are well described actors in the systemic inflammatory response syndrome, leading to a reduction in the endothelial surface layer thickness [4, 5]. Shedded heparan sulfates have a chemotactic impact on leukocytes and additionally promote their accumulation at the site of inflammation [11]. Thus, destruction of the glycocalyx could be a trigger for increased leukocyte adhesion and increased transendothelial permeability leading to the development of tissue edema. Under physiological conditions, endothelial adhesion molecules are covered at a dimension of some tens of nanometers by the intact endothelial surface layer. Degradation of the covering glycocalyx allows direct contact of adhesion molecules to immunocompetent cells in blood plasma and, therefore, firm leukocyte adhesion [4]. In addition, the endothelial surface layer influences the coagulation system. It binds tissue factor and fibrinogen and participates in platelet adhesion to the vascular wall [12].

Interestingly, hypervolemia may also lead to a degradation of the endothelial surface layer and the glycocalyx. In isolated guinea pig hearts, Bruegger et al. [13] demonstrated a shedding of glycocalyx caused by atrial natriuretic peptide, which is released from atrial cells during hypervolemia. Hypervolemia resulting from inappropriately high fluid administration may, therefore, cause iatrogenic damage to the glycocalyx.

The influence of inflammatory mediators on the endothelial glycocalyx and the dramatic consequences of its degradation, the collapse of the endothelial surface layer, were shown by Nelson et al., who found increased plasma levels of glycosaminoglycans in septic patients [14]. In addition, syndecan-1 levels were 10 to 100-fold increased and correlated to the cardiovascular sequential organ failure assessment (SOFA) score in their patients. Moreover, the median glycosaminoglycan levels were higher in patients who did not survive [14].

Fluid Balance: Where Do Fluids Get Lost?

Fasting and fluid losses prior to and during surgery or during an ICU stay lead to a deficit in fluid balance. The first type of fluid loss primarily affects the intravascular and the interstitial space and consists of urine production and insensible perspiration. Physiologically this loss is replaced by free water absorbed from the gastrointestinal system. Because this mode of replacement is limited in fasted patients, physicians have to compensate it artificially by infusing crystalloid solutions. Of course, the composition of the used infusion should be similar to the physiologic condition in order to avoid acid-base disorders, which is the rationale for balanced crystalloid infusions. Second loss (primarily blood losses) affects initially the intravascular compartment [4]. Consequently, the first type of fluid loss is attenuated by redistribution between the intracellular, interstitial and intravascular space slowly and rather causes dehydration, while the second type of loss leads to acute hypovolemia.

Hypovolemia and extravascular dehydration after a fasting period is regularly described in anesthesia text books. It is recommended that these fluid losses be replaced and that perioperative fluid loss, which is caused by insensible perspiration and evaporation from wounds and exposed gut, be adjusted by infusion rates of up to 10 ml/kg per hour or even higher. However, it is now well known that in contrast to these recommendations the fasting period before elective surgery does not lead to hypovolemia in all patients. Even after ten hours of fasting, blood volume is normal in cardiovascular healthy patients and preoperative fluid reloading is, therefore, not justified [15]. Jacob et al. measured plasma and red cell volume in 53 gynecological patients suffering from cervical malignancy directly before surgery and their results may be transferable to similar low invasive surgery. Patients undergoing major abdominal surgery or suffering from severe cardiovascular disease will probably require different treatment. However, there is as yet no validation with direct blood volume measurements in these groups of patients.

Undifferentiated volume loading leads to acid-base-balance disorders and increased liberation of atrial natriuretic peptide, which is known to degrade the endothelial glycocalyx and can, therefore, cause increased vascular permeability [13, 16]. However, fluid losses from insensible perspiration are obviously overestimated in many patients; Lamke et al. in 1977 showed a loss of only 1 ml/kg per hour, even when the abdominal cavity was opened [17]. Based on these considerations, it should theoretically be adequate to substitute only the described losses plus any blood loss in order to obtain a normal blood volume, but in daily clinical routine much greater amounts of fluids are frequently infused. This strategy is based on the assumption that generous fluid administration may prevent hypotension, which is, as well as application of vasoconstrictors, seen as a reason for postoperative renal failure [18]. However, it has not yet been shown that a liberal infusion regime would decrease the incidence of acute renal failure. Moreover, reduced renal function seems to be a physiological stress response of the body to protect its fluid compartments [19]. There is also no evidence for an increased occurrence of postoperative renal dysfunction when normovolemia is secured after surgery [19]. In addition, it is questionable whether fluid administration is an appropriate means of preventing the negative inotropic and vessel-dilatating effects of general anesthesia or sedation.

Nevertheless, our daily observation is that patients require a much greater amount of fluids than suggested by the considerations above. As shown by blood

volume measurements, major surgery indeed causes a deficit of 3 – 6 l in perioperative fluid balance (measurable input minus measurable output) [20, 21]. This shift is not only an intraoperative problem. The peak persists up to 72 h after trauma or surgery [22]. But where has the fluid gone?

The common explanation is a fluid shift into the so-called 'third' space. This third space can be divided into an 'anatomical' and a 'non-anatomical' part. Physiologic fluid shifting from the vessel towards the interstitial space across an intact vascular barrier contains only small amounts of proteins and small molecules and does not cause interstitial edema as long as it can be quantitatively managed by the lymphatic system. Losses into the 'anatomic' space are based on the described physiological mechanism, but in a pathological quantity [1, 4]. Excessive administration of crystalloids leads to an overload of the interstitial space and the capacity of the lymphatic system is surpassed. The consequence of this mechanism is formation of interstitial edema. Redistribution between intravascular and interstitial spaces solves this disturbance only temporarily.

The 'non-anatomic' third space in contrast is believed to be a compartment separated from the interstitial space [1, 4]. Losses towards this compartment are therefore assumed to be trapped and lost for extracellular exchange. Cited examples for classical 'non-anatomic' third space losses are fluid accumulation in traumatized tissues, bowel, and peritoneal cavity.

Despite intensive research using various techniques, a classic third space has never been identified. Fluid is rather shifted from the intravascular to the interstitial space [1]. Regarding this, Chappell et al. [1] classified two types of fluid shifting:

- Type 1, occurring always, represents the physiological, almost colloid free shift out of the vasculature. This shift happens even if the vascular barrier is intact, occasionally also at pathological amounts as described above.
- Type 2 is the pathological shift, which is caused by a dysfunction of the vascular barrier. In contrast to type 1, fluid crossing the barrier now contains proteins close to plasma concentrations [1]. Two factors lead to this type 2 fluid shift: First, surgical manipulation leads to endothelial damage and increases capillary protein permeability excessively. In animal experiments, interstitial fluid increased by about 10 % during realization of an enteral anastomosis without any fluids being infused [23]. Interestingly, a moderate concomitant administration of 5 ml/kg of crystalloid infusion doubled this edema. Second, iatrogenic hypervolemia damages the glycocalyx and can, therefore, cause an extensive shift of fluid and proteins towards the tissue [20, 21].

It has been a common assumption that, in contrast to crystalloids, colloids would stay within the vasculature. This theory was principally questioned by Rehm et al., who described a distinctive context sensitivity of artificial colloids. On the basis of direct blood volume measurement these authors found a volume-effect above 90 % when an iso-oncotic hydroxyethyl starch (HES) solution was infused carefully titrated to the actual blood loss. In contrast, two-thirds of the infused volume left the vascular bed immediately when the same amount was administered as a bolus in a normovolemic patient [20, 21]. Thus volume-efficiency of colloids depends on the situation and the way in which they are given and their high therapeutic potency obviously requires the right indication and careful titration to the actual blood loss. Otherwise, inadequately high amounts of fluid cause

protein loss towards the interstitial space of nearly one third of the total intravascular protein content [4]. This, when considering the double barrier concept, even intensifies fluid loss into the interstitial space and further promotes formation of tissue edema. This is reflected in clinical data published nearly two decades ago. In 1990, Lowell et al. showed a weight gain of more than 10 % in comparison to the preoperative weight in over 40 % of the patients admitted to the ICU after major surgery. Furthermore, the increase in body weight, as a sign for interstitial edema, correlated strongly with mortality in this observation [24].

Fluid Replacement: Which Fluid is the Adequate Drug for Which Disease?

Dehydration or Hypovolemia: What is the Treatment Intention?

As mentioned above, dehydration of the extravascular compartment and acute intravascular hypovolemia, are two different clinical aspects and, therefore, deserve different therapeutic considerations. Urine production and insensible perspiration cause a loss of electrolytes and colloid-free fluid from the interstitial space. Only secondly does this have an impact on the intravascular compartment. Thus, the resulting dehydration has to be treated by refilling the interstitial space and replacing further losses by crystalloid infusions [1]. In practice, only the intravascular compartment can be accessed, even if the intention is to treat the interstitial space. However, crystalloids freely distribute between interstitial and intravascular space if the vascular barrier is intact.

In contrast, acute hypovolemia with its potentially life-threatening consequences at first affects the intravascular compartment. The primary goal of the cardiovascular system is to supply adequate amounts of oxygen to meet the metabolic demands of the body. Circulatory shock, regardless of its etiology, causes tissue hypoperfusion with subsequent tissue oxygen debt, cellular dysfunction and organ injury. Cell death may occur proportional to the duration and the degree of tissue hypoperfusion as quantified by oxygen debt [25]. Hence, the target of volume resuscitation is to maintain adequate tissue perfusion in order to ensure tissue oxygenation. Hypovolemia, as well as hypervolemia, can lead to decreased tissue perfusion with subsequent organ failure [26] and even supplemental oxygen does not improve oxygenation in hypoperfused tissues [27]. Hypovolemia is a frequent cause for hemodynamic deterioration; securing adequate intravascular volume and tissue oxygenation is thus a major mission for physicians.

Because of their free distribution over the intact vascular barrier, crystalloids are not suitable for volume resuscitation in acute hypovolemia. Additionally, lost colloids and proteins cause decreased intravascular oncotic pressure, which would even be aggravated by administration of colloid-free crystalloids and would force the formation of interstitial edema. Thus solutions that mainly remain within the intravascular space and maintain oncotic pressure are needed to treat acute losses of plasma volume effectively, i.e., colloids.

Crystalloids

Crystalloids distribute freely across the intact vascular barrier. Only one fifth of the intravenously infused amount remains intravascular [1]. A four fold amount

of crystalloid infusion is needed to reach the same intravascular volume effect in comparison to colloid infusion [28]. Whether this relation differs in critically ill patients suffering from impaired glycocalyx barrier function is the target of current clinical and experimental investigations. Verheij et al. found no differences in pulmonary permeability and lung injury score when comparing saline fluid loading to colloid fluid loading in patients after cardiac and major vascular surgery with the exception that only fluid loading with HES improved cardiorespiratory function parameters [29].

In line with the double barrier concept [1, 4] and the direct blood volume measurements made by Rehm et al. [20, 21] one could assume that colloids distribute as freely as crystalloids across the vascular barrier if it is seriously impaired. But, whether these findings, comparing crystalloids against colloids for volume resuscitation, are generally applicable to every critically ill patient with a more or less impaired vascular barrier is questionable, because we do not have any valid surrogate parameter for measuring vascular barrier function of a patient at the bedside. However, volume resuscitation, not the compensation of dehydration, with crystalloid infusions led to respiratory distress syndrome, cerebral edema and abdominal compartment syndrome in patients with major trauma [30].

Moreover, large amounts of saline infusion promote development of hyperchloremic acidosis and increase the demand for bicarbonate substitution to maintain a physiological pH-value [31]. Although there is ongoing discussion about the pros and cons of balanced crystalloid solutions, their use is beneficial to avoid acid-base disorders [32].

Colloids

The only natural colloid used clinically is albumin. Artificial colloids include gelatin, dextran, and HES solutions (**Table 1**). Investigations during an observational study observing the effects of HES on renal function showed a considerable variation in colloid use across European countries. HES and gelatin were most used, whereas albumin was used less commonly [33].

Under physiologic conditions, albumin is the molecule mainly accountable for the intravascular osmotic pressure and should therefore be an ideal colloid to restore protein losses from the vasculature. But, as a natural colloid, albumin may cause severe allergic reaction and immunologic complications. A number of trials using albumin for the treatment of hypovolemia in ICU patients are available. A Cochrane review of 30 randomized controlled trials including 1419 patients showed no evidence for a reduced mortality in critically ill patients with hypovolemia or burns compared to crystalloid infusions. Usage of albumin may contrari-

Table 1. Commonly used intravenous solutions

crystalloids	colloids		blood components
	natural colloids	artificial colloids	
glucose solutions	albumin	dextran	whole blood
sodium chloride solutions		gelatin	erythrocyte concentrate
electrolyte solutions, unbalanced		HES 130	fresh frozen plasma
electrolyte solutions, balanced		HES 200	

wise even increase mortality [34]. More recently, the SAFE study including 6997 patients and comparing albumin to normal saline fluid resuscitation found no beneficial effects nor increased mortality after 28 days in the albumin group. In addition, no significant differences in days spent in the ICU, days spent in the hospital and days of mechanical ventilation or renal-replacement therapy were observed [35]. Thus, isooncotic albumin obviously has no adverse effects on the outcome of critically ill patients, but also does not improve mortality. Treatment with albumin in a 20 % concentration, in contrast, increased mortality in patients with shock [36]. Therefore, use of isooncotic albumin may be justifiable in particular cases, but not as a routine strategy for fluid replacement.

Gelatins are polydispersed polypeptides produced by degradation of bovine collagen. The available gelatin products are oxypolygelatins, urea-crosslinked or succinylated gelatins. The average molecular weight of various gelatin solutions is 30,000 to 35,000 Da and their volume-expanding power is comparable. All preparations are said to be safe with regard to organ function and coagulation [37]. However, concerning kidney function, conflicting results have been published. Mahmood et al. compared the effects on renal function of 6 % HES 200/0.62 and HES 130/0.4 solutions with a 4 % gelatin solution. They randomized 62 patients undergoing aortic aneurysm surgery and measured serum urea and creatinine, creatinine ratio, urinary immunoglobulin G and α1-microglobulin. The group treated with gelatin showed higher levels of serum urea and creatinine than the HES treated groups on days 1, 2 and 5 after surgery. Additionally, tubular damage was higher in patients treated with gelatin. Patients of both HES groups showed less compromised renal function and reduced renal injury, with HES 130/0.4 seeming to be advantageous compared to to HES 200/0.62 [38]. An investigation by Boldt et al. showed similar results. Sixty patients, older than 80 years, were treated with 6 % HES 130/0.4 or 4 % gelatin solution during cardiac surgery. Use of gelatin was associated with more distinctive changes in kidney function and endothelial inflammatory response than HES administration [37].

HES, an artificial polymer, is derived from amylopectin, which is a highly branched chain of glucose molecules obtained from waxy maize or potatoes. Conservation from degradation via amylase and water solubility is achieved by hydroxyethylation of the glucose units. HES solutions are available in several preparations and vary with regard to concentration, molecular weight, molar substitution, C_2/C_6 ratio and the solvent. The different generations of HES solutions can be subdivided according to the degree of hydroxyethylation (molar substitution) and molecular weight determining their pharmacological profile.

Whereas small HES molecules (< 50 – 60 kDa) are eliminated rapidly by glomerular filtration, larger molecules are hydrolyzed to smaller fractions and are partially taken up in the reticuloendothelial system [39]. Although this storage seems not to impair the mononuclear phagocytic system, it is remarkable that low molecular weight HES accumulates less compared to high molecular weight HES. The percentage of administered HES 130/0.4 remaining in the plasma 24 h after infusion is lower compared to HES 200/0.5. Further application of HES 200/0.5 results in continuously increasing plasma accumulation [39].

Negative effects of high molecular HES on the coagulation system are well described. Preparations above 200 kDa lead to a reduction in von Willebrand factor and factor VIII, causing decreased platelet adhesion. Newer, low molecular weight preparations, i.e., 6 % HES 130/0.4, have only minimal effects on coagula-

tion as proven in several experimental and clinical studies. In contrast to unbalanced saline, HES 130/0.4 in a balanced solution even increased the expression of activated platelet GP IIb/IIIa, indicating improved hemostasis [40].

Focusing on kidney function, Legendre et al. [41], as well as Cittanova et al. [42], reported an 80 % rate of "osmotic nephrosis-like lesions" and impaired renal function in kidney transplant recipients after administration of HES 200/0.62 to brain-dead organ donors. Further, in septic patients, the use of 10 % HES 200/0.5 was related with a higher incidence of renal failure compared to crystalloids [43]. However, in this study HES was administered without regard to exclusion criteria and dose limitations. The most likely pathomechanism of renal impairment by colloids is the induction of urine hyperviscosity by infusing hyperoncotic colloids in dehydrated patients. Glomerular filtration of hyperoncotic molecules from colloids may cause hyperviscous urine and result in stasis of the tubular flow [40]. Based on this pathogenesis, all hyperoncotic colloids may induce renal damage. Elevated plasma oncotic pressure, regardless of its genesis, has been known to cause acute renal failure since more than twenty years [44]. Thus, strictly avoiding dehydration in patients who are volume-resuscitated with colloids is of high importance. In addition, use of new isooncotic tetrastarch solutions seems not to impair renal function [40]. In contrast to the results of the VISEP study, which showed a higher incidence of renal failure when a pentastarch solution was used for fluid resuscitation, the SOAP study, including more than 3000 critically ill septic patients treated with pentastarch and tetrastarch solutions, showed no greater risk for acute renal failure with these solutions [33]. HES was administered in much lower amounts (13 ml/kg body weight versus 70 ml/kg body weight) and for a shorter period (2 days versus 21 days) in the SOAP study compared to the VISEP study. Especially for the newer tetrastarch solution, 6 % HES 130/0.4, no negative data regarding renal function are available from randomized clinical studies. Contrariwise, even when administered in extremely high application rates (up to 66 l in 21 days) in patients with severe head injury no impairment of renal function was observed [45].

HES also has a known impact on inflammation. Nohé et al. demonstrated inhibition of neutrophil adhesion by synthetic colloids experimentally [46]. Feng et al. showed an attenuated inflammatory response in HES-treated septic rats. Six hours after cecal ligation and puncture, the increase in pulmonary capillary leakage was less distinctive in HES-treated animals than in gelatin-treated rats. In addition, HES could, amongst others, decrease TNF-α, interleukins, myeloperoxidase activity and neutrophil infiltration of the lung [47]. Similar results were achieved from volume resuscitation of rats in hemorrhagic shock. HES 130/0.4 attenuated pulmonary injury by modulating the inflammatory response and oxidative stress following severe hemorrhagic shock [48].

Infusion Management: A Rational Strategy

A rational strategy for application of infusions should be predicated from the physiological basis of circulatory function and considering the disease one is intending to treat. To meet these demands, guidance by appropriate hemodynamic monitoring is as essential as the choice of adequate drug for volume resuscitation on the one hand and fluid substitution on the other hand.

Recent research provides a closer look at the vascular barrier function, its role in disease and the consequences of its impairment. Since consolidated findings regarding the glycocalyx and the endothelial surface layer have lead to a new comprehension of the vascular barrier, Starling's principle has been adjusted to the 'double-barrier concept'. The pathophysiological mechanisms concerning endothelial surface layer alterations play a major role in the development of inflammatory responses and tissue edema. Glycocalyx degradation not only leads to a dramatically increased capillary permeability and distinctive fluid loss towards the interstitial space, but also to deteriorated flow conditions in small vessels and increased accessibility of adhesion molecules to immunocompetent cells in blood plasma. In addition to inflammatory mediators, sepsis and ischemic reperfusion, iatrogenic hypovolemia is known to cause glycocalyx alteration. With regard to the potentially life-threatening consequences of glycocalyx destruction, the currently available data therefore suggest a pivotal challenge derived from the physiological basis of vascular barrier function: Save the endothelial surface layer from degradation!

Further, concerning the metabolic demands of the body, it is a condition to avoid hypovolemia as well as hypervolemia and thus to maintain adequate vascular filling. Keeping the circulating blood volume upright and ensuring an adequate cardiac output is the most important duty to ensure tissue oxygenation and prevent patients from developing multiple organ failure. The majority of studies concerning perioperative fluid and volume therapy have demonstrated an adverse effect of tissue edema on mortality, bowel recovery and hospital stay, but research suffers from a lack of standardization of the fluids used and the definitions of 'restrictive' and 'liberal' fluid therapy. Therefore, the available studies are not directly comparable. Unquestionably it is essential to avoid fluid overload. In contrast, untreated hypovolemia leads to decreased tissue oxygenation and organ failure.

In principle, fluid substitution on the one hand and volume resuscitation on the other are two different therapies for two different diagnoses. Fluid, most suitable balanced crystalloids, is used to treat dehydration resulting from urine loss, fasting and insensible perspiration. The aim of infusing crystalloids is to recharge the extravascular compartment and to imitate the physiological fluid absorption from the gastrointestinal system artificially during surgery. Acute hypovolemia is primarily a decrease in circulating blood volume and should be treated by colloid administration.

Treating extravascular dehydration in a normovolemic patient with colloids will lead to iatrogenic hypervolemia and thus to glycocalyx damage and tissue edema. Treating intravascular hypovolemia with crystalloids will lead to persisting hypovolemia plus a dilution of the plasma volume with colloid free fluid and will, therefore, also cause tissue edema. This applies at least for patients undergoing scheduled surgery because their vascular barrier is normally intact at the beginning of surgery. In critically ill septic patients, the situation may be different and whether crystalloid infusions or modern tetrastarch solutions should be used for volume resuscitation in this special population, suffering from capillary leakage, is a subject of recent discussion. Currently ongoing multicenter studies are addressing this question (CRYSTMAS-Study, BaSES-Study, CHEST-Study).

Summarizing the research concerning the different types of colloids used for volume resuscitation, it seems quite clear that there are beneficial aspects for the use of modern, third generation HES (tetrastarch) preparations. In animal experi-

ments and clinical studies, use of 6 % HES 130/0.4 not only reduced typical perioperative complications like wound infection, pneumonia and anastomosis leakage, but also improved bowel tissue oxygenation and microcirculatory blood flow. Adverse effects on renal function and coagulation, known from older high molecular weight HES, are negligible when low molecular weight HES (e.g. 6 % 130/0.4) is used. Despite these strong hints, further controlled, randomized multicenter studies will be needed to prove the superiority of goal-directed volume resuscitation with modern tetrastarch solutions to rigid fluid administration schemas.

Conclusion

Balancing fluid and volume administration between insufficient and excessive requires well-founded knowledge about the physiologic and pathophysiologic functions of the endothelial glycocalyx barrier. Regarding the physiological basis and the findings achieved from current research, fluid substitution and volume resuscitation should be based on the following principles when an intact vascular barrier can be assumed:

1. Save the endothelial glycocalyx from degradation due to hyperinfusion;
2. Substitute fluid loss or dehydration using crystalloid infusions;
3. Replace volume loss or hypovolemia with colloidal tetrastarch solutions until normalization of the circulating blood volume.

Whether these suggestions can be generally translated to critically ill septic patients suffering from a seriously impaired vascular barrier needs further experimental and clinical investigations.

References

1. Chappell D, Jacob M, Hofmann-Kiefer K, Conzen P, Rehm M (2008) A rational approach to perioperativ fluid management. Anesthesiology 109: 723 – 740
2. Starling E (1896) On the absorption of fluid the connective tissue spaces. J Physiol (Lond) 19: 312 – 326
3. Adamson RH, Lenz JF, Zhang X, et al (2004) Oncotic pressures opposing filtration across non-fenestrated rat microvessels. J Physiol 557: 889 – 907
4. Chappell D, Jacob M, Becker BF, et al (2008) Expedition Glykokalyx. Ein neu entdecktes "Great Barrier Reef". Anaesthesist 57: 959 – 969
5. Chappell D, Westphal M, Jacob M (2009) The impact of the glycocalyx on microcirculatory oxygen distribution in critical illness. Curr Opin Anaesthesiol 22: 155 – 162
6. Rehm M, Haller M, Orth V, et al (2001) Changes in blood volume and hematocrit during acute preoperative volume Loading with 5 % albumin or 6 % hetastarch solutions in patients before radical hysterectomy. Anesthesiology 95: 849 – 856
7. Rehm M, Zahler S, Lotsch M, et al (2004) Endothelial glycocalyx as an additional barrier determining extravasation of 6 % hydroxyethyl starch or 5 % albumin solutions in the coronary vascular bed. Anesthesiology 100: 1211 – 1223
8. Fahraeus R, Lindqvist T (1931) The viscosity of the blood in narrow capillary tubes. Am J Physiol 96: 562 – 568
9. Desjardins C, Duling BR (1990) Heparinase treatment suggests a role for the endothelial cell glycocalyx in regulation of capillary hematocrit. Am J Physiol 258: H647-H654
10. Rehm M, Bruegger D, Christ F, et al (2007) Shedding of the endothelial glycocalyx in patients undergoing major vascular surgery with global and regional ischemia. Circulation 116: 1896 – 1906

11. Bernfield M, Gotte M, Park PW, et al (1999) Functions of cell surface heparan sulfate proteoglycans. Annu Rev Biochem 68: 729–777
12. Shih GC, Hajjar KA (1993) Plasminogen and plasminogen activator assembly on the human endothelial cell. Proc Soc Exp Biol Med 202: 258–264
13. Bruegger D, Jacob M, Rehm M, et al (2005) Atrial natriuretic peptide induces shedding of endothelial glycocalyx in coronary vascular bed of guinea pig hearts. Am J Physiol Heart Circ Physiol 289: H1993-H1999
14. Nelson A, Berkestedt I, Schmidtchen A, Ljunggren L, Bodelsson M (2008) Increased levels of glycosaminoglycans during septic shock: Relation to mortality and the antibacterial actions of plasma. Shock 30: 623–627
15. Jacob M, Chappell D, Conzen P, et al (2008) Blood volume is normal after preoperative overnight fasting. Acta Anaesthesiol Scand 52: 522–529
16. Kamp-Jensen M, Olesen KL, Bach V, et al (1990) Changes in serum electrolyte and atrial natriuretic peptide concentrations, acid-base and hemodynamic status after rapid infusion of isotonic saline and Ringer lactate solution in healthy volunteers. Br J Anaesth 64: 606–610
17. Lamke LO, Nilsson GE, Reithner HL (1977) Water loss by evaporation from the abdominal cavity during surgery. Acta Chir Scand 413: 279–284
18. Sear JW (2005) Kidney dysfunction in the postoperative period. Br J Anaesth 95: 20–32
19. Desborough JP (2000) The stress response to trauma and surgery. Br J Anaesth 85: 109–117
20. Rehm M, Orth V, Kreimeier U, et al (2001) Changes in blood volume during acute normovolemic hemodilution with 5 % albumin or 6 % hydroxyethylstarch and intraoperative retransfusion. Anaesthesist 50: 569–579
21. Rehm M, Orth V, Kreimeier U, et al (2000) Changes in intravascular volume during acute normovolemic hemodilution and intraoperative retransfusion in patients with radical hysterectomy. Anesthesiology 92: 657–664
22. Robarts WM (1979) Nature of the disturbance in the body fluid compartments during and after surgical operations. Br J Surg 66: 691–695
23. Chan ST, Kapadia CR, Johnson AW, Radcliffe AG, Dudley HA (1983) Extracellular fluid volume expansion and third space sequestration at the site of small bowel anastomoses. Br J Surg 70: 36–39
24. Lowell JA, Schifferdecker C, Driscoll DF, Benotti PN, Bistrian BR (1990) Postoperative fluid overload: not a benign problem. Crit Care Med 18: 728–733
25. Shoemaker WC, Appel PL, Kram HR (1988) Tissue oxygen debt as a determinant of lethal and non-lethal postoperative organ failure. Crit Care Med 16: 1117–1120
26. Holte K, Sharrock NE, Kehlet H (2002) Pathophysiology and clinical implications of perioperative fluid excess. Br J Anaesth 89: 622–632
27. Gottrup F, Firmin R, Rabkin J, Halliday BJ, Hunt TK, (1987) Directly measured tissue oxygen tension and arterial oxygen tension assess tissue perfusion. Crit Care Med 15: 1030–1036
28. Marx G, Pedder S, Smith L, et al (2004) Resuscitation from septic shock with capillary leakage: Hydroxyethyl starch (130 kd), but not ringer's solution maintains plasma volume and systemic oxygenation. Shock 21: 336–341
29. Verheij J, van Lingen A, Raijimakers PG, et al (2006) Effect of fluid loading with saline or colloids on pulmonary permeability, oedema and lung injury score after cardiac and and major vascular surgery. Br J Anaesth 96: 21–30
30. Wiedemann HP, Wheeler AP, Bernard GR, et al (2006) Comparison of two fluid-management strategies in acute lung injury. N Engl J Med 354: 2564–2575
31. Waters JH, Gottlieb A, Schoenwald P, Popovich MJ, Sprung J, Nelson DR (2001) Normal saline versus lactated Ringer's solution for intraoperative fluid management in patients undergoing abdominal aortic aneurysm repair: an outcome study. Anesth Analg 93: 817–822
32. Robarts WM (1979) Nature of the disturbance in the body fluid compartments during and after surgical operations. Br J Surg 66: 691–695
33. Sakr Y, Payen D, Reinhart K, et al (2007) Effects of hydroxyethyl starch administration on renal function in critically ill patients. Br J Anaesth 98: 216–224

34. Cochrane Injuries Group (1998) Human albumin administration in critically ill patients: systematic review of randomised controlled trials. Cochrane Injuries Group Albumin Reviewers. BMJ 317: 235 – 240
35. The SAFE Study Investigators (2004) A comparison of albumin and saline for fluid resuscitation in the intensive care unit. N Engl J Med 350: 2247 – 2256
36. Schortgen F, Girou E, Deye N, Brochard L; GRYCO Study Group (2008) The risk associated with hyperoncotic colloids in patients with shock. Intensive Care Med 34: 2157 – 2168
37. Boldt J, Brosch Ch, Röhm K, Papsdorf M, Mengistu A (2008) Comparison of the effects of gelatin and a modern hydroxyethyl starch solution on renal function and inflammatory response in elderly cardiac surgery patients. Br J Anaesth 100: 457 – 464
38. Mahmood A, Gosling P, Vohra RK (2007) Randomized clinical trial comparing the effects on renal function of hydroxyethyl starch or gelatin during aortic aneurysm surgery. Br J Surg 94: 427 – 433
39. Boldt J (2009) Modern rapidly degradable hydroxyethyl starches: current concepts. Anesth Analg 108: 1574 – 1582
40. Boldt J (2007) The balanced concept of fluid resuscitation. Br J Anaesth 99: 312 – 315
41. Legendre C, Thervet E, Page B, Percheron A, Noel LH, Kreis H (1993) Hydroxyethylstarch and osmotic-nephrosis-like lesions in kidney transplantation. Lancet 342: 248 – 249
42. Cittanova ML, LeBlanc I, Legendre C, Mouquet C, Riou B, Coriat P (1996) Effects of hydroxyethyl starch in brain-dead kidney donors on renal function in kidney-transplant recipients. Lancet 348: 1620 – 1622
43. Brunkhorst FM, Engel C, Bloos F, et al (2008) Intensive insulin therapy and pentastarch resuscitation in severe sepsis. N Engl J Med 358: 125 – 139
44. Moran M, Kapsner C (1987) Acute renal failure associated with elevated plasma oncotic pressure. N Engl J Med 317: 150 – 153
45. Neff TA, Doelberg M, Jungheinrich C (2003) Repetitive large-dose infuson of the novel hydroxyethyl starch 130/0.4 in patients with severe head injury. Anesth Analg 96: 1453 – 1459
46. Nohé B, Johannes T, Reutershan J, et al (2005) Synthetic colloids attenuate leukocyte-endothelial interactions by inhibition of integrin function. Anesthesiology 103: 759 – 767
47. Feng X, Yan W, Wang Z, et al (2007) Hydroxyethyl starch, but not modified fluid gelatin, affects inflammatory response in a rat model of polymicrobial sepsis with capillary leakage. Anesth Analg 104: 624 – 630
48. Wang P, Li Y, Li J (2009) Hydroxyethyl starch 130/0,4 prevents the early pulmonary inflammatory response and oxidative stress after hemorrhagic shock and resuscitation in rats. Int Immunopharmacol 9: 347 – 353

IX The Microcirculation

Mitochondrial Function in Septic Shock

M.A. Puskarich and A.E. Jones

Introduction

Shock is the result of failure of the circulatory system to adequately deliver oxygen and nutrients to tissues. At the bedside, the clinician synthesizes data from the history, signs of hypoperfusion on physical exam, vital signs and urine output, and laboratory markers of the adequacy of substrate provision to determine the presence of shock. However, prior to the onset of clinically evident shock, the insult is first experienced at a subcellular level by the mitochondria, leading to their description as "canaries in a coal mine" [1]. Ultimately, shock is the result of failure of adequate oxygen delivery (DO_2) and utilization within mitochondria, which collectively are responsible for nearly all the oxygen consumption and energy production in the body.

Traditionally, resuscitation of the patient in shock focuses on therapies to improve tissue perfusion. This strategy is usually accomplished by focusing attention on normalization or optimization of macrocirculatory physiologic parameters such as mean arterial pressure (MAP). In the case of septic shock, the overarching goal of such resuscitation is to provide adequate DO_2 to meet the metabolic demands of the tissues. Early resuscitation strategies aimed at rapidly achieving predefined goals in the early stages of sepsis using structured protocols (i.e., quantitative resuscitation) have been shown to lead to improvements in patient outcomes [2].

Despite improvements in patient outcomes, mortality rates of patients with septic shock treated with quantitative resuscitation protocols remain in excess of 20 % [2], leaving substantial room for clinical improvement. After macrocirculatory resuscitation, many patients still demonstrate multisystem organ dysfunction and shock physiology. The recent landscape of sepsis research is focusing on two separate, though potentially linked, mechanisms that may explain the persistence of the shock state. The first is the expanding understanding of the role of the microcirculation in the body, and the heterogeneous response of various circulatory beds to the insults of sepsis. The second is the observation that cells and mitochondria receiving adequate perfusion and oxygenation may still have a decreased ability to properly utilize energy to form ATP, referred to as cytopathic hypoxia [3], which can lead to profound metabolic alterations and the inability to supply energy to tissues. These two fields, the microcirculation and the mitochondria, represent attractive targets for novel adjunctive resuscitative agents in the treatment of septic shock.

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Role of the Microcirculation

Effective resuscitation requires rapid identification of tissue hypoperfusion and timely interventions for the restoration of adequate perfusion. Although septic shock research has classically focused on macrocirculatory hemodynamics, which reflect the distribution of blood flow globally throughout the body, a functioning microcirculation is another critical component of the cardiovascular system that is necessary for effective DO_2 to tissues. Alterations of microcirculatory flow in sepsis can occur in the absence of global hemodynamic perturbations (i.e., absence of low arterial pressure and/or low cardiac output) [4, 5]. Microcirculatory 'failure' appears to be one of the critical pathogenic events in sepsis that is associated with acute multiorgan dysfunction and mortality [4, 6]. Improvements in microcirculatory parameters in patients undergoing quantitative resuscitation protocols have been demonstrated to correlate with decreased organ failure at 24 hours, demonstrating the importance of early hemodynamic stabilization [7].

Derangements of small vessel perfusion are largely a function of intrinsic events in the microcirculation. The causes of microcirculatory flow alterations in sepsis are multifactorial and include: Endothelial cell dysfunction, increased leukocyte and platelet adhesion, fibrin deposition, erythrocyte stiffness, altered local perfusion pressures due to regional redistribution of blood flow, and functional shunting [6, 8]. With the advent of new imaging modalities such as sidestream dark field (SDF) videomicroscopy, it is now possible to visualize the microcirculatory network in human subjects. Using intravital videomicroscopy, experimental models of sepsis have demonstrated decreased microcirculatory flow velocity, 'stopped-flow' microvessels, increased heterogeneity of regional perfusion, and low density of perfused capillaries [8]. These derangements can cause marked alterations in oxygen transport including impaired tissue oxygen delivery and consumption leading to anaerobic cellular metabolism [9].

With the advent of these new monitoring modalities, numerous treatments already in clinical practice have been evaluated for their effects on the microcirculation. Administration of intravenous fluids has been demonstrated to improve microcirculatory parameters, although these effects appear to be limited to the early phase of resuscitation [10]. Vasopressors and nitric oxide synthase (NOS) inhibitors have shown mixed effects on microcirculatory flow at best, while nitroglycerin, inotropes (potentially due to their vasodilatory properties), and activated protein C have shown some improvements in flow [11]. Although promising, none of these investigations has been sufficiently powerful to vault microcirculatory monitoring and targeted treatment into clinical practice. If new treatments that improve microcirculatory blood flow in sepsis are identified and are subsequently demonstrated to improve patient-oriented outcomes, however, it would give clinicians a new therapy in their armamentarium for the management of sepsis.

Metabolic Therapies in Sepsis

Altered metabolism is a hallmark of sepsis, as evidenced by hyperglycemia, increased lactate production, decreased lactate clearance, altered resting energy expenditure, and muscle loss. Despite clinical evidence of multiorgan dysfunction syndrome, widespread necrosis of tissues that characterize hypoxic insults is

largely absent in sepsis, suggesting a metabolic rather than ischemic etiology [12]. These data have prompted interest in a field of research referred to as 'metabolic therapies' that collectively were the subject of a roundtable conference at the International Symposium on Intensive Care and Emergency Medicine in 2007. This broadly-defined field encompasses basic nutritional support including small nutrients and pharmaconutrition; function and manipulation of the endocrine system including glucose metabolism; and cellular and mitochondrial dysfunction. Due to the widespread, heterogeneous changes that characterize microcirculatory dysfunction after macrocirculatory optimization, metabolic therapies represent promising novel adjuvant treatments not only for sepsis-induced multiorgan dysfunction syndrome, but also as specific therapies for microcirculatory failure.

Insulin as a Metabolic Therapy

The role of insulin in critical illness has been the subject of significant research interest in the past decade. Because of the known deleterious effects of both hyper- and hypoglycemia, multiple studies have now addressed the issue of tight glucose control in the setting of critical illness, with sometimes conflicting results [13]. There remains the possibility, however, that the results of these studies and the effects of insulin relate less to regulation of glucose and more to other properties of insulin itself. Like other components of the endocrine system, insulin has numerous and far-reaching effects in the body apart from its role in glucose homeostasis, including anti-inflammatory properties and cardiovascular actions.

Sepsis provokes a pro-inflammatory condition that overwhelms compensatory anti-inflammatory mechanisms. The presence, magnitude, and duration of this pro-inflammatory state are major determinates of organ dysfunction, organ failure, and death [14]. Insulin has potent anti-inflammatory properties and in many conditions, including sepsis, has been shown to suppress nuclear factor-kappa B (NF-κB) expression [15], as well as interleukin (IL)-1, IL-6, and tumor necrosis factor (TNF)-α expression and serum levels [16]. Insulin also promotes the expression and increased serum levels of anti-inflammatory cytokines, such as IL-2, IL-4, and IL-10 [16]. Combined, these actions of insulin serve to promote a more homeostatic inflammatory state in the host. These aforementioned effects appear to be direct anti-inflammatory mechanisms of insulin and are independent of modulation of glucose oxidation or membrane polarization [16].

Insulin also has considerable direct cardiovascular effects. In supraphysiologic doses, insulin functions as a potent inotrope, even in conditions refractory to conventional treatments [17]. The microcirculation is also sensitive to insulin's effects, as overall capillary recruitment improves in animal models and healthy subjects under hyperinsulinemic-euglycemic clamp, perhaps as a feed-forward mechanism that insulin utilizes to stimulate its own access to hypoperfused tissue [18]. In critically ill patients, improvements in forearm blood flow have been demonstrated in those receiving intensive insulin treatment [19]. These effects of insulin on inflammation and the microcirculation, combined with the familiarity of clinicians with insulin infusions for tight glucose control, make insulin an attractive therapeutic agent in targeting the microcirculation in sepsis.

Beyond Oxygen Delivery: Cytopathic Hypoxia

Another potential explanation for the persistence of organ dysfunction following restoration of adequate tissue perfusion relates to mitochondrial dysfunction. Classically, resuscitation has focused entirely on the delivery of oxygen to tissues; however, a growing body of evidence suggests that disordered use of oxygen and therefore energy substrates may contribute to the pathogenesis of sepsis [20]. Structural changes in the mitochondria have been demonstrated in various tissues in the setting of sepsis, and multiple studies have demonstrated alterations in mitochondrial activity leading to disordered use of oxygen [20]. Release of mitochondrial damage-associated molecular patterns (DAMPs) has been associated with the systemic inflammatory immune response syndrome (SIRS) response in trauma patients [21], and certain mitochondrial alleles have been associated with a higher rate of death following sepsis [22], further implicating the role of mitochondria in the inflammatory response that characterizes sepsis. Most importantly, it has been observed in the setting of sepsis that tissues, including the heart, are unable to efficiently utilize energy substrates [23] unrelated to oxygen availability [24]. The terms 'cellular metabolic derangement' [12] and 'cytopathic hypoxia' [12, 25] reflect the expansion beyond the bioavailability of oxygen as the cause of shock to include the view that changes in the intrinsic ability of mitochondria to use substrates may play a central role in the pathogenesis of septic shock.

Mitochondrial 'Hibernation'

As our understanding of the pathogenesis of sepsis continues to expand, we now know that cells, and indeed entire organs, are able to downregulate their energy consumption through a process that has been referred to as 'hibernation'. Such downregulation is possible due to the fact that energy demand is tightly coupled to ATP production [3]. Historically, the observation that cellular ATP levels were maintained in sepsis was used to argue against the presence of mitochondrial dysfunction in this setting [24]. However, by downregulating energy consumption, cells can appear to maintain a 'normal' intracellular store of ATP despite potentially dysregulated formation of high-energy phosphate bonds [3]. This may also explain the observation that despite widespread tissue dysfunction in sepsis, areas of necrosis and cell death are notably absent and, if patients recover from the initial insult, tissue function can recover in organs that are normally very sensitive to hypoxic injury. Whether this state of metabolic downregulation and cytopathic hypoxia represents an adaptive or pathologic response is being debated and the effects of its modulation are not fully understood.

Mechanisms of Cytopathic Hypoxia

Multiple mechanisms have been proposed to explain this cytopathic hypoxia. One potential mechanism is that cytopathic hypoxia ultimately results from alterations in mitochondrial metabolism. Several steps of the metabolic pathway have been suggested to cause this decrease in metabolism, including diminished pyruvate delivery into the tricarboxylic acid (TCA) cycle, inhibition of a number of differ-

ent enzymes within the TCA cycle, or defects in electron transport [25]. Implicated mechanisms include inhibition of pyruvate dehydrogenase (PDH), inhibition of cytochrome a,a_3 by NO, and peroxynitrite mediated inhibition of complexes within the electron transport chain [25]. These mechanisms all share disordered utilization of metabolic substrates and oxygen as common pathways leading to cytopathic hypoxia.

Another group of mechanisms suggests the causative role of oxidative damage secondary to reactive oxygen species (ROS) generated in the mitochondria during stress states, including sepsis. The role of the mitochondria as mere 'energy machines' has been debunked, and several studies suggest they play an integral role as generators of ROS and subsequent oxidative damage, leading to alterations in calcium signaling and ultimately influencing apoptosis [26]. One proposed mechanism in this category involves activation of the enzyme poly (ADP-ribose) polymerase (PARP)-1. This enzyme is responsible for repair of DNA damage caused by oxidative damage in an NADH dependent process, and has been hypothesized to interfere with ATP generation by competitive consumption of NADH [25]. The result of such a process is preserved substrate and oxygen utilization, but decoupling of substrate metabolism from ATP generation. Interestingly, insulin has recently been demonstrated to decrease ROS formation, downregulate PARP-1 [27], and maintain the ultrastructural integrity of mitochondria in sepsis [28]. Given insulin's ability to influence both microcirculatory flow and mitochondrial function, it is interesting to consider the possibility that insulin may serve as a potential link between the two in the treatment of multiple organ dysfunction syndrome (MODS). The complexity of such interactions may also explain some of the difficulty of studying insulin in the intensive care unit (ICU).

These two major groups of mechanisms, disordered utilization of substrates and decoupling of substrate utilization from ATP generation, share the common final pathway of decreased energy production in the cell, and may lead to the observation of cellular and tissue 'hibernation' that has been suggested to occur in sepsis. Therapies targeting the mitochondria generally target one of these two mechanisms: Metabolic therapies that attempt to provide either increased substrate or cofactors, or modulators of the oxidative pathways including ROS scavengers, antioxidants, and membrane stabilizers. Some agents have multiple mechanisms of action, and the authors refer the reader to a systematic review on the topic for a comprehensive evaluation of mitochondrial therapies [29]. Ultimately, these mechanisms are not necessarily mutually exclusive and abnormal metabolism, inefficient mitochondrial work, and generation of ROS may all contribute to this state of cytopathic hypoxia and metabolic downregulation.

Studies of cytochrome c replacement in sepsis are particularly insightful in this discussion, and suggest proof of concept. Replacement of cytochrome c improves oxidative phosphorylation, cardiac function, and outcomes in animal models of septic shock [30]. These data suggest that sepsis-associated myocardial depression is linked with impaired oxidative phosphorylation, that reversal of electron transport chain inhibition and resuscitation of the mitochondria is indeed possible, and that improvements in outcomes suggest the potential benefit of reversing this myocardial hibernation. Whether resuscitation of the mitochondria and reversal of cytopathic hypoxia improves other organ dysfunction, and ultimately patient-centered outcomes, remains to be determined.

Altered Metabolism: Pyruvate Dehydrogenase Inhibition in Sepsis

PDH is a key regulator of metabolism, and represents the key, irreversible, rate-limiting step of glucose and lactate entry into the TCA cycle under normal conditions. Activity of PDH is downregulated in models of sepsis [31]. This downregulation is secondary to increased transcription of PDH kinase-4 (PDK-4) [31], a negative modulator of PDH activity. The result is a switch to free fatty acid metabolism that is inherently less energy efficient than glucose and lactate metabolism [32]. The modulation of PDH activity, therefore, is a promising target for the application of metabolic therapies in sepsis. Interest in PDH inhibition has waned somewhat since dichloroacetate, a non-competitive inhibitor of PDK and activator of PDH activity, failed to improve survival in heterogeneous critically ill patients with lactic acidosis [33], despite improving lactate clearance. These results underscore the complexity of metabolic modulation.

Metabolic Therapy: Focus on L-carnitine

Carnitine is a naturally occurring nutrient required in mammalian energy metabolism. It has been shown to facilitate long-chain fatty acid entry into mitochondria, therefore regulating the delivery of substrate for oxidation and subsequent energy production. L-carnitine refers to the levo-isomer of the compound, which is biologically active. It is obtained primarily from dietary intake of protein, though it can be synthesized in the liver and kidneys from the amino acids lysine and methionine. Although it is present throughout the body in mitochondria, carnitine is concentrated in skeletal muscle, the heart, and the smooth muscle of the endothelium.

Healthy muscle uses a combination of free fatty acids (FFA), glucose, and lactate for energy, with FFAs providing 50–70 % in the myocardium [34]. FFAs must be esterified to carnitine to be capable of crossing the mitochondrial membrane via the tandem action of carnitine palmatoyl transferases I and II (CPT-I, II) [35]. Importantly, carnitine also modulates activity of the matrix enzyme, PDH. The PDH complex performs oxidative decarboxylation of pyruvate, a key rate-limiting step, required for lactate disposal. Carnitine accelerates pyruvate oxidation by esterifying and exporting acetyl-CoA out of the mitochondrial matrix, thereby decreasing the acetyl-CoA/CoA ratio [32] (**Fig. 1**). Through this mechanism, carnitine infusion improves FFA as well as carbohydrate metabolism [36]. Because carnitine is an essential component of the rate-limiting steps of oxidation of multiple fuel substrates, carnitine is an attractive therapeutic target for diseases such as sepsis that feature derangements of metabolism.

During stress conditions, the myocardium drastically alters its primary source of energy from FFAs to lactate [37]. The importance of lactate as a fuel in sepsis was demonstrated in one model, in which diminution of lactate supply via beta-blockade led to complete hemodynamic collapse [38]. In addition to the change in substrate preference, septic shock induces profound inefficiencies in myocardial work not explained by cellular or mitochondrial hypoxia [39]. Although the mechanisms of this inefficiency are not completely understood, it is likely a manifestation of cytopathic hypoxia. Research has shown that the cardiac isozyme of CPT-I (the key mediator of FFA transport) is significantly downregulated in sepsis, contributing to decreased FFA metabolism, and likely contributing to this

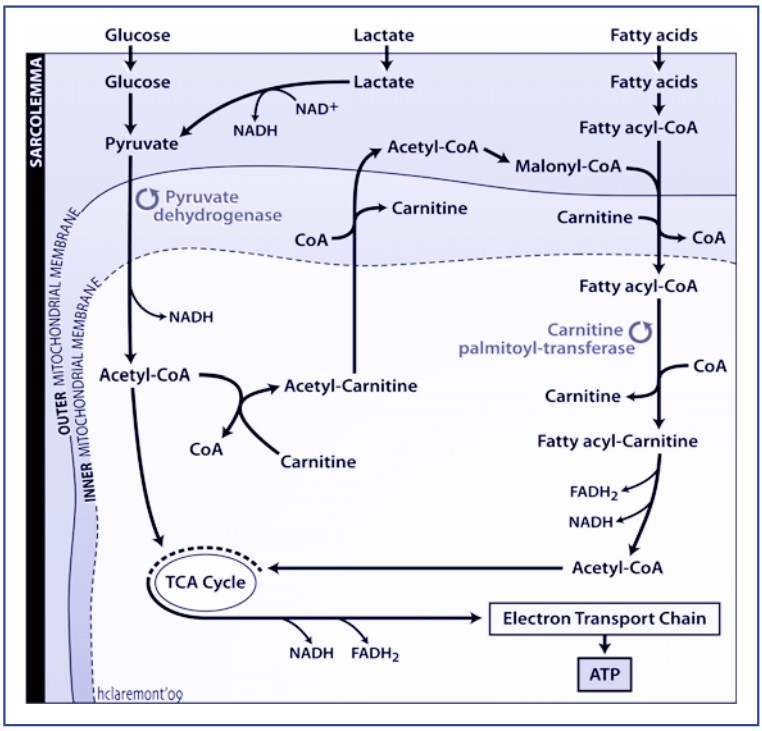

Fig. 1. Role of carnitine in energy metabolism.

inefficiency in metabolism [40]. Simultaneously, excessive acetyl-CoA production stimulated by sepsis alters the acetyl-CoA/CoA ratio and inhibits PDH [32]. This imbalance leads to decoupling of the stoichiometry between glycolysis and pyruvate oxidation. Consequently, the cytosol accumulates lactate, FFA metabolites, and intracellular protons, which together exert a tremendous intracellular cost in terms of the chemical energy required to remove them [23]. Inhibition of both of these enzymes, PDH and CPT, decreases the primary supplies of energy to the failing heart in sepsis and likely plays a role in sepsis-induced cardiac dysfunction.

During septic shock the cardiovascular system experiences a net loss of tissue carnitine, both in the myocardium [41] and endothelium [42]. Tissue carnitine depletion results in an increase in plasma carnitine concentrations. Carnitine resorption in the kidney demonstrates saturation kinetics [43] and, although it is highly efficient (90 – 99 %) in healthy individuals, the increased plasma levels of carnitine in sepsis saturate the renal resorption mechanism resulting in increased urinary excretion, which ultimately leads to whole body carnitine loss [44]. Importantly, carnitine deficiency has been demonstrated to result in impaired cardiac function in both septic and non-septic conditions [35]. Exogenous infusion of carnitine effectively increases carnitine levels in depleted tissues, including the heart, in animal models of sepsis [45].

Carnitine is essential for effective cardiac function and carnitine deficient animals have impaired cardiovascular response to lipopolysaccharide (LPS) [46].

Carnitine replacement enhances cardiac contractility in depressed hearts primarily by stimulating pyruvate oxidation, recoupling glycolysis and oxidation of pyruvate, leading to more efficient heart muscle contraction in shock [47]. Improvement in carbohydrate and lactate metabolism, which are more efficient than FFAs in energy produced per oxygen utilized, is a primary reason for carnitine's ability to improve cardiac efficiency in states of stress [23]. Therefore, as opposed to vasoactive agents which increase the amount of cardiac work, carnitine functions as a metabolic therapy, improving the efficiency of cardiac work, and perhaps representing a novel treatment for cytopathic hypoxia.

Like the rest of the cardiovascular system, the vascular endothelium utilizes carnitine-dependent FFA oxidation [42]. The endothelium appears to be particularly vulnerable to the intermittent ischemia associated with altered microcirculatory flow, and leads to preferential loss of low molecular weight compounds, including carnitine [42]. Animals deficient in carnitine demonstrate an impaired peripheral vascular response to an LPS challenge [46]. Infusion of carnitine can lead to restoration of flow regulation after periods of intermittent ischemia, an effect that may be related to changes in endothelial permeability [48]. Given this role in endothelial dysfunction, carnitine may also prove an attractive therapeutic agent for microcirculatory dysfunction, though studies in this area are lacking.

Preliminary human data suggest that carnitine infusion in septic shock improves patient oriented outcomes. One study has examined the effect of carnitine infusion in patients with septic shock [49]. Gasparetto et al. randomized 115 patients with circulatory shock to receive 12 g of acytl-L-carnitine or placebo over 12 hours. Of these 115 patients, 72 had sepsis as their etiology of shock. Among the 72 septic shock patients, those that received carnitine had significantly higher systolic and mean arterial pressures, lower right atrial pressure, and higher arterial partial pressure of oxygen and hemoglobin oxygen saturation at the end of the carnitine infusion as compared to placebo treated patients. These results suggest the potential for carnitine to improve dysfunction of multiple organ systems in septic shock, and it is one of several agents under investigation for this purpose.

The Interface of the Microcirculation and the Mitochondrion

The relative contributions of mitochondrial dysfunction and microcirculatory failure as causative mechanisms of persistent organ failure after macrocirculatory optimization remain unclear. Whether these two findings are unique phenomena or differing manifestations of the same underlying process is not yet clear. However, should studies continue to implicate one or both of these two mechanisms, the data would suggest a need for a shift in the current paradigm of resuscitation. The interplay of macrocirculatory, microcirculatory, and mitochondrial dysfunction in patients presenting with sepsis would require a multi-tiered approach of assessing and targeting each of these categories, as patients may have differing degrees of dysfunction in each category (**Fig. 2**). While means of monitoring the microcirculation are available, further advancements in technology will be necessary to ease the transition to the bedside. More importantly, assessment of the microcirculation is unlikely to become routine practice without the identification of drugs that can modulate the smallest blood vessels without compromising macrocirculatory hemodynamics. Adequately addressing cytopathic hypoxia,

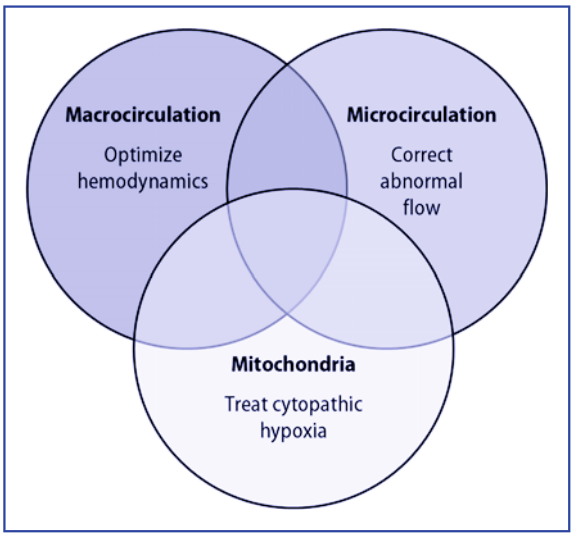

Fig. 2. Theoretical model of sepsis resuscitation

meanwhile, requires the development of methods of monitoring mitochondrial function, further elucidating the exact mechanisms responsible for enzymatic and metabolic failure within the mitochondria during sepsis, and identifying drugs that modulate these targets. Several potential mechanisms, not mutually exclusive, have been identified, and studies attempting to develop various therapies have begun to generate interest [29]. Due to the widespread alterations in metabolism that characterize sepsis, metabolic therapies present attractive, novel co-interventions for the treatment of organ failure in severe sepsis and septic shock.

Conclusion

Persistent organ dysfunction after macrocirculatory optimization remains a major hurdle in the treatment of patients with severe sepsis and septic shock. Evidence is evolving that suggests the contributory roles of microcirculatory dysfunction and alternations in mitochondrial metabolism leading to cytopathic hypoxia in the persistent shock state. The relative contributions of microcirculatory and mitochondrial dysfunction, and whether they represent the same or different underlying processes has yet to be elucidated. Further studies to refine the monitoring of the microcirculation and new methods of evaluating mitochondrial function in patients are urgently needed. As methods of monitoring continue to evolve, therapies that target these two processes will be an exciting frontier of sepsis research.

References

1. Williams RS (2000) Canaries in the coal mine: mitochondrial DNA and vascular injury from reactive oxygen species. Circ Res 86: 915–916
2. Jones AE, Brown MD, Trzeciak S, et al (2008) The effect of a quantitative resuscitation strategy on mortality in patients with sepsis: A meta-analysis. Crit Care Med 36: 2734–2739

3. Levy RJ (2007) Mitochondrial dysfunction, bioenergenic impairment, and metabolic down-regulation in sepsis. Shock 28: 24–28
4. De Backer D, Creteur J, Preiser JC, Dubois MJ, Vincent JL (2002) Microvascular blood flow is altered in patients with sepsis. Am J Respir Crit Care Med 166: 98–104
5. LeDoux D, Astiz ME, Carpati CM, Rackow EC (2000) Effects of perfusion pressure on tissue perfusion in septic shock. Crit Care Med 28: 2729–2732
6. Spronk PE, Zandstra DF, Ince C (2004) Bench-to-bedside review: sepsis is a disease of the microcirculation. Crit Care 8: 462–468
7. Trzeciak S, McCoy JV, Dellinger RP, et al (2008) Early increases in microcirculatory perfusion during protocol-directed resuscitation are associated with reduced milti-organ failure at 24 hours in patients with sepsis. Intensive Care Med 34: 2210–2217
8. Bateman RM, Sharpe MD, Ellis CG (2003) Bench-to-bedside review: microvascular dysfunction in sepsis-hemodynamics, oxygen transport, and nitric oxide. Crit Care 7: 359–373
9. Ellis CG, Bateman RM, Sharpe MD, Sibbald WJ, Gill R (2002) Effect of a maldistribution of microvascular blood flow on capillary O(2) extraction in sepsis. Am J Physiol Heart Circ Physiol 282: H156-H164
10. Ospina-Tascon G, Neves AP, Occhipinti G, et al (2010) Effects of fluids on microvascular perfusion in patients with severe sepsis. Intensive Care Med 36: 949–955
11. Mohammud I, Nonas SA (2010) Mechanisms, detection, and potential management of microcirculatory disturbances in sepsis. Crit Care Clin 26: 393–408
12. Loiacono LA, Shapiro DS (2010) Detection of hypoxia at the cellular level. Crit Care Clin 26: 409–421
13. Marik PE, Preiser JC (2010) Toward understanding glycemic control in the ICU. Chest 137: 544–551
14. Tracey KJ, Fong Y, Hesse DG, et al (1987) Anti-cachectin/TNF monoclonal antibodies prevent septic shock during lethal bacteraemia. Nature 330: 662–664
15. Dandona P, Aljada A, Mohanty P, et al (2001) Insulin inhibits intranuclear nuclear factor kappaB and stimulates IkappaB in mononuclear cells in obese subjects: evidence for an anti-inflammatory effect? J Clin Endocrinol Metab 86: 3257–3265
16. Jeschke MG, Klein D, Bolder U, Einspanier R (2004) Insulin attenuates the systemic inflammatory response inendotoxemic rats. Endocrinology 145: 4084–4093
17. Kline JA, Raymond RM, Leonova ED, Williams TC, Watts JA (1997) Insulin improves heart function and metabolism during non-ischemic cardiogenic shock in awake canines. Cardiovasc Res 34: 289–298
18. Vincent MA, Clerk LH, Rattigan S, Clark MG, Barrett E (2005) Active role for the vasculature in the delivery of insulin to skeletal muscle. Clin Exp Pharmacol Physiol 32: 302–307
19. Zuran I, Poredos P, Skale R, Voga G, Gabršek L, Pareflnik R (2009) Intensive insulin treatment improves forearm blood flow in critically ill patients: a randomized parallel design clinical trial. Crit Care 13: R198
20. Singer M (2007) Mitochondrial dysfunction in sepsis: Acute phase versus multiple organ failure. Crit Care Med 35: S441-S448
21. Zhang Q, Raoof M, Chen Y, et al (2010) Circulating mitochondrial DAMPs cause inflammatory responses to injury. Nature 464: 104–108
22. Huebinger RM, Gomez R, McGee D, et al (2010) Association of mitochondrial allele 4216C with increased risk for sepsis-related organ dysfunction and shock after burn injury. Shock 33: 19–23
23. Watts JA, Kline JA (2003) Bench to bedside: the role of mitochondrial medicine in the pathogenesis and treatment of cellular injury. Acad Emerg Med 10: 985–997
24. Hotchkiss RS, Karl IE (1992) Reevaluation of the role of cellular hypoxia and bioenergetic failure in sepsis. JAMA 267: 1503–1510
25. Fink MP (2002) Bench-to-bedside review: Cytopathic hypoxia. Crit Care 6: 491–499
26. Leverve XM (2007) Mitochondrial function and substrate availability. Crit Care Med 35: S454-S460
27. Horvath EM, Benko R, Gero D, Szabo C (2008) Treatment with insulin inhibits poly(ADP-ribose)polymerase activation in a rat model of endotoxemia. Life Sci 82: 205–209
28. Vanhorebeek I, De Vos R, Mesotten D, Wouters PJ, De Wolf-Peeters C, Van Den Berghe G

(2005) Protection of hepatocyte mitochondrial ultrastructure and function by strict blood glucose control with insulin in critically ill patients. Lancet 365: 53 – 59
29. Dare AJ, Phillips ARJ, Hickey ARJ, et al (2009) A systematic review of experimental treatments for mitochondrial dysfunction in sepsis and multiple organ dysfunction syndrome. Free Rad Biol Med 47: 1517 – 1525
30. Levy RJ, Deutschman CS (2007) Cytochrome c oxidase dysfunction in sepsis. Crit Care Med 35: S468-S475
31. Alamdari N, Constantin-Teodosiu D, Murton AJ, Gardiner SM, Bennett T, Layfield R (2008) Temporal changes in the involvement of pyruvate dehydrogenase complex in muscle lactate accumulation during lipopolysaccharide infusion in rats. J Physiol 586: 1767 – 1775
32. Vary TC, Siegel JH, Nakatani T, Sato T, Aoyama H (1986) Effect of sepsis on activity of pyruvate dehydrogenase complex in skeletal muscle and liver. Am J Physiol 250: E634-E640
33. Stacpoole PW, Wright EC, Baumgartner TG, et al (1992) A controlled clinical trial of dichloroacetate for treatment of lactic acidosis in adults. The Dichloroacetate-Lactic Acidosis Study Group. N Engl J Med 327: 1564 – 1569
34. Dhainaut JF, Huyghebaert MF, Monsallier JF, et al (1987) Coronary hemodynamics and myocardial metabolism of lactate, free fatty acids, glucose, and ketones in patients with septic shock. Circulation 75: 533 – 541
35. Calvani M, Reda E, Arrigoni-Martelli E (2000) Regulation by carnitine of myocardial fatty acid and carbohydrate metabolism under normal and pathological conditions. Basis Res Cardiol 95: 75 – 83
36. Ferrannini E, Buzzigoli G, Bevilacqua S, et al (1988) Interaction of carnitine with insulin-stimulated glucose metabolism in humans. Am J Physiol 255: E946-E952
37. Dhainaut JF, Huyghebaert MF, Monsallier JF, et al (1987) Coronary hemodynamics and myocardial metabolism of lactate, free fatty acids, glucose, and ketones in patients with septic shock. Circulation 75: 533 – 541
38. Levy B, Mansart A, Montemont A, et al (2007) Myocardial lactate deprivation is associated with decreased cardiovascular performance, decreased myocardial energetics, and early death in endotoxic shock. Intensive Care Med 33: 495 – 502
39. Aghajani E, Korvald C, Nordhaug D, et al (2004) E. Coli sepsis induces profound mechanoenergetic inefficiency in the porcine left ventricle. Shock 21: 103 – 109
40. Eaton S, Zammit VA, Pierro A, Spitz L, Stefanutti G, Fukumoto K (2003) Myocardial carnitine palmitoyltrasferase 1 as a traget for oxidative modification in inflammation and sepsis. Biochem Soc Trans 31: 1133 – 1136
41. Lanza-Jacoby S, Holahan M, Beibel DK (1988) Changes in tissue leels of carnitine during E-coli sepsis in the rat. Circ Shock 24: 29 – 34
42. Hulsmann WC (1993) Vulnerability of vascular endothelium in lipopolysaccharide toxicity: effect of (acyl) carnitine on endothelial stability. Mediators Inflamm 2: S21-S23
43. Rebouche CJ (2004) Kinetics, pharmacokinetics, and regulation of L-carnitine and acetyl-L-carnitine metabolism. Ann NY Acad Sci 1033: 30 – 41
44. Nani G, Pittiruti M, Giovannini I, Boldrini G, Ronconi P, Castagneto M (1985) Plasma carnitine levels and urinary carnitine excretion during sepsis. J Parenter Enteral Nutr 9: 483 – 490
45. Yamakawa M, Maeda J, Nakamura T, et al (1996) Distribution of endogenous and exogenous carnitine in rats with sepsis and acute liver failure. Clin Nutr 15: 133 – 140
46. Penn D, Zhang L, Bobrowski PJ, Quinn M, Liu X, McDonough KH (1998) Carnitine deprivation adversely affects cardiovascular response to bacterial endotoxin (LPS) in the anesthetized neonatal pig. Shock 10: 377 – 382
47. Broderick TL, DiDomenico D, Gamble J, et al (1995) L-carnitine improvement of cardiac function is associated with a stimulation in glucose but not fatty acid metabolism in carnitine-deficient hearts. Cardiovasc Res 30: 815 – 820
48. Hulsmann WC, Dubelaar ML (1992) Carnitine requirement of vascular endothelial and smooth muscle cells in imminent ischemia. Mol Cell Biochem 116: 125 – 129
49. Gasparetto A, Corbucci GG, de Blasi RA, et al (1991) Influence of acetyl-l-carnitine infusion on haemodynamic parameters and survival of circulatory-shock patients. Int J Clin Pharm Res 11: 83 – 92

How Can We Use Tissue Carbon Dioxide Measurement as an Index of Perfusion?

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Introduction

Adequate tissue perfusion is an essential component of oxygenation in critically ill and high-risk surgical patients. Tissue oxygenation is satisfied when tissue oxygen demand corresponds to oxygen consumption (VO_2), which is defined as the product of oxygen delivery (DO_2) by the oxygen extraction ratio (O_2ER) [1]. Under conditions where DO_2 does not meet oxygen demand tissue dysoxia occurs leading to organ failure. Early identification and correction of tissue hypoperfusion, focusing on cardiac output and tissue oxygen supply, is of particular importance and may improve outcomes [2]. However, the presence of apparent normal macrocirculatory parameters does not ensure adequate oxygen supply and the absence of compromised tissue perfusion [3, 4]; and oxygen-derived variables are poorly correlated with anaerobic metabolism [5] and may, therefore, be normal when tissue dysoxia is present due to microcirculatory deficit [6]. This leads to difficulties in interpreting oxygen-derived variables for detecting tissue hypoxia: A low VO_2 may be due either to tissue hypoxia whatever its mechanism (e.g., sepsis, hypovolemia) or to reduced oxygen demand without hypoxia [7]. In addition, monitoring tissue dysoxia and the adequacy of tissue oxygenation is difficult to achieve, while measuring VO_2 in intensive care unit (ICU) and surgical patients requires the insertion of invasive pulmonary arterial catheters.

Supported by experimental data, an exciting research topic is the characterization of tissue anaerobic metabolism by the measurement of tissue carbon dioxide (CO_2) production. Under conditions of tissue hypoxia, a decrease in VO_2 is associated with a decrease in aerobic CO_2 production, whereas anaerobic CO_2 production could occur [8]. The rise in partial pressure of CO_2 (PCO_2) has been proposed to be a valuable, earlier and better marker of tissue hypoxia than conventional markers [9, 10], such as serum lactate level, although the potential mechanisms involved remain debated. Tissue PCO_2 reflects metabolic alterations due to perfusion failure in actively metabolized tissues (heart, kidney and brain) [11, 12], and in sites more accessible for clinical practice (buccal, sublingual and skin). In this chapter, we consider the physiology of tissue PCO_2, and outline recent data from experimental and clinical studies that support the use of PCO_2 as a global marker of the adequacy of hemodynamic to cellular respiration.

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Physiological Background for Increased Tissue PCO_2

CO_2 is a metabolic product, about 20 times more soluble than O_2, carried in erythrocytes and blood. The great part of CO_2 content is in form of bicarbonate:

$$CO_2 + H_2O \leftrightarrow H_2CO_3 \leftrightarrow H^+ + HCO_3^-$$

where H_2O is water, H_2CO_3 is carbonate acid, H^+ is hydrogen ion and HCO_3^- is bicarbonate ion [13]. When the erythrocyte concentration of HCO_3^- and H^+ increases, HCO_3^- diffuses into the plasma, whereas H^+ mainly remains in the cells because of a relative impermeability to cations. Under physiological conditions (temperature, pH, hematocrit and oxygen saturation), the relationship between CO_2 content (CCO_2) and PCO_2 is almost linear, so that PCO_2 could be considered as a reliable substitute for CCO_2 [13, 14]. The Fick equation applied to CO_2 is:

$$VCO_2 = CO \times (CaCO_2 - CvCO_2)$$

where VCO_2 is the CO_2 production, CO is the cardiac output and $CaCO_2 - CvCO_2$ the arterial-to-venous CO_2 content difference. Thus, when substituting PCO_2 for CCO_2:

$$VCO_2 = CO \times k \times (PaCO_2 - PvCO_2),$$

where k is the quasi-linear coefficient that is assumed to be constant in physiological conditions. Because $PaCO_2$ may vary with cardiac output, the arterial-to-venous PCO_2 difference (PCO_2gap) should be used when measuring tissue PCO_2:

$$PCO_2gap = k \times (VCO_2 / CO)$$

The main determinants of the PCO_2gap are, therefore, the k factor, the total CO_2 production and the cardiac output:

- Although the k factor (*i.e.*, the PCO_2 to CCO_2 relationship) should remain constant under physiological conditions, it increases with metabolic acidosis.
- Under aerobic conditions, VCO_2 is related to VO_2:

  $$VCO_2 = R \times VO_2$$

  where R is the respiratory quotient that may vary from 0.7 to 1 depending on the metabolic demand (for a constant VO_2, VCO_2 is higher when high carbohydrates are used instead of lipids) [15]. Accordingly, considering the Fick equation, PCO_2gap is proportional to VCO_2 and inversely related to cardiac output. Under stable conditions of both VO_2 and VCO_2, PCO_2gap was found to increase along with the decrease in cardiac output [16, 17]. In other words, when cardiac output is adjusted to VO_2, PCO_2gap should not increase due to increased clearance of CO_2, whereas PCO_2gap should be high following reduction in cardiac output because of CO_2 stagnation phenomenon.
- Conversely, under conditions of tissue hypoxia with a decreased VO_2, tissue CO_2 production was suspected to increase because of H^+ generation and buffering by bicarbonate [18]. However, in these circumstances, the CO_2 production from anaerobic pathways is counterbalanced by a reduced aerobic CO_2 production, so that PCO_2 could be unchanged [19]. However, because the k factor should increase during tissue hypoxia [16], whereas VCO_2 should decrease, the resultant effect on PCO_2gap depends mainly on the flow state.

PCO_2Gap: A Marker of Tissue Hypoxia?

There are two main, partly overlapping, mechanisms that should explain increased PCO_2gap: A reduced cardiac output and altered tissue perfusion. Several studies have emphasized the curvilinear relationship between PCO_2gap and cardiac output (**Fig. 1**) [20–22]. In patients with a preserved microcirculation, Teboul et al. [20] found that low cardiac output was associated with a high PCO_2 gap, whereas the PCO_2gap returned to normal after the cardiac output was increased with infusion of dobutamine. During human cardiac arrest, high values of PCO_2gap have also been reported [23, 24]. Bakker et al. [21] demonstrated the inverse relationship between PCO_2gap and cardiac output in a series of 64 septic shock patients, and found increased PCO_2gap only in patients with lower cardiac output. Nevertheless, these authors also showed that differences in CO_2 production did not account for differences in PCO_2gap, as suggested by similar VO_2 and serum lactate levels in the two groups of patients [21]. In addition, because of the curvilinear relationship of PCO_2gap and cardiac output, large changes in cardiac output without evidence of tissue hypoxia will not result in significant changes in PCO_2gap when blood flow is high [13].

Under conditions of tissue hypoxia but a preserved flow state, even if CO_2 production is higher than normal due to an anaerobic pathway, venous blood flow should be high enough to ensure adequate washout of the CO_2 excess produced by hypoxic cells, so that PCO_2gap should not increase. Conversely, low flow states can result in a widening of PCO_2gap even if no additional CO_2 production occurs, because of the tissue CO_2-stagnation phenomenon [20]. This effect was clearly showed by Vallet et al. [25] in a canine isolated limb model in which reduced DO_2 by decreasing blood flow (ischemic hypoxia) was associated with an increase in PCO_2gap. Conversely, when blood flow was maintained, but arterial PO_2 was reduced by decreasing the input O_2 concentration (hypoxic hypoxia), PCO_2gap did not increase in spite of a marked VO_2 reduction because the maintained blood flow was enough to remove the CO_2 excess [25]. Neviere et al. [26] confirmed that an increased PCO_2gap was mainly related to a decrease in cardiac

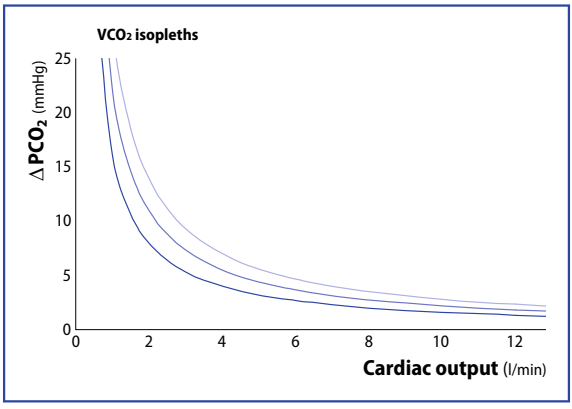

Fig. 1. The curvilinear relationship between cardiac output and venous-to-arterial CO_2 difference (PCO_2gap). For a constant VCO_2, even a small change in cardiac output results in large variations in PCO_2gap in the low values of cardiac output, whereas at high values of cardiac output, changes in PCO_2 gap are limited. Although the relationship is more complex when changes in cardiac output are accompanied by changes in VCO_2, this further underlines the importance of the CO_2 washout phenomenon: Under conditions of preserved tissue perfusion, even a normal flow is sufficient to ensure suitable CO_2 clearance; a normal flow is not sufficient to ensure suitable washout of CO_2 when tissue perfusion is altered leading to enlarged PCO_2 values (tissue CO_2-stagnation phenomenon).

output as PCO_2gap was increased in ischemic hypoxia but not in hypoxic hypoxia for the same degree of O_2 supply-dependency. These studies clearly show that the absence of elevated PCO_2gap does not preclude the presence of tissue hypoxia, and underline the poor sensitivity of PCO_2gap to detect tissue hypoxia. Interestingly, Creteur et al. [27] recently demonstrated a relationship between tissue PCO_2 and microcirculatory perfusion deficit. These authors found that the reperfusion of impaired microcirculation (evaluated using orthogonal polarization spectral [OPS] imaging) was associated with normalized sublingual tissue PCO_2 levels [27].

In summary, taken together, these findings support the concept that low-flow states play a pivotal role in the widening of PCO_2gap under conditions of tissue hypoxia. An enlarged PCO_2gap may suggest that: (1) cardiac output is not sufficient under conditions of suspected tissue hypoxia; and (2) microcirculatory flow is not high enough to clear the CO_2 excess even in the presence of normal (or high) cardiac output. The PCO_2gap should, therefore, be considered as a marker of the ability of an adequate venous return to remove CO_2 excess rather than as a marker of tissue hypoxia.

Use of PCO_2 Gap as a Complementary Tool to O_2-derived Parameters

Several experimental studies have underlined the limited clinical relevance of O_2-derived parameters in detecting and monitoring tissue hypoxia [5, 7, 21, 28]. For example, low mixed venous O_2 saturation (SvO_2) values can be associated with decreased cardiac output or hemoglobin concentration, whereas normal and high values of SvO_2 do not preclude tissue hypoxia in case of impaired O_2 extraction capabilities [5, 29]. In addition, the O_2ER (VO_2/DO_2) should not be a reliable marker of the DO_2 to O_2 demand relationship when VO_2 is less than O_2 demand. Under conditions of tissue hypoxia, a decrease in VO_2 is associated with a decrease in aerobic CO_2 production whereas anaerobic CO_2 production may occur. Thus, the VCO_2 should be less reduced than the VO_2 leading to an increase in the respiratory quotient (VCO_2/VO_2 ratio) [30] according to the Fick equation for VO_2 and VCO_2. Mekontso-Dessap et al. [7] addressed this hypothesis in a retrospective analysis of 89 critically ill patients with normal cardiac index (CI) values (3.6 ± 1.3 l/min/m^2) and similar DO_2. These authors found a good correlation ($r = 0.57$, $p < 0.0001$) between the PCO_2gap-to-$C(v\text{-}a)O_2$ (venoarterial O_2 content difference) ratio, reflecting the respiratory quotient, and arterial lactate concentration in patients with suspected anaerobic metabolism conditions, and that a threshold value of 1.4 predicted hyperlactatemia. In addition, PCO_2gap was higher in patients with anaerobic metabolism. Conversely, except for VO_2, no significant differences were found with regard to O_2-derived parameters (SvO_2, DO_2 and O_2ER).

Recently, Cuschieri et al. [31] showed that the relationship between PCO_2gap and cardiac output still existed when the venous-to-arterial PCO_2gap was calculated with $PcvCO_2$ measured from a central venous blood sample. Under physiological conditions, PCO_2gap ranges from 4 to 6 mmHg [25]. Vallée et al. [32] tested the hypothesis that PCO_2gap, calculated by sampling central venous PCO_2 ($Pcv\text{-}aCO_2$) instead of $PvCO_2$, could be considered as a global index of tissue hypoperfusion in a prospective study of 56 resuscitated septic shock patients to target a central venous O_2 saturation ($ScvO_2$) of ≥ 70 % according to the Surviv-

ing Sepsis Campaign early goal-directed therapy protocol [33]. Interestingly, these authors found that patients who still had altered tissue perfusion (assessed by serum lactate levels > 2 mmol/l) in spite of a normalized DO_2/VO_2 ratio kept an enlarged PCO_2gap (> 6 mmHg). In addition, patients with low values of PCO_2 gap had higher lactate clearance and CI values, and presented a significantly larger decrease in sequential organ failure assessment (SOFA) score than patients with high PCO_2gap. Although these results should be confirmed in further prospective research, the authors reasonably concluded that PCO_2gap might be a useful complementary tool to identify patients who remain inadequately resuscitated when the 70 % $ScvO_2$ threshold value has been reached.

We recently tested the prognostic value of the PCO_2gap in a secondary analysis of 70 patients treated with an individualized goal-directed therapy to optimize cardiac preload during high-risk surgery [34]. In all, CI, DO_2, $ScvO_2$ and PCO_2 gap were recorded. A total of 34 % of patients developed postoperative septic complications. At baseline there was no difference in $ScvO_2$ (82 ± 10 *vs.* 81 ± 9 %; p = 0.75) and PCO_2gap values (7 ± 4 *vs.* 6 ± 2; p = 0.20). In patients who developed complications, mean $ScvO_2$ (78 ± 4 *vs.* 81 ± 4 %, p = 0.017) and minimal $ScvO_2$ (67 ± 6 *vs.* 72 ± 6 %, p = 0.0017) were both lower than in patients without complications, despite similar volumes of fluids perfused and comparable CI and DO_2 values obtained. The optimal $ScvO_2$ cut-off value was 71 %, and $ScvO_2$ < 70 % was independently associated with the occurrence of postoperative complications (odds ratio [OR] 4.2 [95 % confidence interval [CI] 1.1 – 14.4]; p = 0.025). We also found that patients who developed complications had a larger PCO_2gap than patients who did not (7.8 ± 2 *vs.* 5.6 ± 2 mmHg; $p < 10^{-6}$). Interestingly, in patients who developed complications and had $ScvO_2$ value ≥ 71 %, PCO_2gap was also significantly higher (7.7 ± 2 *vs.* 5.5 ± 2 mmHg; $p < 10^{-6}$) than in patients who did not. The area under the receiver operating characteristic (ROC) curve was 0.785 [95 % CI 0.74 – 0.83] for discrimination of patients with $ScvO_2$ ≥ 71 % who did and did not develop complications, with 5 mmHg as the best threshold value (**Fig. 2**). According to DO_2 and CI values, we hypothesized that high PCO_2 gap would reflect a state of insufficient flow relative to CO_2 production. This is in agreement with the study by Bakker et al. [21] who showed that, in

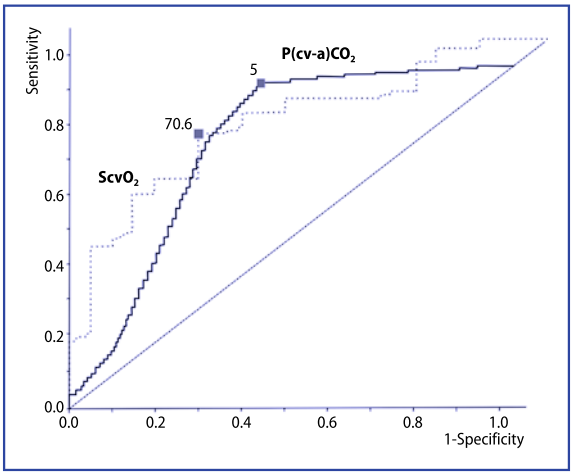

Fig. 2. Receiver operator characteristic (ROC) curve for $ScvO_2$ and $P(cv\text{-}a)CO_2$. The outcome parameter for ROC analysis was the occurrence of postoperative septic complications. The area under the ROC curve was 0.736 (95 %CI: 0.61–0.86) for $ScvO_2$ and 0.785 (95 %CI: 0.74–0.83) for $P(cv\text{-}a)CO_2$ in patients with $ScvO_2$ ≥ 71 % [34].

patients with septic shock, the PCO_2 was smaller in survivors than in non-survivors in spite of quite similar CI, DO_2 and VO_2 values. As a normal PCO_2gap should suggest that cardiac output is high enough to clear the CO_2 from peripheral tissues [13], it can be speculated that patients might have benefited from an increased cardiac output. In this regard, it must be kept in mind that increasing cardiac output to supranormal values has not consistently been found to improve outcome [35, 36].

Tissue PCO_2 Measurements: Back to the Peripheral Tissues

Although there is much evidence showing the vulnerability of the splanchnic region to shock, a consistent finding during low flow states and stagnant perfusion is that increase in tissue PCO_2 should affect all tissues [37]. Gastric tonometry has been proposed as a sensitive method to assess the adequacy of splanchnic perfusion [38]. The principle is based on the measurement of PCO_2 in the gastric lumen, reflecting tissue PCO_2. Nevertheless, technical and pathophysiological concerns have challenged the mucosal PCO_2 reliability during regional capnometry with a saline tonometer [39]. Levy et al. [40] tested the prognostic value of the gastric PCO_2gap, calculated by subtracting the temperature-corrected arterial PCO_2 from gastric PCO_2 using an air-automated tonometer, in 95 consecutive critically ill patients. Enteral feeding was not given during the first 24 hours, so that carbohydrate-induced modifications in CO_2 production can be ruled out [15]. Interestingly, the authors found that gastric PCO_2gap measured at 24h after admission was, as was plasma lactate level, an independent prognostic factor for mortality in the ICU (OR = 1.57, 95 % CI: 1.10 – 2.24), with 20 mmHg as the most predictive threshold value (sensitivity 70 %, specificity 72 %) [40].

Similarly, Marik et al. [9, 41] examined the clinical value of PCO_2gap with sublingual capnometry as a marker of tissue perfusion in a prospective study of 54 hemodynamically unstable ICU patients. They found that PCO_2gap was a better predictor of outcome than traditional markers of tissue hypoxia (SvO_2, DO_2, CI and lactate concentration). They also suggested that changes in PCO_2gap might be more responsive to therapy than those of lactate concentration and SvO_2, which remained relatively unchanged in spite of a decrease in PCO_2gap [9]. Interestingly, similar results were found by Creteur et al. [27] in an elegant study of mechanically ventilated septic shock patients, in whom dobutamine infusion, resulting in a normalized microcirculatory perfusion assessed by sublingual OPS imaging, was associated with normalized sublingual tissue PCO_2. These authors concluded that sublingual microcirculatory blood flow was the main determinant of the sublingual PCO_2gap [27].

In a recent study, Vallée et al. [42] examined whether cutaneous ear lobe PCO_2 could be used as a simple and non-invasive tool to assess tissue microperfusion in 46 patients with early septic shock (≤ 24 h after the onset of septic shock) and 50 hemodynamically stable ICU patients. The ear lobe-to-arterial PCO_2 (Pc-aCO_2) and end-tidal-to-ear lobe PCO_2 (Pc-etCO_2) differences were calculated in all patients every 6 h until 36 h (or death). They found that both gradients discriminated patients in shock from ICU non-septic patients, with cut-off values of 9 mmHg (sensitivity 86 %, specificity 93 %) and 16 mmHg (sensitivity 82 %, specificity 87 %), respectively. They also found that when a significant decrease in both Pc-aCO_2 and Pc-etCO_2 were observed in survivors compared to non-survi-

vors, and when changes in both gradients were related to outcome, no significant differences were found with traditional macrocirculatory parameters (cardiac output, central venous pressure [CVP] and $ScvO_2$). To separate potential microcirculatory from macrocirculatory impairment, these authors also examined the ear lobe microcirculatory blood flow during fluid loading, and found concomitant modifications between microcirculatory blood flow and the PCO_2gap. They observed that improvement in microcirculatory blood flow with fluid challenge was associated with significant decreases in both PCO_2gaps, thus confirming the concept that blood flow is a major determinant of tissue PCO_2 modifications. It is important to note that the decrease in PCO_2gap was also evidenced in non-responders to fluid challenge in spite of any detectable variations in macro-hemodynamic parameters, confirming the potential independence between the macrocirculation and the microcirculation as suggested previously [43].

Conclusion

Early detection and correction of altered tissue perfusion is a cornerstone in the management of ICU and high-risk surgical patients. PCO_2gap, measured through invasive or non-invasive devices, can be considered as a marker of the ability of the venous blood flow to remove the CO_2 produced in excess relative to blood supply. Impairment in tissue perfusion with decreased blood flow should be considered as the main determinant of a rise in PCO_2gap. Experimental and clinical data show that PCO_2gap, as a global index of tissue perfusion, could be useful to assess insufficient flow states in spite of apparent normalized macro-hemodynamic parameters. Furthermore, monitoring of the PCO_2gap could be a useful complementary tool after optimization of O_2-derived parameters is achieved on order to evaluate the adequacy of blood flow for global metabolic conditions.

References

1. Vallet B (1998) Vascular reactivity and tissue oxygenation. Intensive Care Med 24: 3–11
2. Donati A, Loggi S, Preiser JC, et al (2007) Goal-directed intraoperative therapy reduces morbidity and length of hospital stay in high-risk surgical patients. Chest 132: 1817–1824
3. Sakr Y, Dubois MJ, De Backer D, Creteur J, Vincent JL (2004) Persistent microcirculatory alterations are associated with organ failure and death in patients with septic shock. Crit Care Med 32: 1825–1831
4. Vincent JL, De Backer D (2005) Microvascular dysfunction as a cause of organ dysfunction in severe sepsis. Crit Care 9 (Suppl 4): S9–12
5. Silverman H (1991) Lack of relationship betwwen induced changes in oxygen consumption and changes in lactate levels. Chest 100: 1012–1015
6. Trzeciak S, Cinel I, Dellinger RP, et al (2008) Resuscitating the microcirculation in sepsis: the central role of nitric oxide, emerging concepts for novel therapies, and challenges for clinical trials. Acad Emerg Med 15: 399–413
7. Mekontso-Dessap A, Castelain V, Anguel N, et al (2002) Combination of venoarterial PCO2 difference with arteriovenous O2 content difference to detect anaerobic metabolism in patients. Intensive Care Med 28: 272–277
8. Randall HMJr, Cohen JJ (1966) Anaerobic CO2 production by dog kidney in vitro. Am J Physiol 211: 493–505
9. Marik PE, Bankov A (2003) Sublingual capnometry versus traditional markers of tissue oxygenation in critically ill patients. Crit Care Med 31: 818–822
10. Gutierrez G, Palizas F, Doglio G, et al (1992) Gastric intramucosal pH as a therapeutic index of tissue oxygenation in critically ill patients. Lancet 339: 195–199

11. Fries M, Weil MH, Sun S, et al (2006) Increases in tissue Pco2 during circulatory shock reflect selective decreases in capillary blood flow. Crit Care Med 34: 446 – 452
12. Almac E, Siegemund M, Demirci C, Ince C (2006) Microcirculatory recruitment maneuvers correct tissue CO2 abnormalities in sepsis. Minerva Anestesiol 72: 507 – 519
13. Lamia B, Monnet X, Teboul JL (2006) Meaning of arterio-venous PCO2 difference in circulatory shock. Minerva Anestesiol 72: 597 – 604
14. Giovannini I, Chiarla C, Boldrini G, Castagneto M (1993) Calculation of venoarterial CO2 concentration difference. J Appl Physiol 74: 959 – 964
15. Herve P, Simonneau G, Girard P, Cerrina J, Mathieu M, Duroux P (1985) Hypercapnic acidosis induced by nutrition in mechanically ventilated patients: glucose versus fat. Crit Care Med 13: 537 – 540
16. Zhang H, Vincent JL (1993) Arteriovenous differences in PCO2 and pH are good indicators of critical hypoperfusion. Am Rev Respir Dis 148: 867 – 871
17. Van der Linden P, Rausin I, Deltell A, et al (1995) Detection of tissue hypoxia by arteriovenous gradient for PCO2 and pH in anesthetized dogs during progressive hemorrhage. Anesth Analg 80: 269 – 275
18. Wendon JA, Harrison PM, Keays R, Gimson AE, Alexander G, Williams R (1991) Arterial-venous pH differences and tissue hypoxia in patients with fulminant hepatic failure. Crit Care Med 19: 1362 – 1364
19. Groeneveld AB, Vermeij CG, Thijs LG (1991) Arterial and mixed venous blood acide-base balance during hypoperfusion with incremental positive end-expiratory pressure in pig. Anesth Analg 73: 576 – 582
20. Teboul JL, Mercat A, Lenique F, Berton C, Richard C (1998) Value of the venous-arterial PCO2 gradient to reflect the oxygen supply to demand in humans: effects of dobutamine. Crit Care Med 26: 1007 – 1010
21. Bakker J, Vincent JL, Gris P, Leon M, Coffernils M, Kahn RJ (1992) Veno-arterial carbon dioxide gradient in human septic shock. Chest 101: 509 – 515
22. Mecher CE, Rackow EC, Astiz ME, Weil MH (1990) Venous hypercarbia associated with severe sepsis and systemic hypoperfusion. Crit Care Med 18: 585 – 589
23. Grundler W, Weil MH, Rackow EC (1986) Arteriovenous carbon dioxide and pH gradients during cardiac arrest. Circulation 74: 1071 – 1074
24. Weil MH, Rackow EC, Trevino R, Grundler W, Falk JL, Griffel MI (1986) Difference in acid-base state between venous and arterial blood during cardiopulmonary resuscitation. N Engl J Med 315: 153 – 156
25. Vallet B, Teboul JL, Cain S, Curtis S (2000) Venoarterial CO(2) difference during regional ischemic or hypoxic hypoxia. J Appl Physiol 89: 1317 – 1321
26. Nevière R, Chagnon JL, Teboul JL, Vallet B, Wattel F (2002) Small intestine intramucosal PCO(2) and microvascular blood flow during hypoxic and ischemic hypoxia. Crit Care Med 30: 379 – 384
27. Creteur J, De Backer D, Sakr Y, Koch M, Vincent JL (2006) Sublingual capnometry tracks microcirculatory changes in septic patients. Intensive Care Med 32: 516 – 523
28. Ronco JJ, Fenwick JC, Wiggs BR, Phang PT, Russell JA, Tweeddale MG (1993) Oxygen consumption is independent of increases in oxygen delivery by dobutamine in septic patients who have normal or increased plasma lactate. Am Rev Respir Dis 147: 25 – 31
29. Pope JV, Jones AE, Gaieski DF, Arnold RC, Trzeciak S, Shapiro NI (2009) Multicenter study of central venous oxygen saturation (ScvO(2)) as a predictor of mortality in patients with sepsis. Ann Emerg Med 55: 40 – 46
30. Cohen IL, Sheikh FM, Perkins RJ, Feustel PJ, Foster ED (1995) Effect of hemorrhagic shock and reperfusion on the respiratory quotient in swine. Crit Care Med 23: 545 – 552
31. Cuschieri J, Rivers EP, Donnino MW, et al (2005) Central venous-arterial carbon dioxide difference as an indicator of cardiac index. Intensive Care Med 31: 818 – 822
32. Vallée F, Vallet B, Mathe O, et al (2008) Central venous-to-arterial carbon dioxide difference: an additional target for goal-directed therapy in septic shock? Intensive Care Med 34: 2218 – 2225
33. Dellinger RP, Carlet JM, Masur H, et al (2004) Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock. Crit Care Med 32: 853 – 873

34. Futier E, Vallet B, Robin E, Constantin JM, Bazin JE (2010) ScvO2 and P(cv-a)CO2 as complentary tools for GDT during high risk surgery. Crit Care 14 (Suppl 1): P154
35. Shoemaker WC, Appel PL, Kram HB, Waxman K, Lee TS (1988) Prospective trial of supranormal values of survivors as therapeutic goals in high-risk surgical patients. Chest 94: 1176–1186
36. Hayes MA, Timmins AC, Yau EH, Palazzo M, Hinds CJ, Watson D (1994) Elevation of systemic oxygen delivery in the treatment of critically ill patients. N Engl J Med 330: 1717–1722
37. Weil MH (2000) Tissue PCO2 as universal marker of tissue hypoxia. Minerva Anestesiol 66: 343–347
38. Gutierrez G, Palizas F, Doglio G, et al (1992) Gastric intramucosal pH as a therapeutic index of tissue oxygenation in critically ill patients. Lancet 339: 195–199
39. Vincent JL, Creteur J (1998) Gastric mucosal pH is definitely obsolete-please tell us more about gastric mucosal PCO2. Crit Care Med 26: 1479–1481
40. Levy B, Gawalkiewicz P, Vallet B, Briancon S, Nace L, Bollaert PE (2003) Gastric capnometry with air-automated tonometry predicts outcome in critically ill patients. Crit Care Med 31: 474–480
41. Marik P (2001) Sublingual capnography: A clinical validation study. Chest 120: 923–927
42. Vallée F, Mateo J, Dubreuil G, et al (2010) Cutaneous ear lobe PCO2 at 37{degrees}C to evaluate micro perfusion in septic patients. Chest 138: 1062–1070
43. Silva E, De Backer D, Creteur J, Vincent JL (2004) Effects of fluid challenge on gastric mucosal PCO_2 in septic patients. Intensive Care Med 30: 423–429

Use of Non-invasive Tissue Oxygen Saturation Monitoring to Assess Cardiovascular Insufficiency

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Introduction

Cardiovascular insufficiency is characterized by an inadequate oxygen delivery (DO_2) relative to metabolic demands. In the early stages of shock, compensatory autonomic mechanisms, such as vasoconstriction of muscles and skin and eventually lesser vital organs, are activated in an attempt to maintain central blood pressure and vital organ perfusion above an anaerobic threshold. Because in this stage of compensated shock macrocirculatory measures, like arterial pressure or cardiac output, are often inside the range of values defined as normal, these traditional measures of circulatory shock are insensitive as early predictors of subsequent decompensation. Patients in these states of compensated shock are at increased risk of tissue ischemia and subsequent development of multi-organ failure and death. Although macrocirculatory assessments are usually insensitive to assess compensated shock states, microcirculation alterations in muscle and skin blood flow already occur. Thus, measures of tissue cardiovascular reserve should be a sensitive early warning measure of impending cardiovascular collapse due to progressive hemorrhage presenting as compensated shock. In that regard, we present published and preliminary data demonstrating that the non-invasive measurement of tissue oxygen saturation (StO_2) when coupled to a functional hemodynamic monitoring test, such as the vascular occlusion test, may allow early identification of compensated circulatory shock and thus guide initial resuscitation efforts.

Tissue Oxygen Saturation Measurement

The most used technique currently to non-invasively measure StO_2 is near-infrared spectroscopy (NIRS). NIRS is a non-invasive technique based on the differential absorption properties of oxygenated and deoxygenated hemoglobin to assess muscle oxygenation. Using non-infrared light (680–800 nm) that is mostly absorbed in the tissue by hemoglobin, the signal receptor is able to quantify the amount of oxygenated hemoglobin present in the tissue crossed by the near-infrared light. Only the small vessels, like arterioles or capillaries, are monitored with this technique, as big vessels like veins or arteries have too high a concentration of blood to allow the photon emergence.

Non-invasive NIRS StO_2 measures have been studied to asses tissue hypoperfusion in different populations [1, 2]. Although there is a good correlation between the absolute StO_2 value and some other cardiovascular indexes [3, 4], the capacity

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of baseline StO_2 values to identify impending cardiovascular insufficiency is limited (sensitivity, 78 %; specificity, 39 %) and no more accurate than a single systolic blood pressure measurement when discriminating patients with and without cardiovascular insufficiency. Although disappointing, these data are reasonable and expected because a primary goal of auto-regulation is to maintain StO_2 as constant as possible by combined increased local flow and decrease local metabolic rate such that baseline StO_2 remains within the normal range until shock is quite advanced.

However, the addition of a dynamic vascular occlusion test, which induces a controlled ischemic challenge with subsequent release, has been shown to markedly improve and expand the predictive ability of StO_2 to identify tissue hypoperfusion [5]. The vascular occlusion test measures the effect of total vascular occlusion-induced tissue ischemia and release on downstream StO_2. StO_2 is measured on the thenar eminence because the subcutaneous tissue thickness is small and similar across subjects and the thenar muscles are easily subjected to isolated ischemic challenge by simple forearm sphygmomanometer inflation similar to that done when measuring systemic blood pressure. This technique has been described and validated before. Briefly, one initiates the vascular occlusion test by transient rapid vascular occlusion of the arm by sphygmomanometer inflation to 30 mmHg above systolic pressure. This prevents significant blood volume shifts between baseline and vascular occlusion states. The vascular occlusion is sustained for a defined time interval, like 3 minutes, or until StO_2 declines to some threshold minimal value, usually 40 %. Then, the occlusion is released and the rate of StO_2 increase is recorded. From this maneuver one can obtain the rate of deoxygenation (DeO_2), which characterizes the slope of StO_2 as it decreases to the minimal value during the occlusion and reflects the local metabolic rate, and also the rate of reoxygenation (ReO_2), which characterizes the slope of StO_2 as it increases following vascular occlusion and reflects the time required to wash out stagnant blood and is thought to be determined by local cardiovascular reserve and microcirculatory flow (**Fig. 1**).

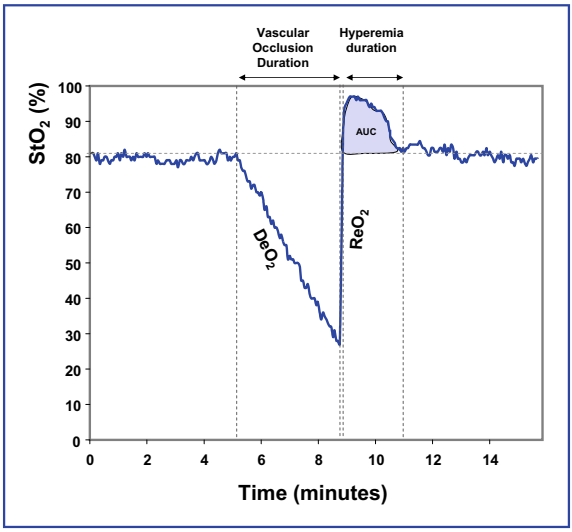

Fig. 1. StO_2 during a vascular occlusion test. Dotted vertical lines note exact times of start and stop of occlusion and beginning of hyperemic reaction. DeO_2: deoxygenation rate; ReO_2: reoxygenation rate; AUC: area under the curve

The vascular occlusion test StO_2 response derives from the functional hemodynamic concept in which the response of a system to a pre-determined stress is the monitored variable. We previously documented that the rate of DeO_2 is a function of local metabolic rate and blood flow distribution. If metabolic rate is increased by muscle contraction, the DeO_2 slope increases, whereas in the setting of altered blood flow distribution the rate of global DO_2 is decreased [6]. We also showed that the ReO_2 slope is dependent on how low StO_2 is at the time of release, being less steep if StO_2 is above 40 % than if the recovery starts at 30 %, suggesting that the magnitude of the ischemic signal determines maximal local vasodilation.

Assessing Cardiovascular Insufficiency in the Microcirculation

Shock is a complex process that involves metabolic, inflammatory, and neurovascular responses simultaneously. There is strong evidence for microcirculatory failure during shock being a major component of the end-organ dysfunction seen. Such microcirculatory dysfunction can be characterized by oxygen shunting, vasoconstriction, thrombosis and tissue edema. As a result of these combined microcirculatory events, the flow distribution within the tissue is impaired [7]. Importantly, microcirculatory alterations improve rapidly in septic shock survivors whereas patients dying by organ failure have a lower percentage of perfused small vessels [8].

In trauma patients, changes in StO_2 capture the vasoconstriction associated with decreased cardiac output during progressive hypovolemia. Initially, the oxygen extraction ratio (O_2ER) is high during hemorrhagic shock because as flow decreases a sustained oxygen influx requires a greater extraction of oxygen from the blood than would otherwise be the case for the same oxygen carrying capacity of the blood at a higher cardiac output. Thus, if autonomic compensatory processes are active then thenar blood flow should occur before the visceral flow. Hence, documenting early impaired thenar blood flow in the setting of otherwise normal hemodynamics suggests either a local circulatory abnormality including the studied limb or compensated shock. This decreased thenar blood flow should manifest itself by a decrease in either the DeO_2 slope, ReO_2 slope, or both. Consequently, when thenar StO_2 vascular occlusion test parameters recover after resuscitation, most other organs should also show resolution of their ischemia.

StO_2 Measurements as a Predictor of Cardiovascular Insufficiency

Given that the vascular occlusion test StO_2 is a good technique to evaluate the tissue consumption/blood flow distribution (DeO_2 slope) and tissue flow reperfusion and vascular recruitment (ReO_2 slope), one can use this non-invasive technique at the bedside to monitor potentially unstable patients for early signs of circulatory insufficiency. Since recent evidence suggests that the microcirculation is affected in the early stages of vascular insufficiency, a vascular occlusion test StO_2 represents an easy, non-invasive and rapid means of assessing and managing patients in shock.

Creteur et al. [9], proved the hypothesis that the alterations in vascular occlusion test StO_2 response were related to the outcome of patients with either severe sepsis or septic shock. Furthermore, compared to hemodynamically stable

patients without infection (controls) and healthy volunteers, these differences in the septic patients were striking. Using NIRS vascular occlusion test StO_2, these authors assessed the slope of increase in StO_2 release as well as the difference between the maximum StO_2 and the StO_2 baseline (Δ). Both the slope of ReO_2 and the Δ were significantly lower in septic patients than in controls and healthy volunteers. In the sample of septic patients, the slopes were also significantly lower in those who had cardiovascular insufficiency. Finally, vascular occlusion test ReO_2 slopes were higher in survivors than in non-survivors and also tended to increase during resuscitation in survivors but not in non-survivors. Finally, the StO_2 ReO_2 slope was found to be a good predictor of ICU death, with a cut-off value of 2.55 %/sec (sensitivity 85 %, specificity 73 %). The authors did not find any correlation between the vascular occlusion test StO_2 DeO_2 or ReO_2 slopes and other macroscopic hemodynamic values like mean arterial pressure, arterial blood lactate concentration, temperature, age, hemoglobin concentration or analgo-sedative doses. In shock patients, no correlation was found between norepinephrine dose and StO_2 ReO_2 slope. These data confirm that the alterations in vascular occlusion test StO_2 ReO_2 are related more to the sepsis process itself and its severity than to mean arterial pressure or vasopressor agent doses. Importantly, the magnitude of this ReO_2 slope alteration is directly related to the septic disease and its presence in the first 24 hours of the septic process and the persistence of a delayed ReO_2 slope is related to patient outcome.

Furthermore, Payen et al. [4] showed a correlation between the StO_2 ReO_2 slope during the first day of shock and outcome in septic patients. Impressively, the StO_2 ReO_2 slope displayed significantly better predictive value in patient outcome than the Simplified Acute Physiology Score (SAPS) II and Sequential Organ Failure Assessment (SOFA) scores.

Gomez et al. [5] showed that trauma patients had similar resting StO_2 levels compared to healthy volunteers, even though trauma patients had increased circulatory stress; still, both groups had similar mean arterial pressures. Furthermore, even though trauma patients had slower StO_2 ReO_2 slope than controls, the stressed trauma patients relied more heavily on capillary recruitment, as manifest by an increased tissue hemoglobin level during reoxygenation than non-stressed trauma patients or controls. Potentially, prior capillary derecruitment that was unmasked by the ischemic challenge was consistent with increased sympathetic tone.

In a more recent study, also in trauma patients, Guyette et al. [10] measured vascular occlusion test StO_2 measures in trauma patients during air transport to the Trauma Center. The aim of the study was to see whether StO_2 measurement, including a vascular occlusion test, was feasible in the pre-hospital environment and useful to predict in-hospital death and ICU admission. Although they did not find differences in baseline StO_2 among survivors, non-survivors and patients admitted to the ICU, they showed significant differences in DeO_2 and ReO_2 slopes between survivors and non-survivors, as well as between patients who needed ICU admission and those who did not. Furthermore, only one of the five patient deaths in their sample had pre-hospital vitals signs that would have met the protocolized criteria for resuscitation (heart rate > 120 bpm, systolic blood pressure < 90 mmHg). This study shows the usefulness of dynamic assessment of the microcirculation in the early stages of trauma injury, when cardiovascular insufficiency is not suspected from the macrocirculatory indexes, providing the possibility to start early appropriate treatment and decide the in-hospital disposition.

Conclusion

The microcirculation is altered in the first stages of shock when, due to physiological compensatory mechanisms, macrocirculatory monitoring values are still in the normal range. NIRS StO_2 measures have been shown to be a valid, fast and non-invasive method to assess the microcirculation. Adding a vascular occlusion test as a provocative dynamic challenge, we can identify the presence of cardiovascular insufficiency earlier than with more traditional monitoring techniques.

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References

1. Cohn SM, Nathens AB, Moore FA, et al (2007) Tissue oxygen saturation predicts the development of organ dysfunction during traumatic shock resuscitation. J Trauma 62: 44 – 54
2. Crookes BA, Cohn SM, Bloch S, et al (2005) Can near-infrared spectroscopy identify the severity of shock in trauma patients. J Trauma 58: 806 – 813
3. Mesquida J, Masip J, Gili G, Artigas A, Baigorri F. (2009) Thenar oxygen saturation measured by near infrared spectroscopy as a noninvasive predictor of low central venous oxygen saturation in septic patients. Intensive Care Med 35: 1106 – 1109
4. Payen D, Luengo C, Heyer L, et al (2009) Is thenar tissue hemoglobin oxygen saturation in septic shock related to macrohemodynamic variables and outcome? Crit Care 13 (Suppl 5): S6
5. Gomez H, Torres A, Polanco P, et al (2008) Use of non-invasive NIRS during vascular occlusion test to assess dynamic tissue O_2 saturation response. Intensive Care Med 34: 1600 – 1607
6. Gomez H, Mesquida J, Simon P, et al (2009) Characterization of StO_2 and VOT: Influence of measurement sites, probe sizes and deflation thresholds. Crit Care 13 (Suppl 5): S3
7. De Backer D, Creteur J, Preiser JC, Dubois MJ, Vincent JL (2002) Microvascular blood flow is altered in patients with sepsis. Am J Respir Crit Care Med 166: 98 – 104
8. Sakr Y, Dubois MJ, De Backer D, Creteur J, Vincent JL (2004) Persistent microcirculatory alterations are associated with organ failure and death in patients with septic shock. Crit Care Med 34: 1825 – 1831
9. Creteur J, Carollo T, Soldati G, Buchele G, De Backer D, Vincent JL (2007) The prognostic value of muscle StO_2 in septic patients. Intensive Care Med 33: 1549 – 1556
10. Guyette F, Gomez H, Suffoletto B, et al (2009) Prehospital dynamic tissue O_2 saturation response predicts in-hospital mortality in trauma patients. Crit Care Med 37 (suppl): A28 (abst)

The Microcirculation of the Critically Ill Pediatric Patient

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Introduction

Hemodynamic monitoring is the cornerstone of critical care, especially when the patient is hemodynamically unstable. It needs to be used with the perspective of tailoring treatment to physiology and the underlying disease process [1]. Monitoring should be easy to apply and negative side effects should be limited. The results should be reliable and reproducible, not least because we also need to monitor response to therapy when cardiovascular insufficiency has been identified. One of the primary goals of hemodynamic monitoring is to alert the physician to impending cardiovascular crisis before organ or tissue injury ensues.

In general, the adequacy of circulatory stability is judged by clinical assessment of parameters that we can measure, e.g., blood pressure, urine output, heart rate and serum lactate concentration. However, these are indirect clinical markers of systemic blood flow and, as such, they are unreliable estimates of overall hemodynamic status during critical illness, irrespective of the experience of the assessing clinician [2, 3]. The logic is obvious when one considers that since blood pressure is a regulated variable, a normal blood pressure does not necessarily reflect hemodynamic stability or perturbation [4].

Early recognition of hemodynamic instability in combination with an understanding of the often complex underlying pathophysiology is therefore essential. The clinical art is, first, to monitor the right parameters and, secondly, apply the right target values, which can vary according to age or underlying pathology. In critical illness, these are not necessarily the same as normal values in health [5]. Pediatric intensivists and anesthesiologists should be familiar with age-appropriate normal values and the physiological differences between adults and children.

Cardiovascular Physiology of the Pediatric Patient

Differences in growth and development, as well as the pathophysiological response to illness, mean that children cannot be regarded as small adults and data obtained from adults cannot be easily extrapolated to children. Different body proportions, a higher metabolic rate, and lack of compensatory reserve for respiratory or circulatory threats are examples of factors that should influence one's approach to critically ill children. Normal age appropriate values are shown in **Table 1**.

The cardiovascular system changes markedly at birth due to dramatic alterations in blood flow patterns. Under normal circumstances, the fetal circulation,

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Table 1. Reference values for heart rate and blood pressure in children [13]. Data are presented as mean and 95 % confidence intervals.

Age	Heart rate [beats/minute]	Mean blood pressure [mmHg]	Systolic blood pressure [mmHg]	Diastolic blood pressure [mmHg]
Term newborn	125 (70–190)	45 (35–60)	70 (50–90)	30 (20–40)
1–11 months	120 (80–160)	60 (45–75)	75 (55–95)	50 (30–70)
2 year	110 (80–130)	70 (50–90)	90 (70–110)	55 (40–70)
4 year	100 (80–120)	75 (50–100)	93 (70–115)	56 (40–70)
6 years	100 (75–115)	75 (50–100)	97 (80–115)	58 (45–75)
8 years	90 (70–110)	75 (60–90)	97 (80–115)	58 (45–75)
10 years	90 (70–110)	75 (60–90)	103 (85–120)	62 (47–77)
12 years	85 (65–110)	80 (65–95)	103 (85–120)	62 (47–77)
14 years	80 (60–105)	80 (65–95)	110 (95–125)	65 (50–80)

with its reduced perfusion of the lungs and intra- and extra-cardiac shunts between the pulmonary and systemic circulations, transitions rapidly to an adult circulation. The precipitous fall in pulmonary vascular resistance and corresponding increase in pulmonary blood flow leads to increased left atrial filling and closing of the intra-atrial connection (foramen ovale). Left ventricular preload rises and the cardiac output increases to meet metabolic demands [6]. In the fetus and newborn, the left ventricle is flattened and the right ventricle is dominant. Newborn babies have less compliant ventricles and therefore have compromised diastolic function. They have a reduced response to inotropes, volume loading, and increased sensitivity to afterload. The immature heart has reduced contractile reserve and a depressed contractile response to exogenous administration of catecholamines.

With the separation of the systemic circulation from the low pressure placental circuit, systemic vascular resistance (SVR) and left ventricular afterload rise steeply in concert with each other. Hence, neonates at birth have little inotropic reserve. They also have reduced preload reserve in comparison with older children and adults. After the transition from fetal to neonatal circulation, the SVR starts to decrease and stroke volumes and cardiac output increase [7]. Stroke volume index (SVI) and cardiac index (CI) continue to increase until the age of 5 years. SVI is stable and CI decreases slightly beyond the age of 5 years. The SVR decreases in the first decade, with the initial major increase followed by a progressive decrease, occurring in the first 48 hours after birth [7]. In infancy and childhood the myocardium adapts progressively to its new loading conditions and develops increased reserve to β adrenergic stimulation.

The compensatory mechanisms in hemodynamic disease appear to differ in children compared with adults. Adults with septic shock have decreased ejection fraction and increased cardiac output through ventricular dilatation and increased heart rate [8]. Children with septic shock do not have ventricular dilatation [9]. Therefore, the most important way to increase cardiac output in young children is to increase heart rate. However, there is a problem here. An adult can increase resting heart rate from 60 to 100 beats per minute, but a proportionate increase in an infant from 140 to 220 beats per minute is not sustainable. In adults with septic shock, the hyperdynamic state ('warm shock') is the hallmark of cardiovascular pathophysiology. In children, the response is more heterogeneous [10]. Only a

small percentage of children who present with septic shock exhibit a hyperdynamic state, with diminished SVR that responds to vasopressor support without a decrease in CI [10]. The main presentation in pediatric septic shock is a hypodynamic state ('cold shock') with low cardiac output and a high SVR [11, 12].

Studies in humans with septic shock suggest that low cardiac output and/or low SVR is detrimental to organ perfusion and survival. Children with septic shock, who maintain a CI between 3.3 and 6.0 l/min/m^2 seem to have a higher survival rate compared to those who have CI outside this range [12].

Hemodynamic Monitoring of the Pediatric Patient

An important goal of hemodynamic monitoring is to be able to detect inadequate tissue perfusion and oxygenation at an early stage, long before it becomes detrimental. As a consequence, the monitor should prompt and guide resuscitation. Three key components in the physiology of oxygen delivery can be identified:

1. Uptake of oxygen in the lung;
2. Transport and delivery of oxygen from the lung to the tissues; and
3. Oxygen uptake and utilization by the tissues.

At present, available devices for bedside monitoring give limited information about these processes. Oxygen saturation (SO_2), measured by continuous pulse oximetry (SpO_2) and arterial blood gas analysis provides information about the oxygen content of the blood (SaO_2), providing we also know the hemoglobin concentration. This covers oxygen uptake. Oxygen delivery (DO_2) and utilization are more difficult to assess. DO_2 is the product of oxygen content and cardiac output. However, at regional level, vascular resistance is a major factor. There is evidence that low cardiac output is associated with an increased morbidity and mortality [10]. Assessment of cardiac output by means of clinical estimation is inaccurate [3], and invasive measurements are little used in children [14, 15]. As an alternative to invasive measurement of cardiac output, central ($ScvO_2$) or mixed (SvO_2) venous oxygen saturation has been used as a surrogate for the adequacy of cardiac output in adults. In children with complex congenital heart disease or intra- and/or extracardiac shunts, SvO_2 is not a useful measure. Central venous or mixed venous oxygen saturation is also invasive and carries risks in small children. Volumetric indices of cardiac function (e.g., M-Mode, femoral artery thermodilution catheter) are used extensively in adult intensive care unit (ICU) in order to derive DO_2. However, in the pediatric ICU, intra- and extracardiac shunts may change their validity and relevance. And again, the risks accompanying the insertion of the catheters (e.g., arterial thrombosis) outweigh the potential benefits. Echocardiographic evaluation of cardiac output is not consistently reliable because even in the hands of experienced operators the variation in measurements between and within individuals is large [16]. Taken together, evaluation of cardiac output is much less straightforward in children than it is in adults.

In order to assess tissue perfusion, various measures are followed, including capillary refill time, temperature, and serum lactate concentration. In circulatory failure there is a hierarchy in regional blood flow with diversion away from skin and muscles towards vital organs such as heart, brain, and kidneys. Thus, monitoring skin perfusion could be an early marker increased sympathetic activity and hypoperfusion. Capillary refill time is a useful clinical parameter during the

acute assessment and resuscitation of dehydrated children [17, 18]. It is non-invasive, easy to use, and cheap. Its use in the pediatric ICU, however, might be of limited value. The correlation with global hemodynamics is poor [19]. Only a weak correlation exists between severely prolonged capillary refill time and SVI and serum lactate concentration [19]. Also, confounding factors such as fever and use of vasoactive medications should be considered. Nonetheless, a dramatic change in this parameter should alert the clinician to the need for a more detailed hemodynamic assessment of the patient.

Lactate metabolism and the prognostic value of high serum lactate concentration in the ICU patient are well documented [20–22]. However, the relationship between lactate and tissue perfusion is not always well defined [23–25], possibly due to the fact that measured lactate is not only the result of the balance between anaerobic production and clearance, but that it may also arise from other sources than hypoxic tissues [26]. Overall these macrocirculatory parameters are currently considered as insensitive markers of tissue perfusion [27]. Ideal hemodynamic monitoring should provide information about whether cells are receiving sufficient oxygen to sustain cellular mitochondrial respiration to produce ATP. Two key elements are the DO_2 and the removal of waste products, like carbon dioxide (CO_2). Important factors that determine DO_2 are cardiac output, blood hemoglobin concentration, SO_2 of the hemoglobin molecule, and convection and diffusion of oxygen from arterioles to cells. In critical illness, DO_2 is often deranged, and many of the common therapeutic interventions in the pediatric ICU (e.g., fluid administration, blood transfusion, inotropes, mechanical ventilation) are, ultimately, used to improve DO_2. At present, no real-time monitoring tool for use at the bedside is available for tracking DO_2.

The Microcirculation as an Essential Hemodynamic Compartment

Circulatory shock is defined as failure of the cardiovascular system to maintain effective tissue perfusion, causing cellular dysfunction and subsequent acute organ system failure if not restored promptly. Although it is the macrocirculation that distributes blood flow throughout the body, it is the microcirculation that is the critical component of the cardiovascular system ensuring regional blood flow to individual tissues. An optimal macrocirculation, however, is the obvious prerequisite for adequate microcirculatory perfusion. Nevertheless, restoration of global hemodynamics does not always mean that adequate regional tissue perfusion is achieved, especially in conditions of impaired autoregulation, such as occurs during critical illness. Previous studies in adult septic shock patients have shown that indices of microcirculatory blood flow can serve as early indicators of tissue hypoperfusion and therefore provide timely information about the potential onset of multiorgan failure [28–30]. In health, microvascular perfusion is controlled locally so that tissue blood flow and substrate delivery are maintained despite changes in arterial pressure [31]. The lower limit of such flow-autoregulation – from first principles based on mean arterial pressure (MAP) and other factors in Poiseuille's equation – varies between organs, patients, disease state, metabolic activity, and associated vasoactive therapies. Thus, there is no absolute threshold blood pressure that defines adequate organ perfusion among organs, between patients, or in the same patient over time [32]. However, because arterial pressure is a primary determinant of organ blood flow, hypotension is always

pathological. Measuring the adequacy of microcirculatory blood flow as a direct indicator of the success of the cardiovascular system to provide adequate oxygen and nutrients to the cells, can be regarded as an important extension of the measurement of systemic hemodynamic variables [33]. However several issues need to be addressed. These are:

1. the reliability and reproducibility of the measurement;
2. the identification of the most relevant microcirculatory parameters which need to be determined; and
3. the prognostic value of these parameters in guiding therapy.

Bedside Measurement of the Pediatric Microcirculation

The microcirculation plays a crucial role in the interaction between blood and tissue, both in physiological and pathophysiological states. Analysis of alterations in microvascular blood flow therefore provides a unique perspective of disease processes at a microscopic level [34]. Orthogonal polarization spectral (OPS) imaging is the first hand-held imaging device that allows bedside visualization of the microcirculation. OPS imaging is based on the optical technique introduced by Slaaf et al. [35], in which green polarized light is used to illuminate the tissue area of interest, which at the bedside is usually the buccal or sublingual mucosa. The green light is absorbed by hemoglobin within the red blood cells (RBCs) in the microcirculation. The reflected light is detected by an orthogonally placed analyzer which filters out surface reflections in order to produce a high-contrast reflected light image of flowing RBCs within the microcirculation [36]. Sidestream darkfield (SDF) imaging is the improved successor to OPS imaging [37] and is based on the dark field illumination technique introduced by Sherman et al. [38]. In this technique, the microcirculation can be observed without the need to use transillumination. Instead SDF imaging uses a stroboscopic light-emitting diode ring-based imaging device so it provides better image quality of the microcirculation [39].

OPS and SDF imaging have been validated in several studies [37, 40–44]. Quantification of images is now standardized [45], reproducible, and validated [46]. The parameters that are used to quantify the images include: The microvascular flow index (MFI), a measure of convective flow; the functional capillary density (FCD) or vessel density index (VDI), for diffusion distance; and the heterogeneity index (HI). In the MFI score [46], four different types of flow are recognized and assigned an integer score from 0 to 3: No flow, score 0; intermittent flow, score 1; sluggish flow, score 2; and continuous flow, score 3. In order to quantify the microcirculatory flow, each video image is divided into four equal quadrants and the MFI for the whole image is taken as the average score of all quadrants for the different types of vessels, small (< 25 μm), medium (26–50 μm) and large (51–100 μm). For the FCD calculation [36], the assessor needs to trace the path of the moving RBCs within the capillaries (i.e., vessels < 10 μm) using a software program (Capiscope version 3.7.1.0, KK Technology 1993–2000). A functional capillary is defined as a capillary that has at least one RBC moving through it during the observation period. Dividing the length of the perfused capillaries by the area gives the density. In order to calculate the VDI the assessor draws a grid on the computer screen field-of-view composed of three equidistant horizontal and three equidistant vertical lines. Vessel density is calculated as the number of vessels crossing the lines divided by the total length of the lines. Assess-

ment of the HI [30] involves evaluating three to five mucosal sites and measuring the MFI in each quadrant, taking the difference between highest MFI minus the lowest site MFI, and then dividing the number by the mean flow velocity.

Calculation and measurement of the above parameters has been discussed and agreed upon in a recent consensus conference [45]. It must be noted, however, that analysis and quantification of moving images is cumbersome and time consuming. Although software products do ease and optimize the task [47], no real-time values can be obtained yet. In addition to other technical difficulties (e.g., blurring of the images due to oropharyngeal secretions and artifacts due to movement or pressure) we consider that these microcirculatory imaging techniques, in their present form, are unsuitable for routine clinical use. Nonetheless, the introduction of OPS and SDF imaging to clinical medicine has opened a new field of monitoring during various disease states [48]. The technique is feasible for use in young children [49], providing they have received adequate sedation.

To date, there have been eight studies published on the use of OPS/SDF in children (**Table 2**). A few studies in newborns and infants have used videophotome-

Table 2. Pediatric studies of the microcirculation using OPS or SDF imaging

Author [ref]	Year	Age range	n	SDF/OPS	Site	Outcome
Genzel-Boroviczeny et al. [53]	2002	Preterm and term, 1–5 days	28	OPS	Skin	Feasibility study: RBC velocity increased from day 1–5 in premature neonates and correlated with decrease in hemoglobin
Genzel-Boroviczeny et al. [54]	2004	Preterm, 19–39 days	13	OPS	Skin	FCD improved 2 hours and 24 hours after blood transfusion
Kroth et al. [55]	2008	Preterm, 0–30 days	25	OPS	Skin	FCD decreased significantly over the first month of life
Top et al. [57]	2009	Term, 0–18 days	14	OPS	Buccal mucosa	FCD was reduced in neonates with severe respiratory failure and improved following use of veno-arterial extracorporeal membrane oxygenation
Weidlich et al. [58]	2009	Preterm, 0–30 days	10	OPS	Skin	FCD decreased 1 day before clinical signs of infection appeared
Hiedl et al. [56]	2010	Preterm, 3–8 days	25	SDF		Patients with persistent ductus arteriosus had reduced FCD, which improved after treatment
Top et al. [49]	2010	0–3 years	45	OPS	Buccal mucosa	FCD of the buccal mucosa decreased after the first week of life
Top et al. [59]	2010	0–15 years	21	OPS	Buccal mucosa	Persistence of depressed FCD was associated with a worse outcome in children with septic shock
Top et al. [60]	2010	0–3 years	8	OPS	Buccal mucosa	Inhaled NO improves the systemic microcirculation in children with hypoxemic respiratory failure

OPS: orthogonal polarization spectral imaging; FCD: functional capillary density; RBC: red blood cell; SDF: sidestream darkfield

tric microscopy or laser Doppler to evaluate RBC velocity in the nailfold capillaries of the thumb [50–52]. OPS imaging of the skin has been used in premature and term infants [53–56]. These observations show that the microcirculation in premature infants can be quantified and RBC velocity can be measured. In older children, the most frequently used site for assessment is the buccal mucosa.

The Microcirculation in Development

Developmental changes in the structure of the microcirculation occur in the first few weeks of life in healthy neonates and children [49, 55]. The FCD in the skin of premature infants decreases significantly over the first month of life, which correlates with decreases in hemoglobin concentration and environmental incubator temperature [55]. The FCD of the buccal mucosa also decreases after the first week of neonatal life. It would seem that developmental changes of the microcirculation in early postnatal life are related to adaptation after birth rather than post-conceptional age. It is believed that an adult pattern of microvasculature in the skin is reached by the age of 3 months [61]. An important factor in this development is local cooling. Therefore, it is unclear whether the same would apply for other microvascular beds not directly exposed to environmental temperatures. In the first week of life, compared with birth, there is also the additional 2- to 3-fold increase in oxygen consumption because of increased work of breathing, and increased gastrointestinal function with feeding. Furthermore, high levels of fetal hemoglobin at this time of life reduce the level of oxygen extraction [62]. These factors, taken together, can be compensated by higher systemic and microcirculatory blood flow. The higher FCD in the first week of postnatal life may be related to higher cardiac output in the first week [62] and autoreglulation of regional blood flow may have an important role [31].

Microcirculation in Disease and the Effects of Treatment

Microcirculatory alterations are now considered to be a key hemodynamic property of septic adult patients due to several landmark investigations using OPS and SDF imaging [27, 28, 32, 64]. Top and co-workers reported that such alterations also occur in the buccal mucosa of septic children [59]. In premature neonates with sepsis, microcirculatory alterations were observed in the skin using OPS imaging [58]. Furthermore, neonates with severe respiratory failure have depressed microcirculatory parameters [57]. In premature neonates with patent ductus arteriosus (PDA) the FCD of the skin is reduced compared with patients without PDA [56]. The mechanism behind this change is unclear. These patients had left-to-right shunting through the PDA, resulting in reduction of cardiac output (due to blood flow 'leaking' away to the pulmonary circulation). The difference disappeared after closure of the PDA [56]. Microcirculatory alterations can be effectively treated in pediatric patients. Genzel-Boroviczeny et al. observed a direct effect of RBC transfusion on the microcirculation in premature infants by its ability to increase FCD [54]. Inhaled NO (iNO) improves outcome in infants diagnosed with persistant pulmonary hypertension of the newborn by improving pulmonary blood flow and oxygenation. It reduces pulmonary vascular resistance, without fall in systemic blood pressure. Top et al. [60] showed that iNO

improves the microcirculation of the buccal mucosa in children with hypoxemic respiratory failure.

Extracorporeal membrane oxygenation (ECMO) can be considered as a therapy of choice for patients with severe respiratory and circulatory compromise, when conservative treatment fails. Top et al. investigated the microcirculatory response of critically ill pediatric patients to ECMO. They demonstrated that respiratory distress was associated with severe microcirculatory alterations and that after treatment with ECMO, at a time when the patient no longer needed ECMO, the microcirculatory parameters were improved [58].

Prognostic Value of the Microcirculation

OPS and SDF have been applied in adults in various clinical settings and have been shown to be associated with the severity of disease and outcome [27, 48, 63–65], In adult patients with septic shock, microcirculatory parameters that did not resolve after 24 hours of admission, were shown to be associated with poor outcome [27]. The presence of abnormal microcirculatory values has been shown to be correlated with other measures of patient severity of illness during sepsis, such as sequential organ failure assessment (SOFA) scores [63]. Patients who develop nosocomial infection after major abdominal surgery have been shown to exhibit impairment of sublingual microcirculatory parameters [65]. De Backer et al. also found that the degree of microvascular derangement in adults with cardiogenic shock was reflected in their survival [64].

In regards to children, Top et al. found that persistent alterations of the microcirculation were associated with poor outcome in children with septic shock [59]. Lack of restoration of the altered microcirculation proved to have a stronger predictive value for mortality than severity of illness score using the pediatric risk of mortality (PRISM) model (**Fig. 1**). In premature neonates, reduction of FCD of the skin can be the first sign of infection. For example, Weidlich et al. observed microcirculatory alterations in premature infants with infection [58]. The authors suggested that these alterations might be predictive of infection, even before clinical suspicion arises.

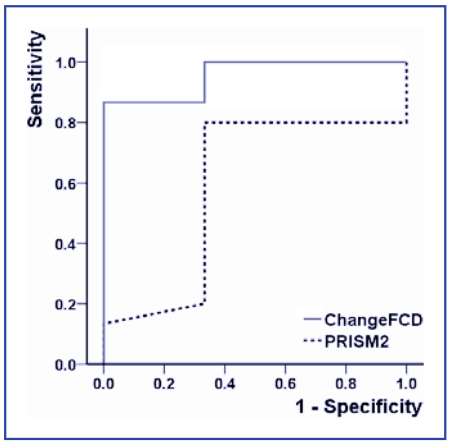

Fig. 1. Receiver operator characteristic (ROC) curve for the change in functional capillary density (ΔFCD) within the first 2 days of septic shock in children. The best cut-off is 0.7. Area under the curve (AUC) for ΔFCD = 0.956 (95 % CI 0.853–1.058). The ROC curve for pediatric risk of mortality (PRISM) shows a low sensitivity and specificity. It has an AUC of 0.59 (95 %CI 0.209–0.969) and is significantly less sensitive and specific than the ΔFCD measured by the ROC curve. From [59] with permission

Conclusion

Direct observation of the microcirculation is, potentially, a valuable addition to the hemodynamic monitoring of the critically ill pediatric patient, where other monitoring modalities are limited. If the current practical limitations for routine use of OPS and SDF imaging can be overcome, such monitoring modalities may improve outcome by directing clinicians to administer resuscitative therapies in a more timely and effective manner.

References

1. Pinsky MR, Payen D (2005) Functional hemodynamic monitoring. Crit Care 9: 566–572
2. Tibby SM, Hatherill M, Marsh MJ, Murdoch IA (1997) Clinicians' abilities to estimate cardiac index in ventilated children and infants. Arch Dis Child 77: 516–518
3. Egan JR, Festa M, Cole AD, Nunn GR, Gillis J, Winlaw DS (2005) Clinical assessment of cardiac performance in infants and children following cardiac surgery. Intensive Care Med 31: 568–573
4. Partrick DA, Bensard DD, Janik JS, Karrer FM (2002) Is hypotension a reliable indicator of blood loss from traumatic injury in children? Am J Surg 184: 555–559
5. Shoemaker WC, Beez M (2010) Pathophysiology, monitoring, and therapy of shock with organ failure. Appl Cardiopulm Pathophysiol 14: 5–15
6. Agata Y, Hiraishi S, Misawa H, et al (1994)Regional blood flow distribution and left ventricular output during early neonatal life: a quantitative ultrasonographic assessment. Pediatr Res 36: 805–810
7. Cattermole GN, Leung PY, Mak PS, Chan SS, Graham CA, Rainer TH (2010) The normal ranges of cardiovascular parameters in children measured using the Ultrasonic Cardiac Output Monitor. Crit Care Med 38: 1875–1881
8. Parker MM, Shelhamer JH, Natanson C, Alling DW, Parrillo JE (1987) Serial cardiovascular variables in survivors and nonsurvivors of human septic shock: heart rate as an early predictor of prognosis. Crit Care Med 15: 923–929
9. Feltes TF, Pignatelli R, Kleinert S, Mariscalco MM (1994) Quantitated left ventricular systolic mechanics in children with septic shock utilizing noninvasive wall-stress analysis. Crit Care Med 22: 1647–1658
10. Ceneviva G, Paschall JA, Maffei F, Carcillo JA (1998) Hemodynamic support in fluid-refractory pediatric septic shock. Pediatrics 102: e19
11. Mercier JC, Beaufils F, Hartmann JF, Azema D (1988) Hemodynamic patterns of meningococcal shock in children. Crit Care Med 16: 27–33
12. Pollack MM, Fields AI, Ruttimann UE (1985) Distributions of cardiopulmonary variables in pediatric survivors and nonsurvivors of septic shock. Crit Care Med 13: 454–459
13. Kliegman R (2007) Nelson Textbook of Pediatrics, 18th Edition. Elsevier, Philadelphia
14. Tibby SM, Murdoch IA (2002) Measurement of cardiac output and tissue perfusion. Curr Opin Pediatr 14: 303–309
15. Tibby S (2008) Transpulmonary thermodilution: finally, a gold standard for pediatric cardiac output measurement. Pediatr Crit Care Med 9: 341–342
16. de Boode WP (2010) Cardiac output monitoring in newborns. Early Hum Dev 86: 143–148
17. Saavedra JM, Harris GD, Li S, Finberg L (1991) Capillary refilling (skin turgor) in the assessment of dehydration. Am J Dis Child 145: 296–298
18. Mackenzie A, Shann F, Barnes G (1989) Clinical signs of dehydration in children. Lancet 2: 1529–1530
19. Tibby SM, Hatherill M, Murdoch IA (1999) Capillary refill and core-peripheral temperature gap as indicators of haemodynamic status in paediatric intensive care patients. Arch Dis Child 80: 163–166
20. Levy B (2006) Lactate and shock state: the metabolic view. Curr Opin Crit Care 12: 315–321

21. Fall PJ, Szerlip HM (2005) Lactic acidosis: from sour milk to septic shock. Journal of intensive care medicine 20: 255–271
22. Hatherill M, Waggie Z, Purves L, Reynolds L, Argent A (2003) Mortality and the nature of metabolic acidosis in children with shock. Intensive Care Med 29: 286–291
23. Marik PE (2006) Sublingual capnometry: a non-invasive measure of microcirculatory dysfunction and tissue hypoxia. Physiol Meas 27: R37–47
24. Creteur J, De Backer D, Sakr Y, Koch M, Vincent JL (2006) Sublingual capnometry tracks microcirculatory changes in septic patients. Intensive Care Med 32: 516–523
25. Fries M, Weil MH, Sun S, et al (2006) Increases in tissue Pco2 during circulatory shock reflect selective decreases in capillary blood flow. Crit Care Med 34: 446–452
26. Levy B, Gibot S, Franck P, Cravoisy A, Bollaert PE (2005) Relation between muscle Na+K+ ATPase activity and raised lactate concentrations in septic shock: a prospective study. Lancet 365: 871–875
27. Sakr Y, Dubois MJ, De Backer D, Creteur J, Vincent JL (2004) Persistent microcirculatory alterations are associated with organ failure and death in patients with septic shock. Crit Care Med 32: 1825–1831
28. Trzeciak S, Rivers EP (2005) Clinical manifestations of disordered microcirculatory perfusion in severe sepsis. Crit Care 9 (Suppl 4): S20–26
29. Spronk PE, Zandstra DF, Ince C (2004) Bench-to-bedside review: sepsis is a disease of the microcirculation. Crit Care 8: 462–468
30. Trzeciak S, Dellinger RP, Parrillo JE, et al (2007) Early microcirculatory perfusion derangements in patients with severe sepsis and septic shock: relationship to hemodynamics, oxygen transport, and survival. Ann Emerg Med 49: 88–98
31. Guyton AC, Carrier O, Jr., Walker JR (1964) Evidence for Tissue Oxygen Demand as the Major Factor Causing Autoregulation. Circ Res 15 (suppl): 60–69
32. LeDoux D, Astiz ME, Carpati CM, Rackow EC: (2000)Effects of perfusion pressure on tissue perfusion in septic shock. Crit Care Med 28: 2729–2732
33. Weil MH, Tang W (2007) Welcoming a new era of hemodynamic monitoring: expanding from the macro to the microcirculation. Crit Care Med 35: 1204–1205
34. Fagrell B, Intaglietta M (1997) Microcirculation: its significance in clinical and molecular medicine. J Intern Med 241: 349–362
35. Slaaf DW, Tangelder GJ, Reneman RS, Jager K, Bollinger A (1987) A versatile incident illuminator for intravital microscopy. Int J Microcirc Clin Exp 6: 391–397
36. Groner W, Winkelman JW, Harris AG, et al (1999) Orthogonal polarization spectral imaging: a new method for study of the microcirculation. Nat Med 5: 1209–1212
37. Goedhart PT, Khalilzada M, Bezemer R, Merza J, Ince C (2007) Sidestream Dark Field (SDF) imaging: a novel stroboscopic LED ring-based imaging modality for clinical assessment of the microcirculation. Opt Express 15: 15101–15114
38. Sherman H, Klausner S, Cook WA (1971) Incident dark-field illumination: a new method for microcirculatory study. Angiology 22: 295–303
39. Balestra GM, Bezemer R, Boerma EC, et al (2010) Improvement of sidestream dark field imaging with an image acquisition stabilizer. BMC Med Imaging 10: 15
40. Harris AG, Sinitsina I, Messmer K (2002) Validation of OPS imaging for microvascular measurements during isovolumic hemodilution and low hematocrits. Am J Physiol Heart Circ Physiol 282: H1502–1509
41. Langer S, Biberthaler P, Harris AG, Steinau HU, Messmer K (2001) In vivo monitoring of microvessels in skin flaps: introduction of a novel technique. Microsurgery 21: 317–324
42. Langer S, Born F, Hatz R, Biberthaler P, Messmer K (2002) Orthogonal polarization spectral imaging versus intravital fluorescent microscopy for microvascular studies in wounds. Ann Plastic Surg 48: 646–653
43. Langer S, Harris AG, Biberthaler P, von Dobschuetz E, Messmer K (2001) Orthogonal polarization spectral imaging as a tool for the assessment of hepatic microcirculation: a validation study. Transplantation 71: 1249–1256
44. Mathura KR, Vollebregt KC, Boer K, De Graaff JC, Ubbink DT, Ince C (2001) Comparison of OPS imaging and conventional capillary microscopy to study the human microcirculation. J Appl Physiol 91: 74–78

45. De Backer D, Hollenberg S, Boerma C, et al (2007) How to evaluate the microcirculation: report of a round table conference. Crit Care 11: R101
46. Boerma EC, Mathura KR, van der Voort PH, Spronk PE, Ince C (2005) Quantifying bedside-derived imaging of microcirculatory abnormalities in septic patients: a prospective validation study. Crit Care 9: R601–606
47. Dobbe JG, Streekstra GJ, Atasever B, van Zijderveld R, Ince C (2008) Measurement of functional microcirculatory geometry and velocity distributions using automated image analysis. Med Biol Eng Comput 46: 659–670
48. De Backer D, Creteur J, Preiser JC, Dubois MJ, Vincent JL (2002) Microvascular blood flow is altered in patients with sepsis. Am J Respir Crit Care Med 166: 98–104
49. Top AP, van Dijk M, van Velzen JE, Ince C, Tibboel D (2010) Functional capillary density decreases after the first week of life in term neonates. Neonatology 99: 73–77
50. Beinder E, Trojan A, Bucher HU, Huch A, Huch R (1994) Control of skin blood flow in pre- and full-term infants. Biol Neonate 65: 7–15
51. Norman M, Herin P, Fagrell B, Zetterstrom R (1988) Capillary blood cell velocity in full-term infants as determined in skin by videophotometric microscopy. Pediatr Res 23: 585–588
52. Jahnukainen T, Lindqvist A, Jalonen J, Kero P, Valimaki I (1996) Reactivity of skin blood flow and heart rate to thermal stimulation in infants during the first postnatal days and after a two-month follow-up. Acta Paediatr 85: 733–738
53. Genzel-Boroviczeny O, Strotgen J, Harris AG, Messmer K, Christ F (2002) Orthogonal polarization spectral imaging (OPS): a novel method to measure the microcirculation in term and preterm infants transcutaneously. Pediatr Res 51: 386–391
54. Genzel-Boroviczeny O, Christ F, Glas V (2004) Blood transfusion increases functional capillary density in the skin of anemic preterm infants. Pediatr Res 56: 751–755
55. Kroth J, Weidlich K, Hiedl S, Nussbaum C, Christ F, Genzel-boroviczeny O (2008) Functional vessel density in the first month of life in preterm neonates. Pediatr Res 64: 567–571
56. Hiedl S, Schwepcke A, Weber F, Genzel-Boroviczeny O (2010) Microcirculation in preterm infants: profound effects of patent ductus arteriosus. J Pediatr 156: 191–196
57. Top AP, Ince C, van Dijk M, Tibboel D (2009) Changes in buccal microcirculation following extracorporeal membrane oxygenation in term neonates with severe respiratory failure. Crit Care Med 37: 1121–1124
58. Weidlich K, Kroth J, Nussbaum C, Hiedl S, Bauer A, Christ F, Genzel-Boroviczeny O (2009) Changes in microcirculation as early markers for infection in preterm infants--an observational prospective study. Pediatr Res 66: 461–465
59. Top AP, Ince C, de Meij N, van Dijk M, Tibboel D (2011) Persistent low microcirculatory vessel density in non-survivors of sepsis in pediatric intensive care. Crit Care Med 39: 8–13
60. Top AP, Ince C, Schouwenberg PH, Tibboel D (2011) Inhaled nitric oxide improves systemic microcirculation in infants with hypoxemic respiratory failure. Pediatr Crit Care Med (in press)
61. Perera P, Kurban K, Ryan TJ (1970) The development of the cutaneous microvascular system in the newborn. Br J Dermatology 82 (S5): 86–91
62. Stopfkuchen H (1987) Changes of the cardiovascular system during the perinatal period. Eur J Pediatr 146: 545–549
63. Trzeciak S, McCoy JV, Dellinger RP, et al (2008) Early increases in microcirculatory perfusion during protocol-directed resuscitation are associated with reduced multi-organ failure at 24 h in patients with sepsis. Intensive Care Med 34: 2210–2217
64. De Backer D, Creteur J, Dubois MJ, Sakr Y, Vincent JL (2004) Microvascular alterations in patients with acute severe heart failure and cardiogenic shock. Am Heart J 147: 91–99
65. Jhanji S, Lee C, Watson D, Hinds C, Pearse RM (2009) Microvascular flow and tissue oxygenation after major abdominal surgery: association with post-operative complications. Intensive Care Med 35: 671–677

X Cardiovascular Monitoring

Heart Rate as Prognostic Marker and Therapeutic Target In MODS

S. Nuding, K. Werdan, and H. Ebelt

Introduction

As early as 1945, the importance of resting heart rate as a prognostic factor was described in a retrospective analysis among the US-military, showing a higher probability of retirement from active military service with a resting heart rate of more than 100 bpm in a routine examination [1]. A high heart rate is an independent risk factor for adverse cardiovascular events and total mortality in patients with coronary artery disease [2], chronic heart failure [3] and in the general population (**Fig. 1**) [4].

In the 'multifactor primary prevention trial in Göteborg', monitoring more than 30,000 healthy men for 12 years, a clear correlation between resting heart rate and all-cause-mortality and coronary-mortality was shown [5]: Compared with individuals with a heart rate < 60 bpm, a heart rate > 90 bpm in trial participants was associated with a two- to three-fold elevated mortality. Another trial revealed resting heart rate to be an independent predictor of sudden cardiac death in a cohort of 7,079 men, none of them with known coronary heart disease [6]. Finally, the Framingham-trial also showed a significant correlation of heart rate and mortality [7].

In the course of a large Registry (Coronary Artery Surgery Trial, CASS), which followed up patients with coronary heart disease and planned coronary artery bypass graft (CABG) procedures for 14.7 years, a significant correlation of ele-

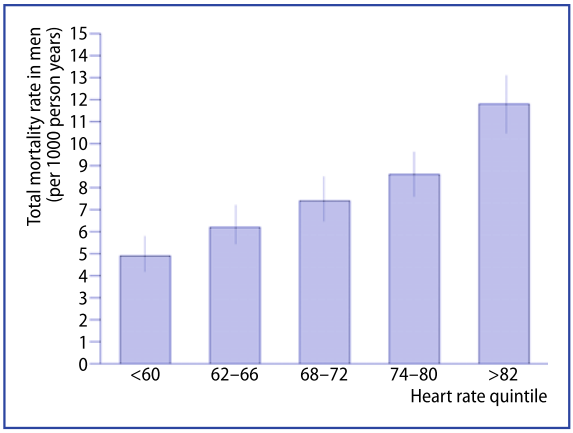

Fig. 1. Heart rate and all cause mortality (mean and standard deviation) in men in a general population. Data from the FINRISC-study [4].

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vated heart rate with mortality existed even after adjustment for variables such as age, sex, diabetes, hypertension, smoking, left ventricular ejection fraction (LVEF), number of affected coronary arteries, recreational activity, and medication [2].

Patients with Multiorgan Dysfunction Syndrome

Multiorgan dysfunction syndrome (MODS) specifies a condition of the acutely ill patient characterized by the presence of altered organ functions such that homeostasis cannot be maintained without intervention [8]. The term 'MODS' thus meets the requirements for a clinical syndrome of critical illness, with consecutive or simultaneous malfunction of several vital organs.

The MODS-related involvement of organs is either primary (e.g., acute lung injury/acute respiratory distress syndrome [ALI/ARDS] in pneumonia or lung contusion, encephalopathy in meningitis, acute heart failure in myocardial infarction, disseminated intravascular coagulation [DIC] in transfusion accident, etc.) or secondary through generalized phenomena (systemic inflammatory response syndrome [SIRS], DIC, disturbed microcirculation, insufficient tissue oxygenation, etc.). The most common causes of MODS are sepsis and cardiogenic or hemorrhagic shock. Burns, pancreatitis or trauma can also trigger MODS.

In MODS, there is a progressive transition of deviation of single physiological parameters from their normal ranges through to complete multiple organ failure. The 2001 Sepsis Definition Conference stated that MODS was best characterized by a validated intensive care medicine scoring system [9]. **Box 1** lists the adequately validated scores used in intensive care medicine today.

Scores that use heart rate as a parameter for score calculation are the Logisitic Organ Dysfunction Score (LODS), Multiple Organ Dysfunction Score, and Acute Physiology and Chronic Health Evaluation (APACHE) II-score. The scoring systems not only allow a grading of disease severity – important for both clinical work and research – but also reliably describe patient prognosis [10]. An APACHE II score ≥ 20 is an accepted inclusion criterion in clinical trials investigating MODS [11, 12].

Basically, MODS is a reversible process. However, it accounts for considerable mortality of patients in intensive care units (ICUs). Up to 83 % of deceased critically ill patients are diagnosed with this syndrome posthumously [13]. Mortality from MODS is reported as between 30 – 100 % and mainly depends on the number of failing organs [14, 15]. At least every second death is a consequence of a failure of the cardiovascular system in a state of intense autonomic dysfunction.

Box 1. Scoring systems to assess multiorgan dysfunction syndrome (MODS)

APACHE II score	Acute Physiology and Chronic Health Evaluation
Elebute Score	Severity of Sepsis Grading
LODS	Logistic Organ Dysfunction Score
MODS	Multiple Organ Dysfunction Score
SAPS II	Simplified Acute Physiology Score
SOFA Score	Sequential Organ Failure Assessment

Increasing scientific activities in this field in recent years reflect the importance of MODS in the prognosis of critically ill patients. A large number of potential therapies have been identified by intensive basic research and for some clinically feasible therapeutic regimes results of randomized clinical trials are available [16]. So far the results of these trials have been very disappointing. A prognostic improvement has been demonstrated for very few therapeutic components in selected subgroups of patients with MODS or single organ dysfunction syndromes (e.g., recombinant human activated protein C for severe sepsis, ventilation with lower tidal volumes for ARDS, early goal-directed therapy in the treatment of severe sepsis and septic shock). Overall, the currently available regimes for the treatment of MODS are very limited, compared with its high incidence and mortality. The present therapy of severe sepsis, septic shock and cardiogenic shock caused by myocardial infarction is based on contemporary guidelines of medical societies [17]. Recommendations for the treatment of sepsis and septic shock are based on so called 'weak' recommendations and low levels of evidence (expert opinions). That is why there is urgent need for innovations that can improve the prognosis of patients with MODS.

Although reducing heart rate has moved into the focus of therapeutic efforts to improve outcomes in cardiovascular patients [18], the question of transferability to critically ill patients remains unanswered. As a rule, the heart rate is elevated in MODS and it has been demonstrated that mortality of patients with MODS is highly correlated with sinus tachycardia. The greater the number of affected organ systems and the more severe the degree of dysfunction, the higher the heart rate [19].

A fast heart rate on the day of admission was an independent and early predictor of death due to MODS in a prospective, multicenter, observational cohort trial of high-risk patients with noncardiac surgery [20]. Parker et al. investigated which hemodynamic parameters correlated with survival in 48 consecutive patients with septic shock and positive blood cultures on a medical ICU. Significant predictors of survival were a heart rate < 106 bpm at admission to ICU, a heart rate < 95 bpm and a systemic vascular resistance index (SVRI) > 1529 dyn/s/cm^5/m^2 24 hours after admission or a lowering of heart rate by > 18 bpm or a lowering of cardiac output index by > 0.5 l/min/m^2 within the first 24 hours [21]. The treatment of these patients followed a standardized protocol in which initially a pulmonary artery occlusion pressure (PAOP) of 15 mmHg and a mean arterial pressure (MAP) > 60 mmHg was achieved by intravenous fluids and, if necessary, by administration of catecholamines. The non-surviving patients were hemodynamically characterized by the fact that, despite these measures, no reduction in the hyperdynamic circulatory situation (inadequate tachycardia, high cardiac output and low peripheral vascular resistance) was reached within 24 hours. In another trial, Leibovici et al. [22] prospectively established the 'relative tachycardia', i.e., body temperature-related heart rate, in septic patients at the time of admission as a prognostic parameter of 30-day survival. In 3,529 patients with SIRS and suspected or proven infection, survivors were distinguished in a univariate analysis by a significantly lower relative tachycardia (mean 2.40 ± 0.48/min/°C vs. 2.55 ± 0.57/min/°C. The multivariate regression analysis found that a relative tachycardia 2.71/min/°C was an independent predictor of 30-day mortality (odds ratio 1.54, 95 % CI 1.10 – 2.17).

Inadequately elevated heart rate, like reduced heart rate variability, is part of the autonomic dysfunction in critically ill patients [19]. **Figure 2** shows heart

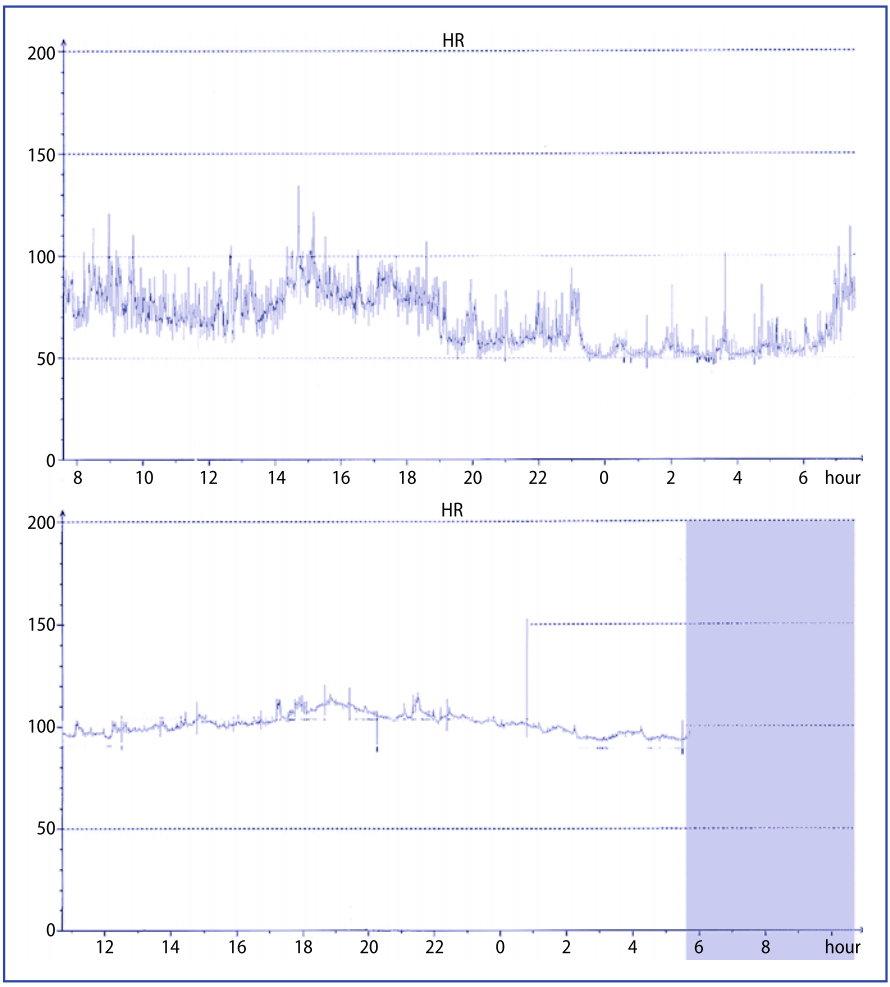

Fig. 2. Reduced heart rate variability in multiorgan dysfunction syndrome (MODS). Heart rate and RR-histogram of a healthy person (upper panel) and a patient with MODS (lower panel). Narrowed base in the RR-histogram, fewer heart rate fluctuations and higher mean heart rate as an expression of reduced heart rate variability in MODS.

rate variability in a healthy person and in a patient with MODS. The prognostic role of heart rate was demonstrated in a group of 80 MODS patients, with patients with a heart rate of ≥ 90 bpm having a significantly lower survival rate than those patients with a heart rate of < 90 bpm (**Fig. 3**) (R. Hoke, unpublished data).

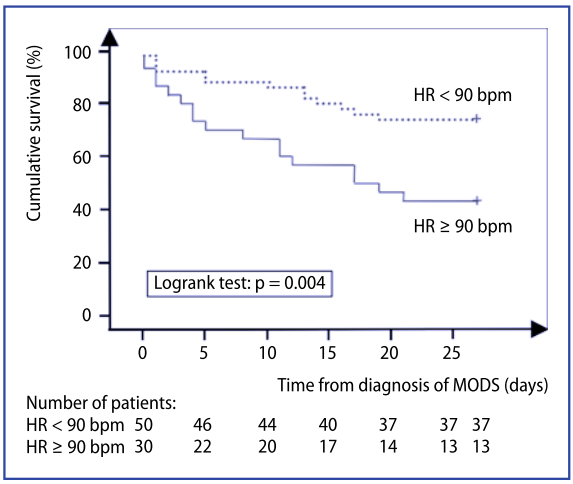

Fig. 3. Effects of baseline heart rate (HR) on 28-day all-cause mortality in 80 critically ill patients with MODS. (.....) baseline heart rate < 90 bpm; (_____) baseline heart rate ≥ 90 bpm. From the thesis of R. Hoke, with permission.

Mechanisms

Different pathophysiological explanations can be discussed for the adverse impact of increased heart rate, such as increased myocardial oxygen demand and reduced coronary blood flow due to shortened diastole. Additionally, it has also been shown that there is an increased disposition to rupture of atherosclerotic plaques at elevated heart rates [23].

Endotoxin, a cell wall component of Gram-negative bacteria and frequent cause of sepsis and consecutive MODS (also increased in heart failure due to bacterial translocation) directly affects the hyperpolarization-activated cyclic nucleotide gated (HCN) channels mediating the pacemaker current, If, of human cardiomyocytes [24]. This means that the electrical activity of the If-current is slowed (**Fig. 4**).

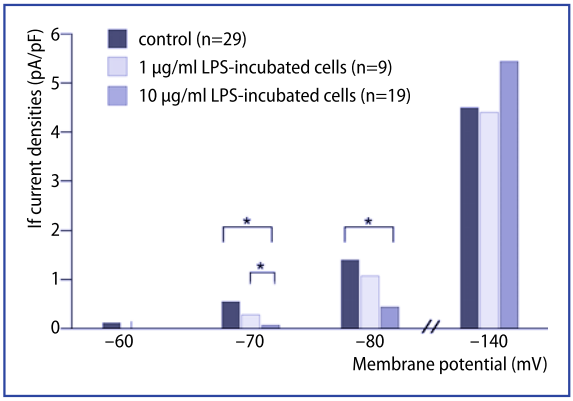

Fig. 4. Effect of lipopolysaccharide (LPS) on the funny current (If) properties in cardiomyocytes: Absolute mean current-density values of control and LPS-incubated myocytes (1 and 10 µg/mL) [24]. * $p < 0.05$

On the other hand, endotoxin also sensitizes the HCN channels for sympathetic stimulation, thereby increasing heart rate. Accordingly, our own data show that in chronically instrumented mice, endotoxin increases heart rate and reduces heart rate variability, while blocking sympathetic and vagal activity in these mice induces bradycardia. The combined effect of endotoxin on the pacemaker current, If, is an inadequately high heart rate and a narrowed heart rate variability, both impairing cardiac function and indicating an unfavorable prognosis [19]. This is a possible explanation for the decreased heart rate variability as a marker of autonomic dysfunction, and thus poorer prognosis in patients with MODS. However, it is also possible to interpret an increased heart rate as a symptom of underlying – manifest or still unknown – illness rather than as a causal factor, but no statistics will be able to prove definite causality in this case.

In summary, there is a large number of studies in healthy and diseased populations that have established an increased heart rate as an independent predictor of increased mortality.

Heart Rate as a Therapeutic Target in Non-MODS Patients

It is well established that a reduction in heart rate is associated with an improvement in prognosis in patients with cardiovascular disease [18, 25]. This is an accepted therapeutic goal in patients with coronary heart disease [17]. For coronary heart disease, chronic heart failure, secondary prevention after myocardial infarction and certain tachyarrhythmias, beta-blockers are part of the standard therapy after exclusion of contraindications. After acute myocardial infarction, beta-blockers significantly reduced mortality; the extent of reduction depends on the *de facto* heart rate reduction achieved [17, 26].

In a systematic review of 35 randomized controlled trials on the use of beta-blockers in patients with heart failure, reducing heart rate was shown to be the major contributor to the reduction of mortality [27]. Beta-receptor-antagonists are drugs with heart rate lowering activity, well established in the treatment of patients with chronic myocardial infarction [17] and heart failure [28]. Because of contraindications – first of all the need for catecholamines for hemodynamic stabilization in circulatory shock – the use of beta-blockers is prohibited in most MODS-patients.

In those MODS-patients with an unfavorable prognosis, high heart rate and concurrent contraindication to the administration of beta-blockers, ivabradine, a selective antagonist of the pacemaker current, If, may be used to attempt to lower the heart rate to a prognostically more favorable range. Based on the results of the BEAUTIFUL-trial, we know that patients with stable coronary heart disease and heart failure with a heart rate > 70 bpm have a worse prognosis [25]; these patients reach a combined end-point (cardiovascular death, hospitalization because of myocardial infarction or newly diagnosed or worsening heart failure) more frequently (34 % higher cardiovascular mortality, 53 % higher risk of hospitalization because of heart failure, 46 % higher risk for hospitalization because of myocardial infarction, and 38 % higher risk of coronary revascularization). Above a heart rate of 65 bpm, every increase in heart rate of 5 bpm was associated with a higher risk of all-cause-mortality (+8 %), hospitalization because of worsening heart failure (+16 %), hospitalization because of myocardial infarction (+7 %) and hospitalization because of coronary revascularization (+8 %).

Furthermore, the SHIFT-trial [3] showed that heart rate is an important target for treatment of heart failure as well. Patients with standard treatment for heart failure with a higher heart rate (≥ 87 bpm) were at a more than two-fold increased risk for cardiovascular death or hospital admission for worsening heart failure compared with those in the lowest heart-rate group (70 to < 72 bpm; hazard ratio [HR] 2·34, p < 0·0001) with every beat increase in heart rate, increasing the risk of a composite of cardiovascular death or hospital admission for worsening heart failure by 3 % (p < 0·0001). The higher the heart rate at baseline, the higher the heart rate reduction with ivabradine and the greater the relative reduction in outcome events compared with placebo.

In a multivariate analysis of data from the GISSI-2 trial, the heart rate of 8,519 patients with acute myocardial infarction at discharge without atrial fibrillation proved to be an independent predictor of survival: 6-month mortality was 0.8 % for a heart rate < 60 bpm vs. 14.3 % for > 100 bpm [29]. In chronic heart failure, a beta-blocker saves 3.8 lives per 100 patients in the first year of treatment, according to a meta-analysis [30]. In addition to heart rate at baseline, the mortality rate also depends on the extent of heart rate reduction, applying equally to patients with and those without beta-blocker. A multivariate analysis of the CIBIS II trial revealed baseline heart rate, heart rate after two months of therapy as well as taking a beta-blocker as independent predictors of survival in patients with heart failure NYHA III and IV [31]. The reason why beta-blockers improve symptoms and prognosis of many cardiovascular patient-populations has not been finally resolved; the reduction in heart rate is generally accepted as the main mechanism [3]. This leads to a reduction in myocardial oxygen consumption and – via an improvement in diastolic filling of the heart – to an economy of cardiac work. The amelioration in exercise-induced angina by calcium channel blockers and beta-blockers correlated linearly with pharmacologically achieved heart rate reduction [26]. Antiarrhythmic properties of beta-blockers probably play a role in terms of improving tachyarrhythmias. For certain patient populations, it has been shown that the beneficial effects of beta-blockers depend on heart rate, i.e., the degree of sympathetic overactivity before beta-blocker administration [32]. An improvement in autonomic dysfunction in cardiovascular patients by administration of beta-blockers is well documented [33, 34]. Several metabolic effects of beta-blockers, including anti-oxidant properties, have been discussed in the past as contributors to the success story of this drug group in modern cardiovascular medicine [35].

The pathophysiological baseline of patients with MODS in many ways parallels the hormonal and functional constellation of heart failure, with sympathetic overactivity, activation of the renin-angiotensin-aldosterone system (RAAS), autonomic dysfunction with an inadequate high heart rate, and in most cases a cardiomyopathy with insufficient cardiac output [14 36]. In addition, there are also certain metabolic alterations such as insulin resistance, increased protein- and lipid-catabolism, decreased clearance of lactate and increased oxidative stress, etc., as well as a depression of the immune system. As with chronic heart failure, downregulation of sympathetic beta-receptors is also found in MODS [37, 38]. Therefore, the possible use of beta-blockers in SIRS and sepsis has been debated for a long time [39].

Heart Rate Reduction in MODS

Early studies in patients with SIRS demonstrated that the β-blocker, propranolol, could effectively reduce energy consumption and muscle wasting in catabolic phases of illness [40]. In pediatric burn patients, propranolol reduced the left ventricular stroke work index (LVSWI), but without altering cardiac output, PAOP or oxygen consumption [41]. In a ligation/perforation model of sepsis in rats, a significant reduction in heart rate could be achieved by a continuous infusion of the beta-adrenergic blocker, esmolol [42]. At the same time, cardiac output, cardiac contractility (measured as the maximum pressure increase over time), the cardiac workload (measured as the product of cardiac output and maximum left ventricular pressure) and the efficiency of cardiac work (i.e., cardiac work related to myocardial oxygen consumption) increased. In this model, it has been convincingly shown that the reduction in heart rate in septic cardiomyopathy does not have to be accompanied by an impairment in cardiac performance, but rather is able to economize the cardiac workload. In a retrospective analysis, MODS patients with beta-blocker administration had improved autonomic function and exhibited a significantly reduced mortality [43]. It remains unclear to what extent there is causality between these coincident findings. Previously, however, it has been pointed out that an increased resting heart rate in cardiovascular diseased patients is a sign of autonomic imbalance with sympathetic overactivity [44].

The well-documented efficacy of beta-blockers has led to their widespread use in cardiovascular medicine. However, due to adverse effects, beta-blockers are contraindicated, absolutely or relatively, for certain patient populations, such as those with acute heart failure, obstructive airway disease, or shock [45].

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Because of its different mechanism of action, ivabradine, the new specific inhibitor of the pacemaker current in the sinoatrial node, provides a possible therapeutic alternative to medicinally induced blockade of beta-receptors. Effects on the vascular system, the bronchial tree or on mood have not been described for ivabradine in contrast to beta-blockers [46].

Ivabradine is a selective inhibitor of the cardiac pacemaker current, If [46]. Ivabradine leads to a dynamic (use-dependent) blockade of the HCN channels and, thus, to a reduction in heart rate in patients with sinus rhythm. Ivabradine reduces myocardial oxygen consumption and increases the duration of diastole [47, 48]. With regard to negative chronotropic effect, the effect of ivabradine is comparable to that of beta-blockers or calcium channel blockers of the verapamil type, but ivabradine does not lead to (unwanted) negative inotropy and antihypertensive effects, as seen with beta-blockers and verapamil [48]. This advantage of selective heart rate reduction has potentially fundamental implications for the treatment of critically ill patients with heart failure either primarily due to reduced LVEF (e.g., acute and chronic heart failure or cardiogenic shock) or secondarily because of systemic dysfunction (i.e., septic cardiomyopathy).

Preliminary clinical data suggest that ivabradine adminsitration may result in a positive influence on ventricular remodeling in patients with left ventricular dysfunction [49]. In animal models of heart failure, ivabradine improved cardiac morphology and function [50].

The impact of ivabradine on parameters of cardiovascular function in critically ill patients is largely unknown. Based on the above-mentioned promising data, we

retrospectively analyzed 22 score-defined MODS-patients in whom ivabradine was used in an individual therapeutic approach. Ivabradine was newly prescribed because of inadequate sinus tachycardia (once or twice daily) for at least two days in these critically ill patients, and was associated with a reduction in heart rate by 14 bpm in all patients and by at least 10 bpm after 48 hours in 65 % of patients (unpublished own data). Patients were included in this analysis if the following criteria were met: Age > 18 years, sinus rhythm, heart rate > 70 bpm, APACHE II score ≥ 20, contraindication to beta-blockers, hemodynamic monitoring by means of a pulmonary artery catheter. Diagnoses, hemodynamic parameters, common critical care scores, and the incidence of bradycardia, defined as a heart rate < 50 bpm were retrospectively extracted from the medical charts.

The results of this analysis are shown in **Table 1** and **Figure 5** and are given in mean values ± standard deviations: The mean age of the population (13 males, 9 females) studied was 62.5 ± 12.3 years. Mean daily ivabradine dose delivered was 7.7 ± 2.5 mg. Etiology of MODS was septic shock, cardiogenic shock, or both, in 13, 5, and 4 subjects, respectively. Bradycardic episodes or discontinuation of ivabradine due to adverse events were not observed.

This initial clinical experience in individual treatment of increased heart rate in patients with MODS showed that ivabradine was able to reduce heart rate by about 10 bpm effectively and consistently and reducing the heart rate did not

Table 1. Results of a retrospective analysis of 22 patients with multiorgan dysfunction syndrome (MODS) treated with ivabradine for 2 days (unpublished own data)

Parameter/time	Baseline	48 hours	p-value
APACHE-II-Score	31±8	28±12	< 0.001
SAPS II	61±13	55±16	0.035
Mean heart rate (bpm)	101±17	87±15	< 0.001
Mean arterial pressure (mmHg)	115±15	118±20	0.47
Mean daily norepinephrine dose (μg/kg/min)	0.136±0.215	0.091±0.091	0.37
Mean daily dobutamine dose (μg/kg/min)	1.2±0.2	0.82±1.6	0.31

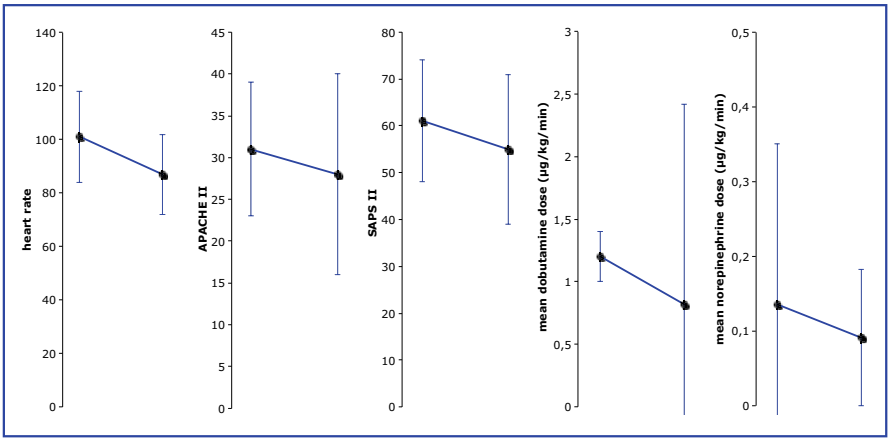

Fig. 5. Effects of ivabradine on selected parameters in 22 critically ill patients with newly diagnosed multiorgan dysfunction syndrome (MODS) who received ivabradine for 48 hours (unpublished own data).

result in hemodynamic instability. A trend towards hemodynamic improvement by reducing heart rate from 101 ± 17 bpm to 87 ± 15 bpm within 48 hours of treatment with ivabradine could be demonstrated. The catecholamine dose could be reduced in temporal association with ivabradine-induced heart rate reduction. Clinical scores of disease severity of MODS and sepsis decreased, which indicated stabilization of patients' health conditions. Ivabradine did not lead to deterioration of liver function parameters; furthermore no hemodynamically unfavorable bradycardia was induced.

These promising data tempted us to initiate a monocenter, randomized, controlled phase 2-trial – the MODIFY trial – to prove the hypothesis of clinical benefit of reducing an elevated heart rate by ivabradine in MODS-patients in a prospective setting (www.clinicaltrials.gov, NCT01186783). The primary end point of this trial is the proportion of patients with a reduction in heart rate by at least 10 beats per minute (bpm). This trial will randomize 70 patients (men and women, aged ≥ 18 years) with newly diagnosed MODS (APACHE II score ≥ 20, diagnosis within ≤ 24 hours), with an elevated heart rate (sinus rhythm with heart rate ≥ 90 bpm) and contraindications to beta-blockers. The treatment period will last 4 days, and all patients will be followed for up to six months.

Conclusion

A high heart rate is an independent risk factor for adverse cardiovascular events and total mortality in patients with coronary artery disease and chronic heart failure, and the general population. It is well established that a reduction in heart rate is associated with an improvement in prognosis in patients with cardiovascular disease. The pathophysiological baseline of patients with MODS in many ways parallels the hormonal and functional constellation of heart failure. As a rule, the heart rate is elevated in the MODS and mortality of MODS patients is highly correlated with inadequate sinus tachycardia. The well-documented efficacy of beta-blockers has led to their widespread use in cardiovascular medicine. However, because of adverse effects, beta-blockers are contraindicated for most critically ill patients. Preliminary clinical data suggest that ivabradine could overcome these negative side effects and could improve parameters of cardiovascular function and disease severity in MODS patients, but further research is needed.

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References

1. Levy R, White P, Stroud W, Hillman C (1945) Studies of blood pressure in Army officers: 4. Transient tachycardia-prognostic significance alone and in association with transient hypertension. JAMA 129: 585 – 588
2. Diaz A, Bourassa MG, Guertin MC, Tardif JC (2005) Long-term prognostic value of resting heart rate in patients with suspected or proven coronary artery disease. Eur Heart J 26: 967 – 974
3. Bohm M, Swedberg K, Komajda M, et al (2010) Heart rate as a risk factor in chronic heart failure (SHIFT): the association between heart rate and outcomes in a randomised placebo-controlled trial. Lancet 376: 886 – 894
4. Cooney MT, Vartiainen E, Laakitainen T, Juolevi A, Dudina A, Graham IM (2010) Elevated

resting heart rate is an independent risk factor for cardiovascular disease in healthy men and women. Am Heart J 159: 612 – 619
5. Wilhelmsen L, Berglund G, Elmfeldt D, et al (1986) The multifactor primary prevention trial in Goteborg, Sweden. Eur Heart J 7: 279 – 288
6. Jouven X, Zureik M, Desnos M, Guerot C, Ducimetiere P (2001) Resting heart rate as a predictive risk factor for sudden death in middle-aged men. Cardiovasc Res 50: 373 – 378
7. Gillman MW, Kannel WB, Belanger A, D'Agostino RB (1993) Influence of heart rate on mortality among persons with hypertension: the Framingham Study. Am Heart J 125: 1148 – 1154
8. American College of Chest Physicians/Society of Critical Care Medicine (1992) Consensus Conference: definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. Crit Care Med 20: 864 – 874
9. Levy MM, Fink MP, Marshall JC, et al (2003) 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. Intensive Care Med 29: 530 – 538
10. Pilz G, Kaab S, Kreuzer E, Werdan K (1994) Evaluation of definitions and parameters for sepsis assessment in patients after cardiac surgery. Infection 22: 8 – 17
11. Opal S, Laterre PF, Abraham E, et al (2004) Recombinant human platelet-activating factor acetylhydrolase for treatment of severe sepsis: results of a phase III, multicenter, randomized, double-blind, placebo-controlled, clinical trial. Crit Care Med 32: 332 – 341
12. Pilz G, Werdan K (1990) Cardiovascular parameters and scoring systems in the evaluation of response to therapy in sepsis and septic shock. Infection 18: 253 – 262
13. Tran DD, Groeneveld AB, van der Meulen J, Nauta JJ, Strack van Schijndel RJ, Thijs LG (1990) Age, chronic disease, sepsis, organ system failure, and mortality in a medical intensive care unit. Crit Care Med 18: 474 – 479
14. Schmidt H, Muller-Werdan U, Hoffmann T, et al (2005) Autonomic dysfunction predicts mortality in patients with multiple organ dysfunction syndrome of different age groups. Crit Care Med 33: 1994 – 2002
15. Vincent JL, de Mendonca A, Cantraine F, et al (1998) Use of the SOFA score to assess the incidence of organ dysfunction/failure in intensive care units: results of a multicenter, prospective study. Working group on "sepsis-related problems" of the European Society of Intensive Care Medicine. Crit Care Med 26: 1793 – 1800
16. Russell JA (2006) Management of sepsis. N Engl J Med 355: 1699 – 1713
17. Antman EM, Anbe DT, Armstrong PW, et al (2004) ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction--executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1999 Guidelines for the Management of Patients With Acute Myocardial Infarction). Circulation 110: 588 – 636
18. Swedberg K, Komajda M, Bohm M, et al (2010) Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. Lancet 376: 875 – 885
19. Werdan K, Schmidt H, Ebelt H, et al (2009) Impaired regulation of cardiac function in sepsis, SIRS, and MODS. Can J Physiol Pharmacol 87: 266 – 274
20. Lobo SM, Rezende E, Knibel MF, et al (2011) Early determinants of death due to multiple organ failure after noncardiac surgery in high-risk patients. Anesth Analg (in press)
21. Parker MM, Shelhamer JH, Natanson C, Alling DW, Parrillo JE (1987) Serial cardiovascular variables in survivors and nonsurvivors of human septic shock: heart rate as an early predictor of prognosis. Crit Care Med 15: 923 – 929
22. Leibovici L, Gafter-Gvili A, Paul M, et al (2007) Relative tachycardia in patients with sepsis: an independent risk factor for mortality. QJM 100: 629 – 634
23. Heidland UE, Strauer BE (2001) Left ventricular muscle mass and elevated heart rate are associated with coronary plaque disruption. Circulation 104: 1477 – 1482
24. Zorn-Pauly K, Pelzmann B, Lang P, et al (2007) Endotoxin impairs the human pacemaker current If. Shock 28: 655 – 661
25. Fox K, Ford I, Steg PG, Tendera M, Robertson M, Ferrari R (2008) Heart rate as a prognostic risk factor in patients with coronary artery disease and left-ventricular systolic dysfunction (BEAUTIFUL): a subgroup analysis of a randomised controlled trial. Lancet 372: 817 – 821
26. Cucherat M (2007) Quantitative relationship between resting heart rate reduction and

magnitude of clinical benefits in post-myocardial infarction: a meta-regression of randomized clinical trials. Eur Heart J 28: 3012 – 3019
27. Flannery G, Gehrig-Mills R, Billah B, Krum H (2008) Analysis of randomized controlled trials on the effect of magnitude of heart rate reduction on clinical outcomes in patients with systolic chronic heart failure receiving beta-blockers. Am J Cardiol 101: 865 – 869
28. Hunt SA, Abraham WT, Chin MH, et al (2005) ACC/AHA 2005 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure): developed in collaboration with the American College of Chest Physicians and the International Society for Heart and Lung Transplantation: endorsed by the Heart Rhythm Society. Circulation 112: e154 – 235
29. Zuanetti G, Mantini L, Hernandez-Bernal F, et al (1998) Relevance of heart rate as a prognostic factor in patients with acute myocardial infarction: insights from the GISSI-2 study. Eur Heart J 19 Suppl F: F19 – 26
30. Brophy JM, Joseph L, Rouleau JL (2001) Beta-blockers in congestive heart failure. A Bayesian meta-analysis. Ann Intern Med 134: 550 – 560
31. Lechat P, Hulot JS, Escolano S, et al (2001) Heart rate and cardiac rhythm relationships with bisoprolol benefit in chronic heart failure in CIBIS II Trial. Circulation 103: 1428 – 1433
32. Palatini P (1999) Heart rate as a risk factor for atherosclerosis and cardiovascular mortality: the effect of antihypertensive drugs. Drugs 57: 713 – 724
33. Niemela MJ, Airaksinen KE, Huikuri HV (1994) Effect of beta-blockade on heart rate variability in patients with coronary artery disease. J Am Coll Cardiol 23: 1370 – 1377
34. Tjeerdsma G, Szabo BM, van Wijk LM, et al (2001) Autonomic dysfunction in patients with mild heart failure and coronary artery disease and the effects of add-on beta-blockade. Eur J Heart Fail 3: 33 – 39
35. Chin BS, Langford NJ, Nuttall SL, Gibbs CR, Blann AD, Lip GY (2003) Anti-oxidative properties of beta-blockers and angiotensin-converting enzyme inhibitors in congestive heart failure. Eur J Heart Fail 5: 171 – 174
36. Muller-Werdan U, Buerke M, Ebelt H, et al (2006) Septic cardiomyopathy – A not yet discovered cardiomyopathy? Exp Clin Cardiol 11: 226 – 236
37. Bernardin G, Strosberg AD, Bernard A, Mattei M, Marullo S (1998) Beta-adrenergic receptor-dependent and -independent stimulation of adenylate cyclase is impaired during severe sepsis in humans. Intensive Care Med 24: 1315 – 1322
38. Reithmann C, Hallstrom S, Pilz G, Kapsner T, Schlag G, Werdan K (1993) Desensitization of rat cardiomyocyte adenylyl cyclase stimulation by plasma of noradrenaline-treated patients with septic shock. Circ Shock 41: 48 – 59
39. Norbury WB, Jeschke MG, Herndon DN (2007) Metabolism modulators in sepsis: propranolol. Crit Care Med 35: S616 – 20
40. Herndon DN, Hart DW, Wolf SE, Chinkes DL, Wolfe RR (2001) Reversal of catabolism by beta-blockade after severe burns. N Engl J Med 345: 1223 – 1229
41. Herndon DN, Barrow RE, Rutan TC, Minifee P, Jahoor F, Wolfe RR (1988) Effect of propranolol administration on hemodynamic and metabolic responses of burned pediatric patients. Ann Surg 208: 484 – 492
42. Suzuki T, Morisaki H, Serita R, et al (2005) Infusion of the beta-adrenergic blocker esmolol attenuates myocardial dysfunction in septic rats. Crit Care Med 33: 2294 – 2301
43. Hennen R, Friedrich I, Hoyer D, et al (2008) [Autonomic dysfunction and beta-adrenergic blockers in multiple organ dysfunction syndrome]. Dtsch Med Wochenschr 133: 2500 – 2504
44. Palatini P, Julius S (1997) Association of tachycardia with morbidity and mortality: pathophysiological considerations. J Hum Hypertens 11 (Suppl 1): S19 – 27
45. Lewis RV, Lofthouse C (1993) Adverse reactions with beta-adrenoceptor blocking drugs. An update. Drug Saf 9: 272 – 279
46. DiFrancesco D (2006) Funny channels in the control of cardiac rhythm and mode of action of selective blockers. Pharmacol Res 53: 399 – 406
47. Joannides R, Moore N, Iacob M, et al (2006) Comparative effects of ivabradine, a selective

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heart rate-lowering agent, and propranolol on systemic and cardiac haemodynamics at rest and during exercise. Br J Clin Pharmacol 61: 127 – 137
48. Colin P, Ghaleb B, Monnet X, Hittinger L, Berdeaux A (2004) Effect of graded heart rate reduction with ivabradine on myocardial oxygen consumption and diastolic time in exercising dogs. J Pharmacol Exp Ther 308: 236 – 240
49. Jondeau G, Korewicki J, Vasiliauskas D (2004) Effect of ivabradine in patients with left ventricular systolic dysfunction and coronary artery disease. Eur Heart J 25: 491 (abst)
50. Mulder P, Barbier S, Chagraoui A, et al (2004) Long-term heart rate reduction induced by the selective I(f) current inhibitor ivabradine improves left ventricular function and intrinsic myocardial structure in congestive heart failure. Circulation 109: 1674 – 1679

Hemodynamic Monitoring in Cardiogenic Shock

J. Poelaert

Introduction

Cardiac failure with a low flow state, clinical and biochemical signs of hypoperfusion albeit increased filling pressures, is defined as cardiogenic shock. These characteristics permit a differential diagnosis from other shock states. Cardiogenic shock is caused by either ventricular or valvular dysfunction, malignant rhythm disturbances, extrinsic factors or several of these. Although the etiologic features of cardiogenic shock are often not easy to determine with routine hemodynamic monitoring tools, routine baseline hemodynamic variables have been shown to be strong predictors of outcome [1–3]. Ambulance-transported hypotensive patients with a systolic blood pressure < 100 mmHg had a hospital mortality rate of 25 % [4]. Tailored hemodynamic support is associated with lower mortality in cardiogenic shock patients who are resistant to standard care [5]. In addition, rapid intervention is warranted in ischemic and valvular heart disease and tamponade. In ischemic heart disease, early revascularization is associated with improved late survival compared to initial medical hemodynamic stabilization [6].

The goals of hemodynamic monitoring include preservation of the functions of the different organs at a circulatory and microcirculatory level. Key features comprise a balanced optimization of cardiac output and mixed venous oxygenation, of preload and afterload. The choice of appropriate monitoring in patients with shock is of particular importance. The impact of monitoring devices on clinical outcome is complex and dependent on many factors, including knowledge and interpretation of resultant data by the managing intensivist and the choice of monitored variables [7]. A monitoring tool is intended to provide information. In particular, its efficacy is demonstrated in its ability to provide measures of overall circulatory function and flow, including evaluation of therapeutic efficacy and prognostic value.

In this chapter, we will discuss various hemodynamic monitoring tools which have the potential to guide hemodynamic management in cardiogenic shock.

Etiology of Cardiogenic Shock

Ventricular failure in cardiogenic shock is the consequence of myocardial ischemia, stunning or necrosis, devastating valvular disease, or extrinsic causes. Myocardial ischemia implies at least 75 % stenosis of the coronary lumen whereas necrosis entails cell death and irreversible damage. Inferior myocardial infarction

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in conjunction with cardiogenic shock is often due to an infero-posterior infarction with the right coronary artery (RCA) the main cause in less than 50 % of cases. In cases of shock caused by left ventricular (LV) myocardial infarction, the infarction is infero-posterior in one third and posterior in 15 – 18 %.

Although the right ventricle is involved in only 5 % of all cases of cardiogenic shock, nearly always with a RCA occlusion, in-hospital mortality is over 50 %. Cardiogenic shock caused by right ventricular (RV) infarction is more common in younger patients, has a high prevalence of single vessel disease, low rate of anterior myocardial infarction, and high mortality in comparison with patients with LV shock [8]. The resultant cardiac failure is characterized by pressure overload, volume overload or/and ventricular dysfunction.

In the context of a coronary ischemic syndrome, cardiogenic shock may be induced by myocardial stunning, with important prognostic consequences [9]. Intracellular overload of calcium, in particular from the sarcoplasmatic reticulum, loss of sensitivity of the myofilaments to calcium and a reduced number of myofilaments all play a role in the pathophysiologic background of myocardial stunning [10]. Increasing evidence has shown that the myocardial ATP-dependent potassium channel (K_{ATP}) plays an important role in many myocardial cell functions, including a close cross-talk between the sarcoplasma reticulum and the mitochondrium [11], and that it is involved in ischemia reperfusion injury and myocardial stunning.

Choice of Bedside Monitoring Tool

The ideal hemodynamic monitoring tool is relatively easy to define: In addition to wide applicability and non-invasiveness, beat-to-beat information on systolic function and contractility, preload and afterload should be presented. If possible, this tool should be mainly nurse driven and applicable at the bedside and valid for all ages. *Anno* 2011, this monitoring device is not yet available, so that the integration of various monitoring tools is required.

Invasive Hemodynamic Monitoring

Historically, central venous and pulmonary artery catheters have served as both intra-operative and intensive care unit (ICU) monitoring tools for many hemodynamically unstable patients. The correct interpretation of hemodynamic data is the key factor in the success of many monitoring tools, rather than the choice of monitoring tool itself [12, 13]. Information on hemodynamic variables alone is insufficient to determine the real etiology of cardiac failure. Nevertheless, the pul-

Box. Complications of the central venous or pulmonary artery catheter

- arrhythmias – complete heart block
- pneumothorax
- knotting
- pulmonary infarction
- pulmonary artery rupture
- infection – sepsis – endocarditis
- thrombosis – embolism

monary artery catheter (PAC) has been and is still used as a diagnostic and monitoring tool in patients with shock. As with all invasive tools, complications of central venous and pulmonary artery catheterization may occur and need to be recognized (**Box**). Moreover, there is a lack of correlation between central venous pressure (CVP) or pulmonary artery occlusion pressure (PAOP) and stroke volume or end-diastolic volume [14]. The thoracic fluid content appears to be far more important to drive cardiac function [15], suggesting that estimation of any cardiac chamber volume is a more useful predictor of ventricular preload than the CVP or PAOP. A dynamic approach of optimal filling using the concept of fluid responsiveness provides an improved means of optimizing stroke volume [16, 17].

Arterial pressure waveform analysis monitors provide online and bedside information on fluid responsiveness and cardiac index. There are various calibrated and non-calibrated devices available. Vascular compliance (K) can be estimated from the patient's specific biometric values [18, 19], permitting calculation of stroke volume (SV) as SV = K × pulsatility. Pulsatility is obtained from a standard deviation of the pressure wave over a 20 sec. interval [19–21]. Although not a diagnostic tool, arterial pressure waveform analysis can be used to optimize hemodynamics with respect to assessment of fluid responsiveness and optimization of stroke volume (**Table 1**). More recent upgrades of software of the FloTrac system allow more accurate estimations of cardiac output. However, rapid changes in vascular motor tone may impair proper cardiac output evaluation [21, 22].

The potential limitations of the FloTrac technique could be circumvented with the use of a calibrated system (PiCCO, LiDCO). Both techniques are heavily dependent on alterations in vascular compliance, necessitating recalibration [23–25]. Although in stable patients, LiDCO, PiCCO and FloTrac provide comparable data [20], investigations in experimental or human shock have demonstrated the inadequacies of these systems in terms of reactivity to altering vascular tone, stressing the need for recalibration during hemodynamic management and resuscitation [26]. Furthermore, diagnosis and management of patients with pulmonary hypertension is difficult with arterial pressure waveform analysis systems (**Table 1**).

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Non-invasive Cardiovascular Monitoring

Intermittent monitoring

Bedside imaging with echo-Doppler offers a full window on the heart as cardiac muscle and pump of the circulation. Non-trauma, hypotensive patients in the emergency ward benefited from early echocardiographic investigation by a more timely and differentiated diagnosis and subsequent treatment [4]. As with other (invasive) hemodynamic monitoring tools, the advantages and limitations of echocardiography must be recognized to permit the comprehensive evaluation of a hemodynamically unstable patient (**Table 1**). Because the investigator visualizes the motion of the different cardiac wall segments and the morphology and function of the cardiac valves real-time, it is clear that echo-Doppler provides additional information not attained with other tools, including identification of the presence of pericardial effusions. It is an illusion that the same information can be obtained with routine invasive hemodynamic monitoring.

In a hypotensive patient, a bedside transthoracic – and therefore non-invasive – investigation of cardiac function at the level of the short axis view permits differentiation between a cardiac and a non-cardiac cause of hypotension [27] (**Fig. 1**). A

Table 1. Summary of different hemodynamic monitoring tools in cardiogenic shock

Technique	Indications	Shortcomings	Contraindications
NIBP	HD assessment	No continuous monitoring	
Doppler echocardiography (TTE)	LV, RV heart failure Evaluation of valve morphology/function HD evaluation	Absence of respiratory/O2 transport data No continuous monitoring Long learning curve Decreased visualization (TTE)	Absence of skilled investigator
Finapres technology	Beat-beat arterial pressure monitoring Stroke volume estimation	Validity in shock not well defined	Cold extremities
Arterial pressure monitoring	HD evaluation Metabolic/electrolyte disturbances Inability to measure non-invasively	Complications (bleeding, infection, thrombosis) Absence of O2 transport measurements	Infection *in situ* Coagulopathy, Raynaud's/Berger's disease Proximal obstruction (thoracic outlet syndrome, A-V shunt, congenital malformations)
Flo-trac	Stroke volume estimation Assessment of fluid responsiveness	Absence of information on LV/RV function, pulmonary artery pressures, O2 transport Cautious interpretation when altering vascular tone No recalibration	Cfr. arterial pressure monitoring
PiCCO, LiDCO	Stroke volume estimation Assessment of fluid responsiveness	Absence of information on LV/RV function, pulmonary artery pressures, O2 transport Cautious interpretation when altering vascular tone	Cfr. arterial pressure monitoring
CVP catheter	Intravascular volume assessment Major vascular access		Infection *in situ* Thrombosis of major vessels
Pulmonary artery catheter	LV/RV heart failure Stroke volume estimation HD evaluation Respiratory and O2 transport data	Invasiveness Indirect information of ventricular function PAOP < LVEDP: non-compliant LV, aortic regurgitation PAOP > LVEDP: PEEP ventilation, increased intrathoracic pressure, COPD, left atrial disease (thrombus, myxoma) Mitral valve disease	Tricuspid/pulmonary valve stenosis, valve plasty/prosthesis Tetralogy of Fallot Arrhythmias: ventricular Coagulopathy Pacemaker/defibrillator wires

COPD: chronic obstructive pulmonary disease; CVP: central venous pressure; HD: hemodynamic; LV: left ventricle; LVEDP: left ventricular end-diastolic pressure; NIBP: non-invasive blood pressure; PAOP: pulmonary artery occlusion pressure; PEEP: positive end-expiratory pressure; RV: right ventricle; TTE: transthoracic echocardiography.

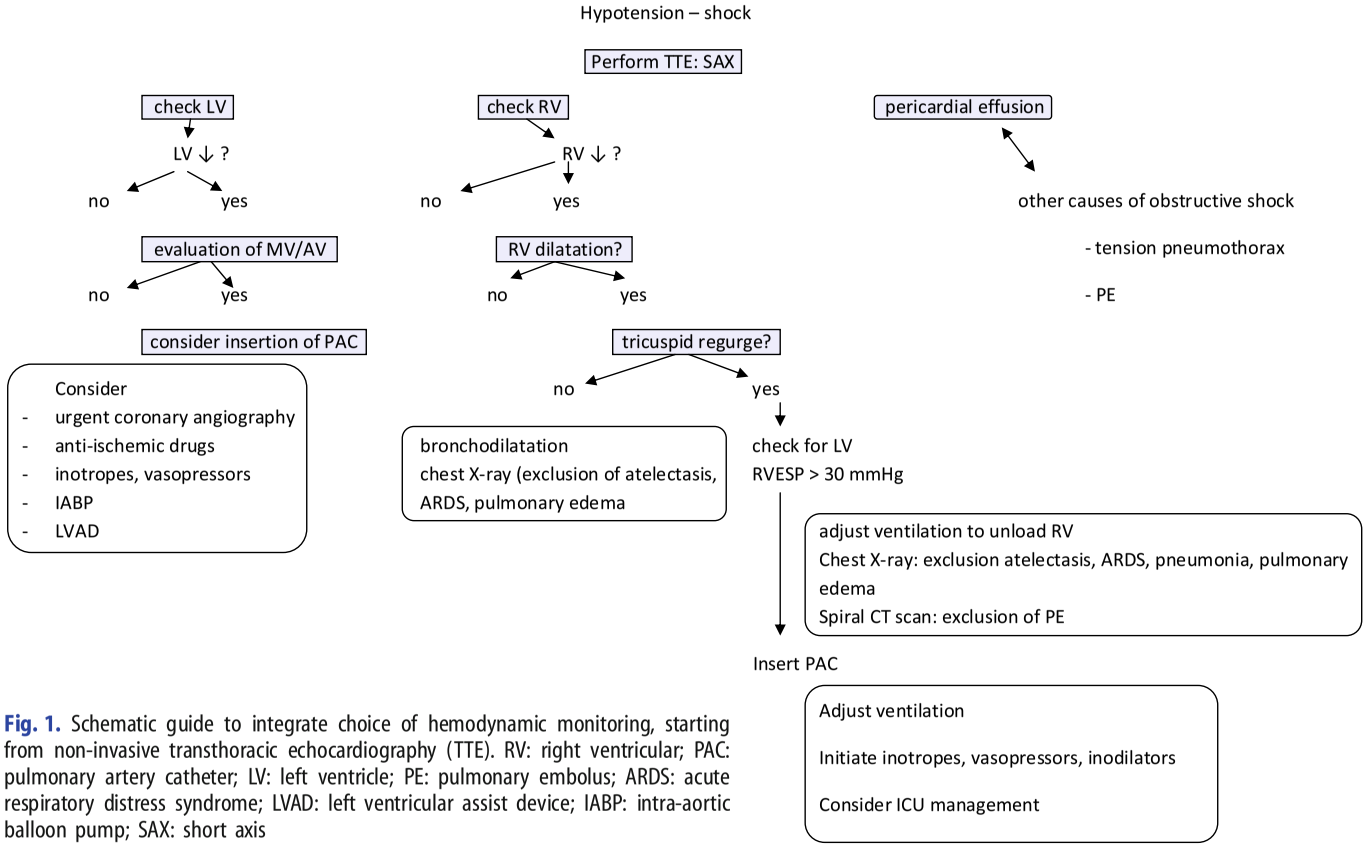

Fig. 1. Schematic guide to integrate choice of hemodynamic monitoring, starting from non-invasive transthoracic echocardiography (TTE). RV: right ventricular; PAC: pulmonary artery catheter; LV: left ventricle; PE: pulmonary embolus; ARDS: acute respiratory distress syndrome; LVAD: left ventricular assist device; IABP: intra-aortic balloon pump; SAX: short axis

small left ventricle suggests hypovolemia [28] or a ventricle loaded with a high sympathomimetic intrinsic or extrinsic load [29, 30]. In contrast, a dilated, barely contracting left ventricle, suggesting volume or/and pressure overload, needs inotropic support. After myocardial infarction, supporting myocyte contractility with calcium influx-increasing inotropic drugs results in a depression of global pump function because of a reduction in the number of myocytes [31]; the impact on myocardial cell function in cardiogenic shock is unknown.

Correct and full interpretation of a short axis transthoracic view directly impacts on bedside management. Other details of ventricular wall characteristics could help in further fine-tuning additional management. For example, the finding of a hypertrophied ventricular wall implies either long-standing systemic hypertension or severe aortic stenosis in most cases [32, 33].

Despite good image quality on modern echocardiographs, in ischemic heart disease they allow only a rough estimation of the diseased coronary artery. Direct visualization of the relative motion of the different wall segments provides an ideal window for detecting myocardial ischemia, on condition that there are no other interfering factors and the regional wall motion abnormality is detected after previous normal motion of the segment in question. These two conditions indicate the difficulties encountered when trying to diagnose myocardial ischemia with Doppler-echocardiography (**Table 1**). In contrast, Doppler echocardiography is a perfect tool to confirm the localization of an occluded coronary artery with respect to a malperfused myocardial region after a positive electrocardiogram (EKG) or ST segment monitoring has averted the clinician. Newer technologies are currently being developed utilizing vector related technology to allow early diagnosis of myocardial ischemia [34, 35].

Assessment of ventricular function is essential for the correct diagnosis of ventricular failure. Visualization of regional wall motion by means of two-dimensional echocardiography provides a complete and direct window on global ventricular function. The presence of regional wall motion abnormalities related to new and significant EKG changes encourages use of thrombolysis, even after coronary artery bypass grafting (CABG) with threatened graft closure [36], or coronary angiography with potential subsequent percutaneous coronary intervention (PCI). Early support by intra-aortic balloon pump is desirable to improve outcomes [37].

Continuous monitoring

The Finapres method offers continuous non-invasive measurement of blood pressure [38]. This technology is based on intermittent inflation of a finger cuff in conjunction with an infrared plethysmograph. The unloaded diameter of the finger arteries is the point at which the finger cuff pressure and the intra-arterial pressure are equal. At this point the transmural pressure across the finger arterial wall is zero. Subsequent clamping of the finger cuff with varying pressures, indirectly measures the intra-arterial pressure. Alterations in hematocrit or arterial tone will interact with the unloaded diameter, necessitating intermittent recalibration.

The latest development using this technology is the Nexfin monitor, providing continuous beat-to-beat measurement of blood pressure, heart rate, stroke volume, and cardiac output with good within-subject precision when compared to Riva-Rocci/Korotkoff auscultatory blood pressure measurements [39]. However, the validity of this technology in patients with shock and hypoperfusion is largely undefined and necessitates further assessment.

Preload and Fluid Responsiveness

Optimization of preload conditions in hypotensive patients is often the first resuscitative action undertaken to restore hemodynamics. Immediate management has been related to improved outcomes [40, 41], as exemplified by early goal-directed therapy schemes [42]. Although the Surviving Sepsis Campaign recommends protocol-driven fluid management for patients with severe sepsis, there are no reports of similar protocols for patients with cardiogenic shock, except a single case study [43].

Invasive Pressure Measurements

PAOP and CVP have traditionally been used to assess intravascular volume status. Their use assumes that pressure accurately reflects end-diastolic volume, which is often not the case. In addition, correct analysis of the wave patterns may identify the presence of tricuspid or mitral regurgitation. Correct filling state is of extreme importance in a heart which is functioning at the upper part of the Starling curve, nearly reaching overfill. Many issues encountered in daily ICU practice, such as rhythm disorders, cardiac pacing, high positive end-expiratory pressure (PEEP) ventilation, and irregular breathing patterns, can impede the proper interpretation of these pressures (**Table 1**). Furthermore, invasive filling pressures estimate preload rather than fluid responsiveness, and do not including a dynamic facet in mechanically ventilated patients, which could be extremely important in patients with increased intra-thoracic or intra-abdominal pressures.

Clinically, passive leg raising (PLR) augments cardiac preload and is therefore most preferable to evaluate optimal preloading conditions [44]. In cardiac patients, PLR will rarely lead to improved hemodynamics owing to decreased LV diastolic function and should be used with extreme caution [45].

X

Non-invasive Doppler echocardiography

From a short axis view, LV end-diastolic area (LVEDA) < 5.5 cm^2/m^2 was shown to be associated with low preload conditions [28]. Although a pure static variable of load, PLR may make LVEDA a true dynamic descriptor of fluid responsiveness. A normal right ventricle is depicted as a crescent shaped structure. A dilated right ventricle (i.e., RV diameter > 0.6 times the diameter of the left ventricle) suggests either RV myocardial ischemia, volume or/and pressure overload [27].

Other variables are used in conjunction with mechanical ventilation and they rely on the variation of intrathoracic pressures with ventilation. Variations in inferior (transthoracic) [46] and superior (transesophageal) caval vein (SVC) [47] with intermittent hyperinflation of the lungs induced by mechanical ventilation can be used. The caval index can be calculated from (maximal SVC diameter – minimal SVC diameter/maximum SVC diameter) [48]. In contrast to stroke volume variation indices, this index appears to be the sole variable that is independent of respiratory rate [49]. Acute RV failure, illustrated by RV dilatation, after acute pulmonary embolism, in conjunction with a hyperdynamic left ventricle will be associated with an absence of ventilation-induced variation of the caval index. Again, starting the echocardiographic investigation with the short axis view will already reveal RV dilatation. Variation of stroke volume exemplified by

variations of the left sided time-velocity-integral (TVI) will provide the same information [50] (**Fig. 1**).

Assessment of flows across cardiac valves reveals transvalvular pressure gradients. Typically, from a tricuspid regurgitant flow, which is readily available in ICU patients, a pressure gradient can be assessed to calculate correctly RV systolic pressure including right atrial pressure [49, 51].

Knowledge of the presence of a dilated right ventricle in conjunction with increased RV systolic pressure may be important in the direct management of ventilator settings [52], optimization of preload [53], or reduction of afterload conditions [54–57], with an indirect impact on outcome. Finally, this finding may be a trigger to introduce continuous monitoring of pulmonary artery pressures, e.g., in acute pulmonary embolism and cardiogenic shock [58], permitting local administration of thrombolysis.

Assessment of Ventricular Function

LV function is the most important determinant of prognosis after acute myocardial infarction or cardiogenic shock [59]. None of the invasive monitoring tools is able to clearly demonstrate ventricular dysfunction, independent of loading conditions (**Table 1**). Indirectly however, a low cardiac index may be related with increased filling pressures and high systemic vascular resistance, suggesting an augmented burden of ventricular ejection. At the level of the short axis, global ventricular function can be readily visualized. In addition to fractional area contraction (ejection fraction at a two-dimensional level), various other clinical measures are available (**Table 2**). The reader is referred to review articles for a complete overview of this issue [60]. A load-dependent variable that is attracting more and more interest is the systolic velocity of the mitral annulus, assessed with tissue Doppler imaging. Velocities beneath 8 cm/s suggest decreased systolic function whereas velocities above 15 cm/s imply normal LV systolic function. Both preload [58] and afterload [61] appear to have an impact on the amplitude.

Table 2. Overview of ventricular function evaluation tools. Important to remark that most of the tools are load sensitive.

Load-dependent indices		Load-independent indices
Isovolumic indices	Mean dP/dt (Finapres, Doppler) ICT (echo-Doppler)	ESPVR (conductance or micromanometer catheter)
Ejection phase indices	FS, FAC, EF (echo-Doppler, REF-PAC) SV, CO (all systems)	Mean velocity of fiber shortening corrected for end-systolic meridioneal wall stress (echo-Doppler)
Echo specific variables	Systolic wave (TDI) (echo-Doppler) Strain rate (echo-Doppler)	

EF: ejection fraction (%); ESPVR: end-systolic pressure-volume relationship; FAC: fractional area contraction (%); FS: fractional shortening (%); ICT: isovolumic contraction time; PAC: pulmonary artery catheter; REF-PAC: pulmonary artery catheter with right ventricular ejection fraction; SV: stroke volume; TDI: tissue Doppler imaging.

Conclusion: Assembling the Whole Hemodynamic Picture

Monitoring tools with an immediate bedside approach allow rapid diagnosis of LV or RV failure and, thus, immediate application of therapeutic intervention(s), which is, indirectly, related to improved outcome [62, 63]. In this respect, a transthoracic echo-Doppler investigation will suggest a likely diagnosis and appropriate initial management for the patients with cardiogenic shock. Rapid PCI should be considered, in particular in those patients with concomitant cardiac failure, younger than 75 years [64], even if pharmacological reperfusion with fibrinolysis has been performed previously, in conjunction with insertion of an intra-aortic balloon pump when appropriate [37]. More continuous monitoring tools must be introduced, of which the PAC offers the most complete information when pulmonary artery pressures have to be monitored.

Intelligent computerized systems, based on analysis of heart rate [65] or a combination of variables may make a difference in the practical approach to monitoring [66].

References

1. Fincke R, Hochman JS, Lowe AM, et al (2004) Cardiac power is the strongest hemodynamic correlate of mortality in cardiogenic shock: a report from the SHOCK trial registry. J Am Coll Cardiol 44: 340 – 348
2. Hasdai D, Holmes DR Jr, Califf RM, et al (1999) Cardiogenic shock complicating acute myocardial infarction: predictors of death. GUSTO Investigators. Am Heart J 138: 21 – 31
3. Hasdai D, Holmes DR Jr, Topol EJ, et al (1999) Frequency and clinical outcome of cardiogenic shock during acute myocardial infarction among patients receiving reteplase or alteplase. Results from GUSTO-III. Global Use of Strategies to Open Occluded Coronary Arteries. Eur Heart J 20: 128 – 135
4. Jones AE, Tayal VS, Sullivan DM, Kline JA (2004) Randomized, controlled trial of immediate versus delayed goal-directed ultrasound to identify the cause of nontraumatic hypotension in emergency department patients. Crit Care Med 32: 1703 – 1708
5. Mimoz O, Rauss A, Rekik N, Brun-Buisson C, Lemaire F, Brochard L (1994) Pulmonary artery catheterization in critically ill patients: a prospective analysis of outcome changes associated with catheter-prompted changes in therapy. Crit Care Med 22: 573 – 579
6. Hochman JS, Sleeper LA, Webb JG, et al (1999) Early revascularization in acute myocardial infarction complicated by cardiogenic shock. SHOCK Investigators. N Engl J Med 341: 625 – 634
7. Hata JS, Stotts C, Shelsky C, et al (2011) Reduced mortality with noninvasive hemodynamic monitoring of shock. J Crit Care (in press)
8. Jacobs AK, Leopold JA, Bates E, et al (2003) Cardiogenic shock caused by right ventricular infarction: a report from the SHOCK registry. J Am Coll Cardiol 41: 1273 – 1279
9. Busani S, Rinaldi L, Severino C, Cobelli M, Pasetto A, Girardis M (2010) Levosimendan in cardiac failure after subarachnoid hemorrhage. J Trauma 68: E108 – 110
10. Garcia Gonzalez MJ, Dominguez Rodriguez A (2006) Pharmacologic treatment of heart failure due to ventricular dysfunction by myocardial stunning: potential role of levosimendan. Am J Cardiovasc Drugs 6: 69 – 75
11. Dorn GW, II, Scorrano L (2010) Two close, too close: Sarcoplasmic reticulum-mitochondrial crosstalk and cardiomyocyte fate. Circ Res 107: 689 – 699
12. Magder S (1998) More respect for the CVP. Intensive Care Med 24: 651 – 653
13. Magder S (2005) How to use central venous pressure measurements. Curr Opin Crit Care 11: 264 – 270
14. Kumar A, Anel R, Bunnell E, et al (2004) Pulmonary artery occlusion pressure and central venous pressure fail to predict ventricular filling volume, cardiac performance, or the response to volume infusion in normal subjects. Crit Care Med 32: 691 – 699

15. van Lieshout JJ, Harms MP, Pott F, Jenstrup M, Secher NH (2005) Stroke volume of the heart and thoracic fluid content during head-up and head-down tilt in humans. Acta Anaesthesiol Scand 49: 1287 – 1292
16. Reuter DA, Kirchner A, Felbinger TW, et al (2003) Usefulness of left ventricular stroke volume variation to assess fluid responsiveness in patients with reduced cardiac function. Crit Care Med 31: 1399 – 1404
17. Wiesenack C, Prasser C, Rodig G, Keyl C (2003) Stroke volume variation as an indicator of fluid responsiveness using pulse contour analysis in mechanically ventilated patients. Anesth Analg 96: 1254 – 1257
18. Langewouters G, Wesseling K, Goedhard W (1985) The pressure dependent dynamic elasticity of 35 thoracic and 16 abdominal human aortas in vitro described by a five component model. J Biomechnics 18: 613 – 620
19. Breukers RM, Sepehrkhouy S, Spiegelenberg SR, Groeneveld AB (2007) Cardiac output measured by a new arterial pressure waveform analysis method without calibration compared with thermodilution after cardiac surgery. J Cardiothorac Vasc Anesth 21: 632 – 635
20. Button D, Weibel L, Reuthebuch O, Genoni M, Zollinger A, Hofer CK (2007) Clinical evaluation of the FloTrac/Vigileo system and two established continuous cardiac output monitoring devices in patients undergoing cardiac surgery. Br J Anaesth 99: 329 – 336
21. Constant I, Laude D, Elghozi JL, Murat I (1999) Assessment of short-term blood pressure variability in anesthetized children: a comparative study between intraarterial and finger blood pressure. J Clin Monit Comput 15: 205 – 214
22. Shelley KH, Murray WB, Chang D (1997) Arterial-pulse oximetry loops: a new method of monitoring vascular tone. J Clin Monit 13: 223 – 228
23. Jonas MM, Tanser SJ (2002) Lithium dilution measurement of cardiac output and arterial pulse waveform analysis: an indicator dilution calibrated beat-by-beat system for continuous estimation of cardiac output. Curr Opin Crit Care 8: 257 – 261
24. Beaulieu KE, Kerr CL, McDonell WN (2005) Evaluation of a lithium dilution cardiac output technique as a method for measurement of cardiac output in anesthetized cats. Am J Vet Res 66: 1639 – 1645
25. Breukers RB, Jansen JR (2004) Pulmonary artery thermodilution cardiac output vs. transpulmonary thermodilution cardiac output in two patients with intrathoracic pathology. Acta Anaesthesiol Scand 48: 658 – 661
26. Cooper ES, Muir WW (2007) Continuous cardiac output monitoring via arterial pressure waveform analysis following severe hemorrhagic shock in dogs. Crit Care Med 35: 1724 – 1729
27. Poelaert JI, Schupfer G (2005) Hemodynamic monitoring utilizing transesophageal echocardiography: The relationships among pressure, flow, and function. Chest 127: 379 – 390
28. Leung JM, Levine EH (1994) Left ventricular end-systolic cavity obliteration as an estimate of intraoperative hypovolemia. Anesthesiology 81: 1102 – 1109
29. Boden WE, Smulyan H, Potts J, Johnson LW, Obeid AI, Eich RH (1978) Elevated ejection fractions in patients with the anginal syndrome and normal coronary arteriograms. Cathet Cardiovasc Diagn 4: 249 – 263
30. Giacomin E, Palmerini E, Ballo P, Zaca V, Bova G, Mondillo S (2008) Acute effects of caffeine and cigarette smoking on ventricular long-axis function in healthy subjects. Cardiovasc Ultrasound 6: 9
31. Zhang H, Chen X, Gao E, et al (2010) Increasing cardiac contractility after myocardial infarction exacerbates cardiac injury and pump dysfunction. Circ Res 107: 800 – 809
32. Dunn F, Burns J, Hornung R (1991) Left ventricular hypertrophy in hypertension. Am Heart J 122: 312 – 315
33. Treasure CB, Klein JL, Vita JA, et al (1993) Hypertension and left ventricular hypertrophy are associated with impaired endothelium-mediated relaxation in human coronary resistance vessels. Circulation 87: 86 – 93
34. Nesser HJ, Winter S (2009) Speckle tracking in the evaluation of left ventricular dyssynchrony. Echocardiography 26: 324 – 336
35. Pirat B, Khoury DS, Hartley CJ, et al (2008) A novel feature-tracking echocardiographic method for the quantitation of regional myocardial function: validation in an animal model of ischemia-reperfusion. J Am Coll Cardiol 51: 651 – 659

36. Dauerman HL, Cutlip DE, Sellke FW (1996) Intracoronary thrombolysis in the treatment of graft closure immediately after CABG. Ann Thorac Surg 62: 280–283
37. Abdel-Wahab M, Saad M, Kynast J, et al (2010) Comparison of hospital mortality with intra-aortic balloon counterpulsation insertion before versus after primary percutaneous coronary intervention for cardiogenic shock complicating acute myocardial infarction. Am J Cardiol 105: 967–971
38. Gillard C, Henuzet C, Lallemand J, Moscariello A, Guillaume M, Van Meerhaeghe A (2006) Operating characteristics of the Finapress system to predict elevated left ventricular filling pressure. Clin Cardiol 29: 107–111
39. Eeftinck Schattenkerk DW, van Lieshout JJ, van den Meiracker AH, et al (2009) Nexfin noninvasive continuous blood pressure validated against Riva-Rocci/Korotkoff. Am J Hypertens 22: 378–383
40. Feissel M, Michard F, Faller JP, Teboul JL (2004) The respiratory variation in inferior vena cava diameter as a guide to fluid therapy. Intensive Care Med 30: 1834–1837
41. Michard F, Teboul JL (2000) Using heart-lung interactions to assess fluid responsiveness during mechanical ventilation. Crit Care 4: 282–289
42. Rivers E, Nguyen B, Havstad S, et al (2001) Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med 345: 1368–1377
43. Dorrian S, Lim M (2006) Early goal-directed therapy in the emergency department. Emerg Med Australas 18: 206–207
44. Monnet X, Rienzo M, Osman D, et al (2006) Passive leg raising predicts fluid responsiveness in the critically ill. Crit Care Med 34: 1402–1407
45. Kawaguchi M, Hay I, Fetics B, Kass DA (2003) Combined ventricular systolic and arterial stiffening in patients with heart failure and preserved ejection fraction: implications for systolic and diastolic reserve limitations. Circulation 107: 714–720
46. Barbier C, Loubieres Y, Schmit C, et al (2004) Respiratory changes in inferior vena cava diameter are helpful in predicting fluid responsiveness in ventilated septic patients. Intensive Care Med 30: 1740–1746
47. Vieillard-Baron A, Augarde R, Prin S, Page B, Beauchet A, Jardin F (2001) Influence of superior vena caval zone condition on cyclic changes in right ventricular outflow during respiratory support. Anesthesiology 95: 1083–1088
48. Vieillard-Baron A, Chergui K, Rabiller A, et al (2004) Superior vena caval collapsibility as a gauge of volume status in ventilated septic patients. Intensive Care Med 30: 1734–1739
49. Sagie A, Schwammenthal E, Padial LR, Vazquez de Prada JA, Weyman AE, Levine RA (1994) Determinants of functional tricuspid regurgitation in incomplete tricuspid valve closure: Doppler color flow study of 109 patients. J Am Coll Cardiol 24: 446–453
50. Slama M, Masson H, Teboul JL, et al (2002) Respiratory variations of aortic VTI: a new index of hypovolemia and fluid responsiveness. Am J Physiol Heart Circ Physiol 283: H1729–33
51. Yock P, Popp R (1984) Noninvasive estimation of right ventricular systolic pressure by Doppler ultrasound in patients with tricuspid regurgitation. Circulation 70: 657–662
52. Vieillard-Baron A, Prin S, Chergui K, Dubourg O, Jardin F (2002) Echo-Doppler demonstration of acute cor pulmonale at the bedside in the medical intensive care unit. Am J Respir Crit Care Med 166: 1310–1319
53. Vieillard-Baron A, Chergui K, Augarde R, et al (2003) Cyclic changes in arterial pulse during respiratory support revisited by Doppler echocardiography. Am J Respir Crit Care Med 168: 671–676
54. Jardin F, Vieillard-Baron A (2003) Right ventricular function and positive pressure ventilation in clinical practice: from haemodynamic subsets to respirator settings. Intensive Care Med 29: 1426–1434
55. Schmitt J, Vieillard-Baron A, Augarde R, Prin S, Page B, Jardin F (2001) Positive end-expiratory pressure titration in acute respiratory distress syndrome: impact on right ventricular outflow impedance evaluated by pulmonary artery Doppler flow velocity measurements. Crit Care Med 29: 1154–1158
56. Poelaert J, Visser C, Everaert J, Koolen J, Colardyn F (1993) Acute hemodynamic changes of inverse ratio ventilation in adult respiratory distress syndrome. A transesopahgeal echo Doppler study. Chest 104: 214–219

57. Poelaert JI, Reichert CL, Koolen JJ, Everaert JA, Visser CA (1992) Transesophageal Echodoppler evaluation of the hemodynamic effects of positive-pressure ventilation after coronary artery surgery. J Cardiothorac Vasc Anesth 6: 438 – 443
58. Amà R, Segers P, Roosens C, Claessens T, Verdonck P, Poelaert J (2004) Effects of load on systolic mitral annular velocity by tissue Doppler imaging. Anesth Analg 99: 332 – 338
59. Massel D, Marchiori G (2004) Precision and accuracy of the bedside examination in detecting an ejection fraction of less than 40 % following acute myocardial infarction. Can J Cardiol 20: 411 – 416
60. Kass D, Beyar R (1991) Evaluation of contractile state by maximal ventricular power divided by the square of end-diastolic volume. Circulation 84: 1698 – 1708
61. Borlaug BA, Melenovsky V, Redfield MM, et al (2007) Impact of arterial load and loading sequence on left ventricular tissue velocities in humans. J Am Coll Cardiol 50: 1570 – 1577
62. Faris R, Coats AJ, Henein MY (2002) Echocardiography-derived variables predict outcome in patients with nonischemic dilated cardiomyopathy with or without a restrictive filling pattern. Am Heart J 144: 343 – 350
63. Poelaert J, Roosens C (2007) Myocardial Doppler velocities as a marker of prognosis in the ICU. Crit Care 11: 167
64. King SB III, Smith SC Jr, Hirshfeld JW Jr, et al (2008) 2007 Focused Update of the ACC/AHA/SCAI 2005 Guideline Update for Percutaneous Coronary Intervention: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 117: 261 – 295
65. Chua KC, Chandran V, Acharya UR, Lim CM (2008) Computer-based analysis of cardiac state using entropies, recurrence plots and Poincare geometry. J Med Eng Technol 32: 263 – 272
66. Ross JJ, Denai MA, Mahfouf M (2009) A hybrid hierarchical decision support system for cardiac surgical intensive care patients. Part II. Clinical implementation and evaluation. Artif Intell Med 45: 53 – 62

Non-invasive Estimation of Left Ventricular Filling Pressures by Doppler Echocardiography

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Introduction

The determination of elevated ventricular filling pressure is important in order to optimize unloading therapy. Invasive measurement techniques are common but sometimes impractical in critical care patients. Central venous pressure (CVP) is easy to measure using a central venous catheter, which are used routinely in intensive care units (ICUs). In contrast, left ventricular (LV) filling pressures are more difficult to identify, necessitating insertion of a pulmonary artery catheter (PAC), which is a very invasive procedure with potential complications and cannot be left more than 72 hours.

The LV filling pressure is an important determinant of cardiac output that may be altered in critical care patients during hemodynamic failure, weaning, drug withdrawal or increased LV afterload. Different hemodynamic characteristics of critically ill patients not only force us to individualize treatments, but to continuously monitor the evolution and response to particular strategies.

Pulsed-wave Doppler echocardiography is a practical tool for the non-invasive estimation of LV filling pressures and several indices derived from transmitral and pulmonary venous flow velocity recordings have been validated for estimating LV filling pressures in multiple scenarios. The basic principle of all these methods is that blood flow is driven from the left atrium into the left ventricle by the instantaneous pressure gradient across the mitral valve and that mitral flow velocity therefore reflects the level of left atrial pressure. However, since the transmitral pressure gradient and flow velocity are determined not only by left atrial pressure, but depend also on ventricular factors, such as relaxation rate and compliance, the correlation between Doppler variables and left atrial pressure is too weak for an accurate estimation and may vary between different subsets of patients. In fact, the rate of LV relaxation affects LV pressure fall in early diastole and consequently plays an important role in determining the early diastolic wave (E) velocity. Thus, when the rate of LV relaxation is high, E wave velocity and its deceleration may be increased even if the left atrial pressure is low. Conversely, when relaxation is markedly impaired (such as in LV hypertrophy), E wave velocity and its deceleration rate may be relatively low even in the presence of elevated left atrial pressure. The opposite effects of left atrial pressure and impaired LV relaxation make it difficult to estimate LV filling pressure in a given patient on the basis of transmitral flow wave velocity alone.

To overcome the confounding effects of the multiple interacting factors that affect transmitral flow velocities, several strategies are followed. First of all,

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Doppler indices should be considered in the context of the clinical picture (age, heart rate, mechanical ventilation, volume status, drugs infused, disease etiology, etc.), left atrium and LV dimensions, and systolic function. For example, in a patient with a dilated left ventricle and poor systolic function we know that LV relaxation is impaired. Consequently, a high amplitude E wave with rapid deceleration must be due to high left atrial pressure and a non-compliant left ventricle. On the other hand, in a patient with poor systolic function and a delayed or reduced E wave followed by a slow deceleration and an increased late diastolic A wave velocity, LV filling pressures are normal or mildly elevated. Consequently, several studies have shown that in patients with severe systolic dysfunction and normal sinus rhythm, the correlation between simple variables, such as E/A and deceleration time, and LV filling pressure is excellent [1–4].

The estimation of LV filling pressures in conditions where LV dysfunction is less apparent can be improved by the analysis of the pulmonary vein flow velocity pattern. The pulmonary vein flow velocity pattern mirrors the changes in left atrial pressure. When the left atrial pressure is elevated and, particularly, when there is a high V-wave because of a non-compliant left atrium, the systolic forward flow velocity (S wave) decreases while the diastolic velocity (D wave) increases. Although systolic pulmonary venous flow velocity is determined by multiple factors, the systolic forward flow velocity in patients with LV systolic dysfunction is strongly and inversely related to the LV filling pressures. In particular, a systolic fraction < 40 % is a reliable index of a pulmonary artery occlusion pressure (PAOP) > 18 mmHg [5–7]. However, in young normal subjects, in patients with eccentric mitral regurgitation, and in those with a cardiac allograft, a blunted S wave may be present even when LV filling pressures are low. Conversely, in patients with good LV systolic function and vigorous displacement of the mitral annulus, the S wave can be relatively high in spite of high filling pressures.

Another useful index for estimating LV filling pressure is the difference between the duration of the reverse pulmonary vein flow wave (Ar) and of the mitral forward A wave (**Fig. 1**). In normal subjects, the duration of these two waves is almost equal. When the left atrium contracts against a stiff ventricle, the forward flow across the mitral valve stops early while the reversed flow into the pulmonary vein increases. Thus, an Ar wave is an accurate sign of a LV end-diastolic pressure (LVEDP) > 15 mmHg [8]. This index has the additional advantage of being independent of age, mitral regurgitation and LV systolic function. It should be noted that although this index is strongly correlated with LVEDP, its correlation with PAOP is rather poor. One of the big limitations of this index, especially in critical care patients, is the difficult of recording Ar wave duration in patients under mechanical ventilation, or with dilated left atrium and pulmonary veins.

Despite these limitations, the analysis of pulmonary vein flow in combination with transmitral flow in order to differentiate normal from pseudonormal velocity patterns improves the estimation of LV filling pressures in patients with moderately impaired function and dilated left ventricles.

There remains, however, a sizeable number of patients in whom even this method is not reliable enough. Two methods have been recently proposed to estimate LV filling pressures. The first method combines transmitral E wave velocity with its propagation velocity (Pv) into the left ventricle recorded by color M-mode Doppler. The second method combines transmitral E wave velocity with

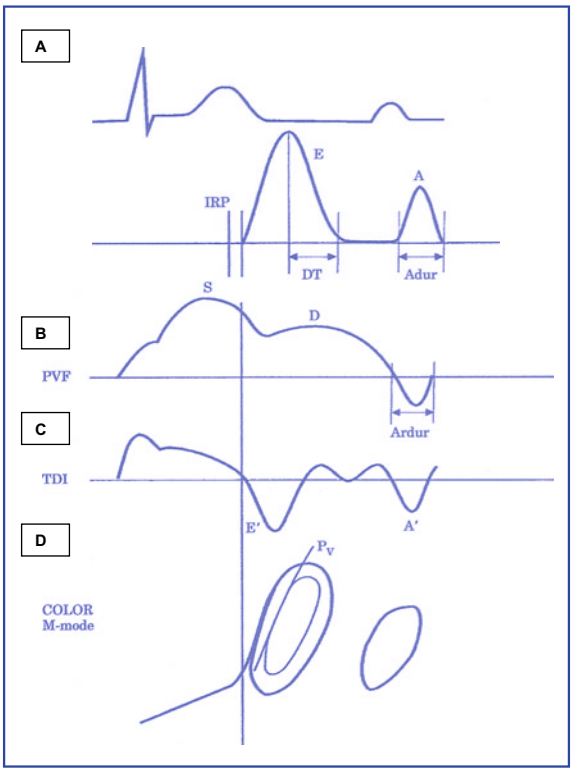

Fig. 1. Doppler parameters used in the estimation of left ventricular filling pressures. A) Pulsed Doppler of transmitral flow (MVF): isovolumic relaxation period (IRP); early diastolic (E) and late diastolic (A) wave amplitude; deceleration time (DT); late diastolic wave duration (Adur). Derived measurements: ratio between early diastolic and late diastolic wave amplitude (E/A); deceleration rate (E/DT). B) Pulsed Doppler of pulmonary vein flow (PVF): systolic forward flow wave amplitude (S); diastolic forward flow wave amplitude (D); diastolic reverse flow duration (Ardur). Derived measurements: systolic fraction (S/S +D), difference between diastolic reverse flow duration of pulmonary venous flow and late diastolic wave duration of mitral flow (Ar-A duration). C) Tissue Doppler of mitral annulus (TDI): amplitude of early diastolic wave (E'); amplitude of late diastolic wave (A'); Derived measurements: ratio between early diastolic wave amplitude of transmitral flow and early diastolic wave amplitude of mitral annulus (E/E'). D) Color M-mode Doppler of transmitral inflow: propagation velocity of early diastolic flow (Pv) calculated as the slope of the first aliasing (45 cm/s) from the mitral valve plain to 4 cm into the left ventricle. Derived measurements: ratio between early diastolic wave amplitude of transmitral flow and its propagation velocity into the left ventricle (E/Pv).

the early diastolic velocity of the mitral annulus motion recorded by pulse-wave tissue Doppler. Both of these methods are based on the concept that normalizing transmitral E wave velocity by an index that reflects the rate of LV relaxation that is independent from preload, reduces the confounding effect of the relaxation rate and improves the correlation with left atrial pressure.

The Pv of this wavefront can be assessed by color M-mode in the apical four-chamber view with the beam aligned with the center of the LV inflow. The slope of the first color aliasing (set at 45 cm/s) from the mitral annulus to 4 cm into the left ventricle is then identified, either visually or by isovelocity maps. This measurement is strongly related to the time constant (tau) of the LV pressure decay and the E/Pv ratio with PAOP (**Box**).

Box. Parameters for identification of patients with an elevated left ventricular filling pressure. DT: deceleration time of early diastolic wave of transmitral flow; E/A: ratio between early diastolic and late diastolic wave amplitude of transmitral flow; E/E′: ratio between early diastolic wave amplitude of transmitral flow and early diastolic wave amplitude of mitral annulus; E/Pv: ratio between early diastolic wave amplitude of transmitral flow and its propagation velocity into the left ventricle; SF: systolic fraction.

- Enlarged left atrium size
- E/A ratio > 2
- DT < 150 msec
- SF of pulmonary vein flow < 40 %
- E/E′ ratio > 15
- E/Pv > 2

Tissue Doppler in Critical Care Patients

Tissue Doppler imaging measures myocardial velocities, which are low frequency, high-amplitude signals filtered from conventional Doppler imaging. The velocity of early diastolic mitral annulus motion (E') has also been found to be related to tau and to be relatively independent of left atrial pressure and left atrial relaxation [9, 10]. However, preload independence of E' has remained controversial, and the effects of acute alterations in preload, afterload, and contractility on E', and their related influence on E/E', have not been established [11].

Several published works have tried to investigate the relationship between E/E' measures and PAOP [4, 12, 13], some in conventional studies of cardiac illness and others in critical care patients [14–16]. It is still debated whether the exact numbers in which the ratio E/E' correlated with pulmonary pressure numbers can be validated. A nice study indicated that an E/E' ratio > 10 was a reliable index to estimate a PAOP > 12 mmHg. Ommen et al. [17] showed that an E/E' ratio < 8 accurately identified patients with a normal pressure and a ratio > 15 those with an elevated PAOP. In patients with intermediate values (> 8 and < 15) PAOP may vary widely and the other Doppler flow methods can be used. These numbers appear in the recommendations of the European Association of Echocardiology and the American Society of Echocardiology for the evaluation of LV diastolic function [18]. It remains unresolved whether better results can be obtained using the lateral or the septal E'. In patients with ischemic heart disease, it is probably best to average the values obtained from the lateral, septal, anterior and inferior mitral annulus.

Some studies have pursued these numbers. Dokainish et al. [19] presented a study of patients with preserved cardiac function and impaired cardiac function in which a E/E' ratio ≥ 13 had a sensitivity of 87 % and specificity of 88 % of correlation with PAOP superior to 28 mmHg. Kusunose et al. [20] and Senechal et al. [21] validated tissue Doppler imaging in patients with atrial fibrillation. The first group showed that a PAOP greater than 15 mmHg was equivalent to an E/E' ratio > 11 with a sensitivity of 90 % and specificity of 90 %; the second group showed that the same PAOP pressure was equivalent to an E/E' ratio > 16 with a sensitivity of 91 % and specificity of 85 %.

Intensivists seek simple and reproducible parameters that help us know what is happening to the patient. Changing scenarios, so common in unstable patients, can only be resolved if the information is clear, which is why we like to associated numbers with physiologic concepts, such as 'high capillary pulmonary pressure'.

The most recent research in critically ill patients provides some information, first from a study by Combes et al. [22], and then Dini et al. [23] reported that a E/E' ratio ≥ 13 had a sensitivity of 87 % and a specificity of 90 % to adequately predict a PAOP > 15 mmHg. Vignon et al. [24] showed a correlation of E/E' < 8 for PAOP < 18 mmHg with a sensitivity of 83 % and a specificity of 88 %. Lamia et al. [25] studied the relationship between E/E' and PAOP during weaning; they found a sensitivity of 94 % and a specificity of 94 % between E/E' > 8 and high PAOP.

Conclusion

The E/E' index is used in the echocardiographic assessment of diastolic function. Although this method has been found to be useful in various clinical scenarios, it has limitations. The E/E' appears to be an accurate predictor of PAOP and could potentially represent a tool for non-invasive bedside hemodynamic assessment with a view to guiding therapy in critical care patients. One of the most appreciated echocardiography characteristics in critically ill patients is the lack of invasiveness, and its reliability and continuous measurement. Exact numbers are still controversial, but trends help us understand better the characteristics of each patient.

References

1. Mulvagh S, Quinones ME, Kleiman NS (1992) Estimation of left ventricular end-diastolic pressure from Doppler transmitral flow velocity in cardiac patients independent of systolic performance. J Am Coll Cardiol 20: 112 – 119
2. Appleton CP, Galloway JM, Gonzales MS, et al (1993) Estimation of left ventricular filling pressures using two-dimensional and Doppler echocardiography in adult patients with cardiac disease. J Am Coll Cardiol 22: 1972 – 1982
3. Giannuzzi P, Imparato A, Temporelli PL, et al (1994) Doppler-derived mitral deceleration time of early filling is a strong predictor of pulmonary capillary wedge pressure in post-infarction patients with left ventricular systolic dysfunction. J Am Coll Cardiol 23: 1630 – 1637
4. Vanovershelde JLJ, Robert AR, Gerbaux A, Michel X, Hanet C, Wijns W (1996) Noninvasive estimation of pulmonary arterial wedge pressue with Doppler transmitral flow velocity pattern in patients with known heart disease. Am J Cardiol 75: 383 – 389
5. Kuecherer HF, Kusumoto FM, Muhiudeen IA, Cahalan MK, Schiller NB (1991) Pulmonary venous flow patterns by transesophageal pulsed Doppler echocardiography: relation to parameters of left ventricular systolic and diastolic function. Am Heart J 122: 1683 – 1693
6. Brunazzi MC, Chirillo F, Pasqualini M, et al (1994) Estimation of left ventricular diastolic pressures from precordial pulsed-Doppler analysis of pulmonary venous and mitral flow. Am Heart J 128: 293 – 300
7. Pozzoli M, Capomolla S, Pinna G, Cobelli F, Tavazzi L (1996) Doppler echocardiography reliably predicts pulmonary artery wedge pressure in patients with chronic heart failure with and without mitral regurgitation (1996). J Am Coll Cardiol 27: 883 – 893
8. Rossvoll O, Hatle LK. (1993). Pulmonary flow velocities recorded by transthoracic Doppler ultrasound: relation to left ventricular diastolic. J Am Coll Cardiol 21: 1687 – 1696
9. Nagueh SF, Sun H, Kopelen HA, Middleton KJ, Khoury DS (2001) Hemodynamic determinants of the mitral annulus diastolic velocities by tissue Doppler. J Am Coll Cardiol 37: 278 – 285
10. Nagueh SF, Middleton KJ, Kopelen HA, Zoghbi WA, Quinones MA (1997) Doppler tissue imaging: a noninvasive technique for evaluation of left ventricular relaxation and estimation of filling pressures. J Am Coll Cardiol 30: 1527 – 1533

11. Jacques D, Pinsky M, Severyn D, Gorcsan J (2004). Influence of alterations in loading on mitral annular velocity by tissue doppler echocardiography and its associated ability to predict filling pressures. Chest 126: 1910 – 1918
12. Garcia MJ, Ares MA, Asher C, Rodriguez L, Vandervoort P, Thomas JD (1997) An index of early left ventricular filling that combined with pulsed Doppler peak E velocity may estimate capillary wedge pressure. J Am Coll Cardiol 29: 448 – 454
13. Firstenberg MS, Levine BD, Garcia MJ, et al (2000) Relationship of echocardiographic indices to pulmonary capillary wedge pressures in healthy volunteers. J Am Coll Cardiol 36: 1664 – 1669
14. Vignon P, AlloV, Lesage J, Martaille JF, François B, Gastinne H (2007) Diagnosis of left ventricular diastolic dysfunction in the setting of acute changes in loading conditions. Crit Care 11: R43
15. Strugess D, Marwick T, Joyce C, Jones M, Venkatesh (2007) Tissue Doppler in critical illness: a retrospective cohort study. Crit Care 11: R97
16. Vargas F, Gruson D, Valentino R, et al (2004) Transesophageal Pulsed Doppler echocardiography of pulmonary venous flow to assess left ventricular filling pressure in ventilated patients with acute respiratory distress syndrome. J Crit Care 19: 187 – 197
17. Ommen SR, Nishimura RA, Appleton CP, et al (2000) Clinical utility of Doppler echocardiography and tissue Doppler imaging in the estimation of left ventricular filling pressure. A comparative simultaneous Doppler catheterization study. Circulation 102: 1788 – 1794
18. Nagueh S, Appleton C, Gillebert T, et al (2009) Recommendation for the Evaluation of Left Ventricular Diastolic Function by Echocardiology. Eur J Echocard 10: 165 – 119
19. Dokainish H, Nguyen J, Sengupta R, et al (2010) New, simple echocardiographic indexes for the estimation of filling pressure in patients with cardiac disease and preserved left ventricular ejection fraction. Echocardiography 27: 946 – 953
20. Kusunose K, Yamada H, Nishio S, et al (2009) Clinical utility of single-beat E/e' obtained by simultaneous recording of flow and tissue Doppler velocities in atrial fibrillation with preserved systolic function. JACC Cardiovasc Imaging 2: 1147 – 1156
21. Senechal M, O'Connor K, Debois J, et al (2009) A simple Doppler echocardiography method to evaluate pulmonary capillary wedge pressure in patients with atrial fibrillation. Echocardiography 25: 57 – 63
22. Combes A, Arnoult F, Trouillet JL (2004) Tissue Doppler imaging estimation of pulmonary artery occlusion pressure in ICU patients. Intensive Care Med 30: 75 – 81
23. Dini FL, Ballo P, Badano L, et al (2010) Validation of an echo-dopper decision model to predict left ventricular filling pressure in patients with heart failure independently of ejection fraction. Eur J Echocardiogr 11: 703 – 710
24. Vignon P, AitHssain A, François B, et al (2008) Echocardiographic assessment of pulmonary artery occlusion pressure in ventilated patients: a transesophageal study. Crit Care 12: R18
25. Lamia B, Maizel J, Ochagavia A, et al (2009) Echocardiographic diagnosis of pulmonary artery occlusion pressure elevation during weaning from mechanical ventilation. Crit Care Med 37: 1696 – 1701

Hemodynamics from the Periphery

S. Romagnoli, S.M. Romano, and D. Payen

Introduction

Although, until now, there is no evidence for an improved outcome of critically ill patients by measurement of cardiac output, the estimation of flow, other than pressure, is considered of high importance in the management of patients in the perioperative period and in critical care as it provides valuable insights into systemic oxygen delivery (DO_2) and global tissue perfusion that can be used to optimize treatment strategies.

Since its first applications for bed-side assessment of cardiac function in the 1970s, the pulmonary artery catheter (PAC) with the thermodilution technique has become the reference technique for cardiac output measurement in scientific communities worldwide. However, due to the lack of benefit on outcomes and its intrinsic invasiveness, its use is progressively declining in most clinical scenarios and alternative, less invasive techniques have been developed challenging the role of the PAC for the cardiac output monitoring market. Among these new technologies, pulse contour methods (PCMs), which estimate flow, i.e. cardiac output, by analyzing an arterial pressure wave, are currently increasingly applied in intensive care units (ICUs) and operating rooms. In the category of PCMs, reside several instruments largely different in terms of principles of functioning, invasiveness, vantages and limitations.

The respective algorithms of the devices differ considerably; some need manual calibration, others are self-calibrating, others are not-calibrated, and finally they differ in the accuracy of cardiac output determination. The purpose of this chapter is to provide an overview of the commercially available arterial pressure waveform-based techniques for hemodynamic monitoring, and to discuss their inherent advantages, disadvantages and limitations, clarifying their main differences.

From Otto Frank's Theory to Modern Pulse Contour Methods

The estimation of cardiac output via pulse contour analysis is an indirect method, since flow is not measured directly (as with the electromagnetic probe) but is computed from a pressure pulsation. The first attempt to determine stroke volume (SV) from the shape of the arterial pulse curve can be traced as far back as 1904 [1]. The German physiologist, Otto Frank, first postulated the theory by which cardiac output can be obtained from the arterial pressure wave. According to his original theory, the SV could be estimated by the relation between the area

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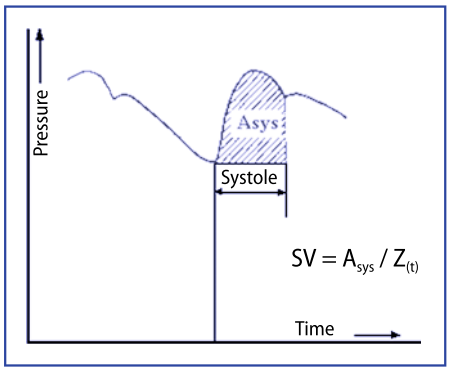

Fig. 1. Original theory by Otto Frank [1]. SV: stroke volume; $A_{(sys)}$: area subtended by the systolic portion of the pressure curve; $Z_{(t)}$: dynamic impedance of the cardiovascular system.

subtended by the systolic portion of the pressure curve (generated by the bolus of blood ejected from the left ventricle into the aorta) and the dynamic impedance [Z(t)] of the cardio-circulatory system [SV = A(t) / Z(t)] (**Fig. 1**).

The *in vivo* estimation of cardiovascular impedance is the great issue of Frank's technique, because it represents all elastic and mechanical characteristics of the whole systemic circulation, which governs the relationship in time between the changes in pressure and volume [2]. It can also be seen as the factor that constitutes the total opposition to the propagation of the pressure wave. The huge complexity of impedance estimation is related to the number of factors that affect its value. As O'Rourke established [3], vascular impedance, like electrical, acoustic, and mechanical impedance, is a complex quantity affected by a number of factors. For instance, when blood pressure increases, the arteries distend and more tension is applied to collagenous elements of the arterial wall, so that distensability falls and pulse-wave velocity rises. As a consequence of the more rapid wave velocity, wave reflection (key factors in determining impedance) returns earlier from peripheral sites. With this increased velocity, reflected waves from the periphery may reach the left ventricle during the systolic phase, when the aortic valve is still open, contributing strongly to the total impedance.

Moreover, the compliance of the arterial tree (strongly affecting the impedance), is not a linear function since it is higher when pressure is lower and decreases non-linearly when pressure increases. Wave reflection can occur at any discontinuity along the arterial tree. Possible reflecting sites are the arterial branching sites and the junctions of small arteries with high-resistance arterioles [3]. Non-uniform arterial elasticity (the progressively increasing stiffness of peripheral arteries) is, technically speaking, another source of wave reflection. Present evidence indicates that the arterioles are the major sites of wave reflection in the systemic circulation. As blood flows through the systemic vessels, mean pressure falls but little over long distances in the aorta and major arteries, then drops sharply in the arterioles. Hence, resistance is low over long lengths of artery, but it then rises steeply and suddenly over very short segments. As a consequence, the cardiovascular impedance can be influenced by vasoconstriction/vasodilatation conditions, which may vary over time. Compliance is also influenced by other stimuli, such as waking-up, anesthesia, fluid therapy, hematocrit, vasoconstrictor and vasodilator drugs, and so on.

Because of these considerations relevant to the dynamic impedance, Frank affirmed that *in vitro* models are not sufficient to work on impedance, being over

simplified. He referred to the Windkessel model, a first order air chamber model with two totally independent compartments: a diastolic phase and a systolic phase. Frank really knew that many physiological factors simultaneously interact and that the *in vitro* models can only qualitatively describe a phenomenon, but cannot quantify it. Therefore, it could only approximate the phenomenon, especially when a patient is considered. Unfortunately, with the passing of time, knowledge of the limitations of the original 'pulse contour method', well known by the early researchers, seems to have been disregarded, so that other authors have more recently treated the Windkessel model without taking into account its origin.

The pulse contour methods, explicitly or implicitly, base their operation principle on the two-compartment Windkessel model described by Otto Frank. Based on this theory, the model was implemented, correcting non-linear and pressure-dependent changes using age, mean blood pressure, the section of the aorta and heart rate. These factors were used to correct the impact of the reflecting waves from the peripheral vessels. In other words, a 'nonlinear element model', that is a 'three-element' model is used instead of a two-compartment one. The insertion of new parameters such as mean pressure, heart rate and age could improve the measurement quality. These factors are factors of approximation, which may have different contributory roles according to the surrounding conditions. The following formula drawn by Wesseling et al. [4] is:

$$V_{cz} = CO_Z \times [0.66 + 0.005 \times HR - 0.01 \times Age \times (0.014 \times Pmean - 0.8)]$$

Since the specific systemic dynamic impedance of the circulation is not measured *in vivo*, it is determined *a priori*, leading to the introduction of a corrective factor (Z_{AO}):

$$CO_Z = A_{SYS} / Z_{AO}$$

Z_{AO} is determined by the ratio between $A_{sys\ cal}$ (area measured during the calibration) and cardiac output obtained from a reference system (for example, thermodilution; CO_{ref}):

$$Z_{AO} = A_{sys\ cal} / CO_{ref}$$

Since the equation corrects the waves reflected by the peripheral vessels, the measured peripheral vessel pressure wave can be used as an alternative to the aortic wave.

Use of a calibration system is one of the most widely employed expedients to allow pulse contour method systems to face the problem of evaluation of dynamic impedance. Keeping in mind the difficulty/impossibility of considering all these simultaneously acting physical entities in a classical analysis, the pulse contour methods can be classified into three different groups [5]:

I) Pulse contour methods that are calibrated by a system measuring SV, such as the dilution of an indicator (for example dilution of a thermal indicator or lithium dilution);
II) Pulse contour methods that require preloaded data on demographic and anthropometric characteristics of the patients;
III) Pulse contour methods that work without any calibration or pre-loaded data.

Pulse Contour Methods with External Calibration and/or Pre-loaded Data (types I and I + II)

The PiCCO™ (Pulsion Medical Systems, Munich, Germany) system analyzes the area under the curve (AUC) of the systolic part of the arterial pressure waveform. To compensate for inter-individual differences in vascular impedance and to track changes of these variables as a result of changing clinical conditions, manual calibrations are necessary. PiCCO™ calibrates the cardiac output through trans-cardiopulmonary thermodilution with cold saline (< 10 °C) injected by a central venous catheter three to five times, recording the temperature variation in the femoral artery, using the Stewart-Hamilton principle. As usual, when a calibration with a reference method accounts for a condition of aortic impedance, it 'fixes' this calibration [6, 7]. Data with regard to recalibration intervals are scarce, with a trend in the literature toward short recalibration intervals, in particular in hemodynamically unstable patients [8].

According to the PiCCO algorithm, SV is calculated as follows:

$$\text{Cardiac output} = \text{cal} \times \text{HR} \times ({}_{\text{systole}}(\text{P(t)/SVR} + \text{C(p)} \times \text{dP/dt}) \times \text{dt}$$

Where 'cal' is a factor of calibration obtained by transthoracic thermodilution; '$({}_{\text{systole}}$ P(t)/SVR' is the area under the systolic pressure curve divided by SVR (systemic vascular resistance); C(p) is the aortic compliance; and dP/d the pressure waveform.

However, it should be underlined that the 'measurement' of the nonlinearity relationship comes from fittings obtained from patient databases. The PiCCO™ system needs regular recalibration when a significant hemodynamic variation occurs [8]. This could be a problem because changes in the status of really unstable clinical patients are not predictable *a priori*.

The system has been validated in various conditions using the PAC as a reference method. It has been shown to be a reliable instrument, although its use is discussed in several situations [9–16].

The LiDCO (Lithium Dilution Cardiac Output; LiDCO LtD, London, UK) system also needs external calibration [17]. The proprietary algorithm of the LiDCO device is based on pulse power analysis rather than on the shape of the arterial waveform or the AUC for calculating cardiac output. The system calculates the SV from the pulse power after calibration with an indicator solution: Lithium is used as an indicator and is injected (0.002–0.004 mmol/kg) using either central or peripheral venous access. Lithium chloride as the indicator solution is detected by a lithium-sensitive electrode, connected to an arterial line, which estimates cardiac output from the lithium washout curve according to the Stewart–Hamilton equation. This information is subsequently used to calibrate the continuous pulse power analysis-based cardiac output measurement.

$$\text{Cardiac output} = \text{Li} \times 60/\text{A} \times (1 - \text{PCV})$$

where Li is the dose of lithium in mmol, A is the area of the dilution curve, PCV is the volume of packed cells calculated as a concentration of hemoglobin/3.

Technical limitations of LiDCO include vulnerability to hemoglobin and plasma sodium concentrations; the maximum daily dose of 3 mmol lithium, which limits the number of calibration measurements; and that calibrations cannot be performed in patients receiving neuromuscular blocking agents, because these drugs react with the lithium sensor.

Similar to the PiCCO system, LiDCO uses direct calibration, but was recently reported to be able to monitor SV variations with no requirement for direct calibration (LiDCO*rapid*™), by analyzing the pressure waveform [18]. This new version should be able to track trends in cardiac output, but scientific evidence is not yet available.

Several aspects need to be stressed. The two devices described above favor estimated flow variations more than absolute values. Consequently, when a hemodynamic variation occurs or when the device shows modifications, calibration has to be performed to assess the validity of such a modification (modification in patient condition and/or in instrument calibration). Patient characteristics are used to estimate the arterial impedance. LiDCO*rapid*™ uses a nomogram-based estimate of the patient-specific scaling factor developed using *in vivo* calibration data from post surgical patients [19]. LiDCO*rapid*™ may thus be considered to belong to the second group of pulse contour methods. Moreover, LiDCO*rapid*™ provides SV and cardiac output values based on the PulseCO algorithm, scaled to the patient's specific characteristics. The PulseCO algorithm, however, has to be calibrated with standard methods as for the devices belonging to the first group of pulse contour methods.

Pulse Contour Methods with Pre-calibration (type II)

The FloTrac-Vigileo® (Edwards Lifesciences, Irvine, California, USA) does not need a cardiac output dilution indicator for calibration, but works with preloaded patient demographics and physical characteristics (age, gender, height, and weight), like the non-invasive method, Modelflow [20], but to obtain absolute values direct calibration is necessary [21]. The algorithm analyzes the statistical distribution of data points of the pressure wave sampled at 100 Hz and is based on the principle that pulse pressure is proportional to SV, measured as the standard deviation of the arterial pressure around the mean arterial pressure (MAP). The standard deviation is then multiplied by a scaling parameter derived from a multivariate polynomial equation that includes the demographic and physical characteristics of the patient, as stated before. Skewness (symmetry of the waveform) and kurtosis are also considered to adjust for vascular tone and to compensate for the differences in pressure waveform due to arterial site. The system is designed to run with a dedicated pressure transducer (FloTrac sensor™) connected to any arterial line. The free-of-calibration system works on pre-estimated *in vitro* and/or *in vivo* data [22–25] but, however, despite its simplicity of use, reliability is uncertain especially during conditions of hemodynamic instability and when vasopressors are administered. Many versions of the algorithm have been produced. The third generation has been recently released and conflicting results have been published for each of the versions compared to various "gold standard" methods [26–31].

To calculate vessel compliance, the system instrument uses the characteristics of the arterial waveform and the best fit method referring to the patient's age, gender, weight and height [32], as does the LiDCO*rapid*™ procedure.

It is clear that the accuracy of the results depend largely on the adequacy of pre-calibration and/or the fit of pre-estimated data to the patient, which is unpredictable. To our knowledge, systematic comparative studies of different pulse contour methods are still lacking; moreover, the clinical reliability of these methodologies has not been adequately investigated. For example, as demonstrated by

Biancofiore et al., in cirrhotic patients undergoing liver surgery with hyperdynamic circulation, the Vigileo system showed a degree of error and unreliability higher than that considered acceptable for clinical purposes [33].

In addition, some components of dynamic impedance may change during the evolution of life-threatening conditions and types of shock. As an example, we have shown that aortic compliance is largely reduced after lipopolysaccharide (LPS) challenge in rabbits in relation to vessel wall edema [34].

Pulse Contour Methods that do NOT use External Calibration and/or Pre-estimated Data (Type III)

The Pressure Recording Analytical Method (PRAM), analyzes the entire area over zero pressure, taking in consideration not only the pulse pressure value but the whole pressure: Pulsatory and continuous contributions. PRAM clearly introduced variables obtained during the whole cardiac cycle, without pre-calibration and/or pre-estimated data coming from other patients. Data are then applied to the investigated patient by the P/t of each point of the whole cardiac cycle [35].

The PRAM method also includes the contribution of the area [36], a difference compared to the 'modern' pulse contour methods. The entire area under the pressure curve can be seen as a combination of: a) Pulsatile contribution mainly related to the systolic component; b) continuous contribution mainly related to the diastolic phase. The term 'mainly' is essential, since other phases exist. These can however be neglected when they are compared to the main specific phases.

To summarize, the 'classic' pulse contour methods looked mainly at the contribution of the pulse area, whereas PRAM adds the continuous section under the pulse area.

Similar to the additional contributions of the area, the concept of 'dynamic impedance' has to be considered. Dynamic impedance can be viewed with a pulsatile component (mainly related to ventricular contractility) and a continuous component, mainly related to vascular system mechanics, and their overlapping. To obtain an accurate analysis of the pressure waveform, a precise description throughout the cardiac cycle is warranted. To reach the goal of precision, the rate for sampling the pressure wave is at 1000 Hz frequency, whereas other systems work at 100 – 200 Hz. Such a high rate for sampling is necessary to identify even small shifts in characteristic points of pressure wave during each cardiac cycle. As an example, a 20 ms shift in the dicrotic pressure point leads to different flow and coupling between heart and circulation. Because of this, this method is largely dependent on the accuracy to detect pressure waves as well as on the under- and overdamping of the signal (**Figs. 2** and **3**) [37]. For this reason, for many years, PRAM has been the only method able to distinguish the systolic phase from the diastolic one by means of identification of the dicrotic notch.

The determination of SV without pre-calibration allows definition of an energy performance parameter during a cardiac cycle (cardiac cycle efficiency), independent of age, sex, etc. In fact, a similar SV could be obtained in a different homeostasis status and, for this reason, with different energy yields of the cardio-circulatory system. This non-dimensional value is a functional one, related to the equilibrium between continuous versus pulsatile energy. The trend in this parameter, especially after therapeutic intervention, can inform on less or more energy lost and has been shown to have prognostic value [38 – 42].

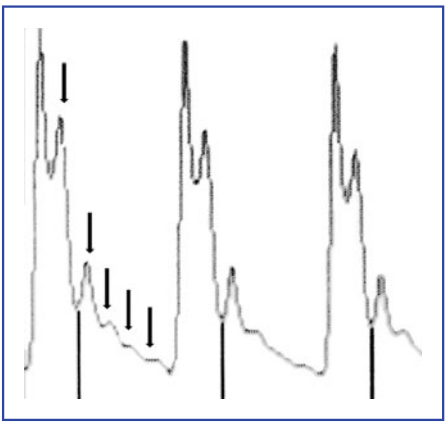

Fig. 2. Underdamped arterial pressure waveform. Systolic pressure overshoot and additional small, non-physiologic pressure waves (arrows) distort the waveform and make it difficult to discern the dicrotic notch. Note the systolic overshoot.

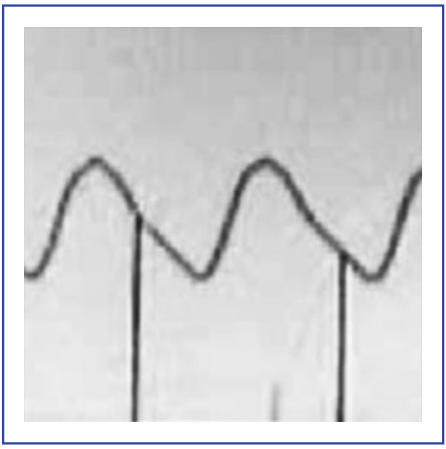

Fig. 3. Overdamped arterial pressure waveform. The overdamped pressure waveform shows a diminished pulse pressure when compared with the normal waveform due to an underestimation of systolic blood pressure and an overestimation of diastolic blood pressure.

X

Conclusion

Since Otto Frank's first experiments, it has been clear that pulse contour methods depending on direct calibration and/or pre-estimated parameters, either *in vitro* or from patients 'comparable' to the one studied, are able to explain pathophysiological phenomena in a qualitative way but they can only approximately explain clinical and hemodynamic data on a quantitative basis.

Obviously, type I and II pulse contour methods may be 'marginally' affected by a correct damping of the blood pressure signal. In fact, the pressure wave form is just one of the parameters, not always the most important one, among factors influencing the impedance estimation and therefore the cardiac output evaluations.

The type III pulse contour method is extremely sensitive to the feasibility of the measured pressure waveform, which anyway is the cornerstone of correct hemodynamic monitoring [37]. It is for the most important conditions that require monitoring that the type I and II systems may have limitations, since contractility, arterial tone, mechanics and heart rate are modified in a complex way. Rapid hemodynamic changes during surgery (large vessel grafting, hemorrhage)

and/or therapeutic interventions (inotropic drugs, vasoactive drugs, intra aortic balloon pump, fluids and so on) at different steps of the disease are the challenge for these simple to use techniques. These techniques have to be able to detect unpredictable acute situations.

Pulse contour methodologies are useful continuous monitoring tools for left sided systemic hemodynamic assessment. Applying *in vivo* impedance moves these tools from a cardio-centric model to an integrated physiological system. Great efforts have to be made to make these technologies clear, easy to use, and accurate in clinical conditions. They need to be validated in comparison with other accurate methods in real conditions, removing the taboos about the concept of external calibration concepts as a reference. Although a 'magic cardiac output number' does not exist, an evaluation of changes over time may help the clinician to better characterize patient situations.

References

1. Frank O (1899) Die Grundform des arteriellen Pilses. Erste abhandlung. Mathematische Analyse. Z Biol 37: 483 – 526
2. Kuecherer HF, Just A, Kircheim H (2000) Evaluation of compliance in humans. Am J Physiol Heart Circ Physiol 278: H1411 – 413
3. O'Rourke MF (1982) Vascular impedance in studies of arterial and cardiac function. Physiol Rev 62: 570 – 623
4. Starmer CF, McHale PA, Cobb FR, Greenfield JC Jr (1973) Evaluation of several methods for computing stroke volume from central aortic pressure. Circ Res 33: 139 – 148
5. Romagnoli S, Romano SM (2010) Estimation of hemodynamic parameters by arterial waveform: available technologies. Anesth Analg 110: 257 – 258
6. Langewouters GJ, Wesseling KH, Goedhard WJ (1985) The pressure dependent dynamic elasticity of 35 thoracic and 16 abdominal human aortas in vitro described by a five component model. J Biomechanics 18: 613 – 20
7. Gödje O, Hoke K, Lamm P, et al (1998) Continuous, less invasive, hemodynamic monitoring in intensive care after cardiac surgery. Thorac Cardiovasc Surg 46: 242 – 249
8. Gödje O, Hoke K, Goetz AE, et al (2002) Reliability of a new algorithm for continuous cardiac output determination by pulse-contour analysis during hemodynamic instability. Crit Care Med 30: 52 – 58
9. Halvorsen PS, Espinoza A, Lundbland R, et al (2006) Agreement between PiCCO pulse contour- analysis, pulmonal artery thermodilution during of-pump coronary artery bypass surgery. Acta Anesthesiol Scand 50: 1050 – 1057
10. Hamzaoui O, Monnet X, Richard C, Osman D, Chela D, Tebul JL(2008) Effects of changes in vascular tone on the agreement between pulse contour and transpulmonary thermodilution cardiac output measurements within an up to 6-hour calibration-free period. Crit Care Med 36: 434 – 440
11. Mielck F, Buhre W, Hanekop G, Tirilomis T, Hilgers R, Sonntag H (2003) Comparison of continuous cardiac output measurements in patients after cardiac surgery. J Cardiothorac Vasc Anesth 17: 211 – 216
12. Simon AM, Monedero P, Asenjo EC (2006) Erroneous measurement of haemodynamic parameters by PICCO^{TM} monitor in a critically ill patient with renal replacement therapy: a case report. Crit Care 10: 410 – 411
13. Baulig W, Schuett P, Goedje O, Schmid ER (2007) Accuracy of a novel approach to measuring arterial thermodilution cardiac output during itra-aortic counterpulsation. J Clin Monit Comput 21: 147 – 153
14. Yamashita K, Nishiyama T, Yokoyama T, Abe H, Manabe M (2008) The effects of vasodilatation on cardiac output measured by PiCCO. J Cardiothorac Vasc Anesth 22: 688 – 692
15. Bein B, Meybohm P, Cavus E, et al (2007) The reliability of pulse contour-deived cardiac output during hemorrhage and after vasopressor administration. Anesth Analg 105: 107 – 113

16. Ong T, Gillies MA, Bellomo R (2004) Failure of continuous cardiac output using the PiCCO device during induced hypothermia: a case report. Crit Care Resusc 6: 99 – 101
17. Pittman J, Bar YS, Sum PJ, Sherwood M, Mark M (2005) Continuous cardiac output monitoring with pulse contour analysis: A comparison with lithium indicator dilution cardiac output measurement. Crit Care Med 30: 2015 – 2021
18. LiDCOrapid User's Manual, Software V1. LiDCO Ltd, 16 Orsman Road, London N1
19. Cecconi M, Fawcett J, Grounds RM, Rhodes A (2008) A prospective study to evaluate the accuracy of pulse power analysis to monitor cardiac output in critically ill patients. BMC Anesthesiology 8: 3
20. Bogert LWJ, van Lieshout JJ (2005) Non-invasive pulsatile arterial pressure and stroke volume changes from the human finger. Exp Physiol 90: 437 – 446
21. Remmen JJ, Aengevaeren, WR, Verheugt FW, et al (2002) Finapres arterial pulse wave analysis with Modelflow is not a reliable non-invasive method for assessment of cardiac output. Clin Sci 103: 143 – 149
22. Pratt B, Roteliuk L, Habit F, Frazier J, Wallen R (2007) Calculating arterial pressure-based cardiac output (APCO) using a novel measurement and analysis method. Biomed Instrum Technol 41: 403 – 411
23. Manecke GR, Auger WR (2007) Cardiac output determination from arterial pressure wave: clinical testing of a novel algorithm that does not require calibration. J of Cardioth and Vascul Anesth 21: 3 – 7
24. Sander M, Spies CD, Grubitzsch H, Foer A, Muller M, Heymann C (2006) Comparison of uncalibrated arterial waveform analysis in cardiac surgery patients with thermodilution cardiac output measurements. Crit Care 10: R164
25. Mayer J, Boldt J, Schollhorn T, Rohm KD, Mengistu AM, Suttner S (2007): Semi-invasive monitoring of cardiac output by a new device using arterial pressure waveform analysis: a comparison with intermittent pulmonary artery thermodilution in patients undergoing cardiac surgery. Br J Anaesth 98: 176 – 182
26. McGee WT, Horswell JL, Calderon J, et al (2007) Validation of a continuous, arterial pressure-based cardiac output measurement: a multicentric, prospective clinical trial. Crit Care 11: R105
27. Senn A, Button D, Zollinger A, Hofer CK (2009) Assessment of cardiac output changes using a modified FloTrac/Vigileo™ algorithm in cardiac surgery patients. Crit Care 13: R32
28. Chatti R, de Rudniki S, Marquè S, et al (2009) Comparison of two versions of the Vigileo-FloTracTM system (1.03 and 1.07) for stroke volume estimation: a multicentre, blinded comparison with esophageal Doppler measurements. Br J Anaesth 102: 463 – 469
29. Donati A, Nardella R, Gabbanelli V, et al (2008) The ability of PiCCO versus LiDCO variables to detect changes in cardiac index: a prospective clinical study. Minerva Anestesiologia 74: 1 – 8
30. Compton FD, Zukunnft B, Hoffmann C, Zidek W, Shaeffer JH (2008) Performance of a minimally uncalibrated cardiac output system (FlotracTM/VigileoTM) in haemodynamically unstable patients. Br J Anesth 100: 451 – 456
31. Wilde RBP, Geerts BF, van den Berg PCM, Jansen RC (2009) A comparison of stroke volume variation measured by the LiDCOplus and FloTrac-Vigileo system. Anaesthesia 64: 1004 – 1009
32. Monnet X, Anguel A, Naudin B, Jabot J, Richard C, Teboul JL (2010) Arterial pressure-based cardiac output in septic patients: different accuracy of pulse contour and uncalibrated pressure waveform devices. Crit Care 14: R109
33. Biancofiore G, Critchley LA, Lee A, et al (2009) Evaluation of an uncalibrated arterial pulse contour cardiac output monitoring system in cirrhotic patients undergoing liver surgery. Br J Anaesth 102: 47 – 54
34. Cholley BP, Lang RM, Berger DS, Korcarz C, Payen D, Shroff SG (1995) Alterations in systemic arterial mechanical properties during septic shock: role of fluid resuscitation. Am J Physiol Heart Circ Physiol 38: H375 – 384
35. Romano SM, Conti AA, Giglioli C, et al (2006) Blood flow assessment by arterial pressure wave without external calibration. Comput Cardiol 33: 293 – 296
36. Romano SM, Pistolesi M (2002) Assessment of cardiac output from systemic arterial pressure in humans. Crit Care Med 30: 1834 – 1841

37. Romagnoli S, Romano SM, Bevilacqua S, et al (2011) Dynamic response of liquid-filled catheter systems for measurement of blood pressure: precision of measurements and reliability of Pressure Recording Analytical Method with different disposable systems. J Crit Care (in press).
38. Romano SM, Olivotto I, Chiostri M, Figlioli C, Margheri M, Gensini GF (2006) Minimally invasive and non invasive hemodynamic monitoring of the cardiovascular system: available options and future perspectives. Curr Cardiol Rev 4: 37 – 39
39. Sorbara C, Romagnoli S, Rossi A, Romano SM (2007) Circulatory failure: bedside functional haemodynamic monitoring. In: Atlee JL, Gullo A, Sinagra G, Vincent JL. Perioperative Critical Care Cardiology, 2nd ed. Springer, Milan, pp 89 – 110
40. Giglioli C, Landi D, Gensini GF, et al (2010) Cardiac efficiency improvement after slow continuous ultrafiltration is assessed by beat-to-beat minimally invasive monitoring in congestive heart failure patients: a preliminary report. Blood Purif 1: 44 – 51
41. Modesti PA, Gamberi T, Bazzini C, et al (2009) Response of serum protome in patients undergoing infrarenal aortic aneurysm repair. Anethesiology 111: 844 – 854
42. Scolletta S, Ranaldi G, Carlucci F, Franchi F, Romano SM, Biagioli B (2010) Relationship between N-terminal pro-B-type natriuretic peptide (Nt-proBNP) and cardiac cycle efficiency in cardiac surgery. Biomed Pharmacother 64: 511 – 515

Totally Non-invasive Continuous Cardiac Output Measurement with the Nexfin CO-Trek

A. Perel and J.J. Settels

Introduction

Cardiac output is one of the most important physiological parameters as it is the major determinant of oxygen delivery (DO_2). Its measurement is of special importance since so many of our efforts in the care of critically ill and high-risk surgical patients are aimed at optimizing its value by various therapeutic means. The importance of measuring cardiac output is further highlighted by the many studies that have repeatedly shown that clinical evaluation and conventional monitoring alone are inaccurate and unreliable for the assessment of cardiac output, and that adequate resuscitation cannot be based on normalization of vital signs alone [1–4]. Although there is little evidence that the measurement of cardiac output *per se* improves outcome, this is also true for all other hemodynamic parameters that are in common daily use.

The main technology for the measurement of cardiac output has been the thermodilution technique used with the pulmonary artery catheter (PAC). However, many newer technologies offer a less invasive approach than the PAC while measuring cardiac output with similar accuracy. The most recent significant development in this field is the introduction of uncalibrated continuous cardiac output technologies. Uncalibrated continuous cardiac output is usually based on pulse contour technology, by which various formulas are used to compute cardiac output values from the blood pressure waveform, without using intermittent thermodilution for calibration. The absolute accuracy of some of these technologies has not been shown to equal that of intermittent thermodilution [5]. However, most of these devices have good tracking accuracy which provides a very useful tool for the assessment of hemodynamic events with short time constants, e.g., fluid loading, passive leg raising, start of inotropes, etc. The Nexfin HD, which belongs to this category of continuous cardiac output monitors, offers in addition a unique feature – total non-invasiveness.

The Nexfin HD monitor (**Fig. 1**, BMEYE, Amsterdam, The Netherlands) is a device that measures continuous cardiac output by an inflatable finger cuff which is the only interface with the patient. The Nexfin HD measures cardiac output by combining continuous blood pressure monitoring and a novel pulse contour method (Nexfin CO-Trek) which is based on the systolic pressure area and a physiological three-element Windkessel model. The cardiac output is calculated without external calibration although it can be calibrated externally. The parameters that are measured by the Nexfin HD include continuous blood pressure (systolic, diastolic, mean), heart rate, continuous cardiac output, stroke volume (SV), systemic vascular resistance (SVR), and an index of left ventricular (LV) contractility (dP/dt).

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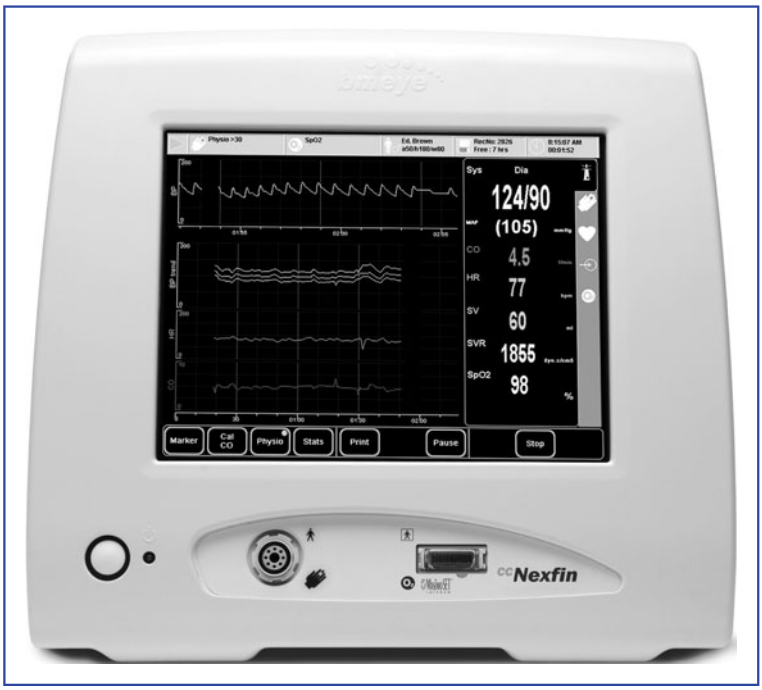

Fig. 1. The Nexfin monitor.

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The Principles of Continuous Cardiac Output Measurement using the Nexfin HD

The Nexfin HD applies three major steps in the measurement of continuous cardiac output: 1. Measurement of continuous beat-by-beat finger blood pressure; 2. Transformation of the finger blood pressure curve into a brachial arterial blood pressure waveform; 3. Calculation of the continuous cardiac output from the brachial pressure pulse contour.

Measurement of Continuous Finger Blood Pressure

For measuring continuous beat-by-beat blood pressure, a cuff is wrapped around the middle phalanx of the 2nd, 3rd or 4th finger (**Fig. 2**). The finger cuff includes an LED emitter-detector that measures the diameter of the finger arteries running on both sides of the finger's palmar aspect. The cuff pressure is increased and decreased to keep the diameter of the finger arteries constant throughout the cardiac cycle ('volume clamp method') (**Fig. 3**). Continuous recording of the cuff pressure therefore generates a real-time arterial pressure waveform. After initial calibration which typically takes 1 – 2 minutes, the Nexfin uses an auto-calibration algorithm ('Physiocal') that periodically recalibrates the system. During these periodic calibrations, the pressure is maintained at three levels resulting in three different volume changes, the shape of which determines the calibration. Depending on the stability of the pressure signal, the length of the calibration interval

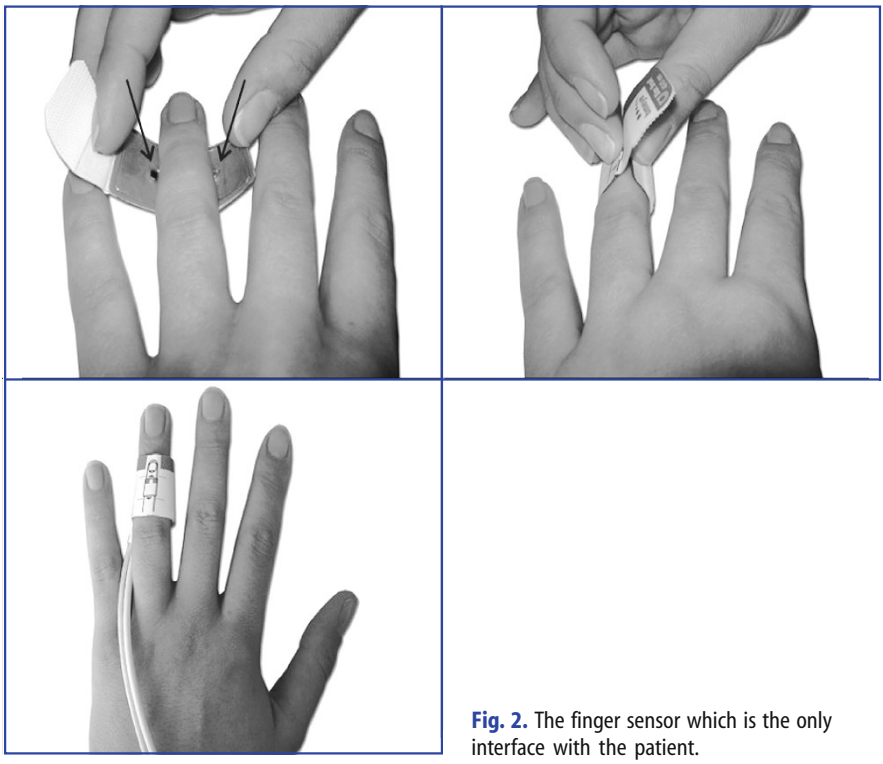

Fig. 2. The finger sensor which is the only interface with the patient.

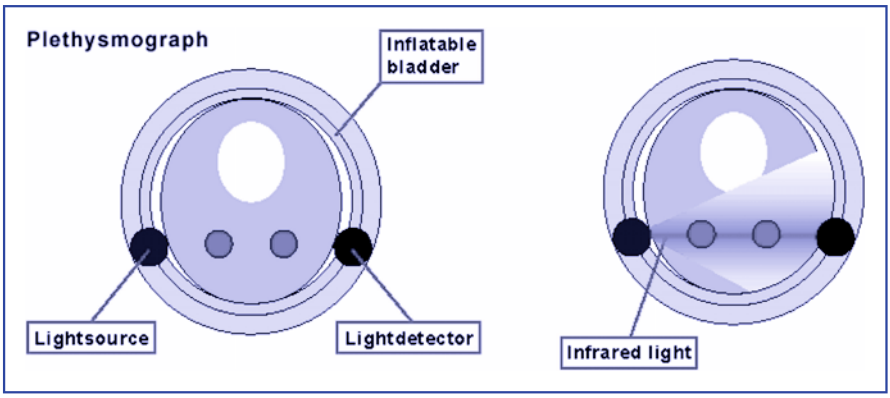

Fig. 3. The finger sensor includes 2 LEDs and an inflatable cuff which measures beat-to-beat real-time continuous blood pressure.

varies between 5 beats and 70 beats. Intervals ≥ 30 beats indicate a stable measurement condition. Periodic calibration with the Physiocal improves the accuracy of the continuous blood pressure measurement during significant changes in vascular tone. The volume clamp and Physiocal methods were previously used in the Ohmeda 2300 Finapres continuous blood pressure monitor. A 'heart reference

system' (HRS) measures and automatically corrects for the vertical height difference between the finger cuff and the heart level, allowing free movement of the hand while continuous cardiac output is monitored.

Transformation of the Finger Blood Pressure Curve Into a Brachial Artery Waveform

The continuous cardiac output measured by pulse contour algorithms may be significantly influenced by the site of the blood pressure measurement [5]. As a rule, the more peripheral the site where the blood pressure is measured, the greater the chance that the algorithm may not be able to compensate for changes in shape and amplitude of the waveform in extreme hemodynamic conditions. The Nexfin HD transforms finger blood pressure to brachial blood pressure waveform using a transfer function based on a vast clinical database and correcting for the brachial-finger pressure gradient. Thus the continuous cardiac output measured by the Nexfin uses the brachial pressure waveform as a robust substitute for aortic pressure as input for continuous cardiac output measurement. Calibration with an upper arm cuff is no longer needed.

Calculation of Continuous Cardiac Output from the Brachial Arterial Pressure Waveform

The original concept of the pulse contour method for estimation of beat-to-beat SV was first described by Otto Frank in 1899 as the classic two-element Windkessel model (see later). According to this model, the interaction between the cardiac systole and the arterial input impedance (Z_{in}) determines the SV and the systolic and diastolic arterial pressures. Pulse contour methods in general use this close interaction in the hemodynamic version of Ohm's law ($\Delta P/Q = Z_{in}$). Thus, when the arterial input impedance (Z_{in}) is known, a given pressure (P) allows for the calculation of the related flow (Q).

Pulse contour algorithms for non-calibrated continuous cardiac output measurement were initially developed by Wesseling and coworkers, who described the corrected characteristic impedance or *cZ* method in 1983 [6], and the Modelflow method in 1993 [7]. The cZ method computes beat-to-beat stroke volume by integrating the area under the systolic portion of the measured arterial pressure pulse (**Fig. 4 A**) and dividing this area by the characteristic input impedance (cZ). A correction to the characteristic impedance, which is derived by a distributed transmission line model, is then applied in order to account for changes in mean arterial pressure (MAP) and heart rate (HR): $Z_c = K / (a + b \times HR + c \times MAP)$. The limitation of this pulse contour algorithm is that a calibration factor (K) had to be determined at least once for each patient, and that the non-linear pressure dependency of compliance, as well as the effects of strong vasoconstriction and vasodilatation in peripheral arterioles, were not modeled.

To overcome these limitations, Wesseling developed the Modelflow method (1993) [7] by simulation of a flow waveform in a physiological, three-element, non-linear, age-dependent Windkessel model of the aortic arterial input impedance as a description of the cardiac afterload of the left ventricle. This model includes the following elements (**Fig. 4 B**):

1. Characteristic impedance (Z_c). During ejection into the blood-filled proximal aorta, the left heart encounters the combined effects of the proximal aortic

compliance (C) and its blood mass, or inertance (L). This combined effect is called the characteristic impedance and is calculated as $Z_c = \sqrt{L/C}$, where inertia increases the resistance to ejection and compliance facilitates ejection.
2. The total arterial compliance (Cw) equals the sum of the compliances of all arteries, is determined mainly by the ascending and descending aorta, and represents the ability of the aorta and larger vessels to elastically store the ejected stroke volume.
3. The total peripheral resistance (Rp) equals the sum of the resistances of all small arteries, arterioles and capillaries. It represents the resistance to outflow of blood to all vascular beds during diastole when inflow into the aorta is zero.

SV is then calculated by the integration of the systolic portion of the resulting modeled flow waveform. The method can be calibrated for each individual patient by adjusting a calibration factor to improve absolute precision [7]. Tracking changes in SV with this method has been found to be excellent even in the presence of large changes in pressure, heart rate and strong vasodilation or vasoconstriction [8]. However, the Modelflow method is less accurate in estimating the initial absolute level of cardiac output at the start of monitoring and is less suited for the use of finger blood pressure, which gives less satisfactory results than invasive radial arterial pressure.

The Nexfin CO-Trek algorithm, which was introduced in 2007, computes beat-to-beat stroke volume using an updated pulse contour method that contains elements from these two previous methods (**Fig. 4**). The Nexfin CO-Trek method

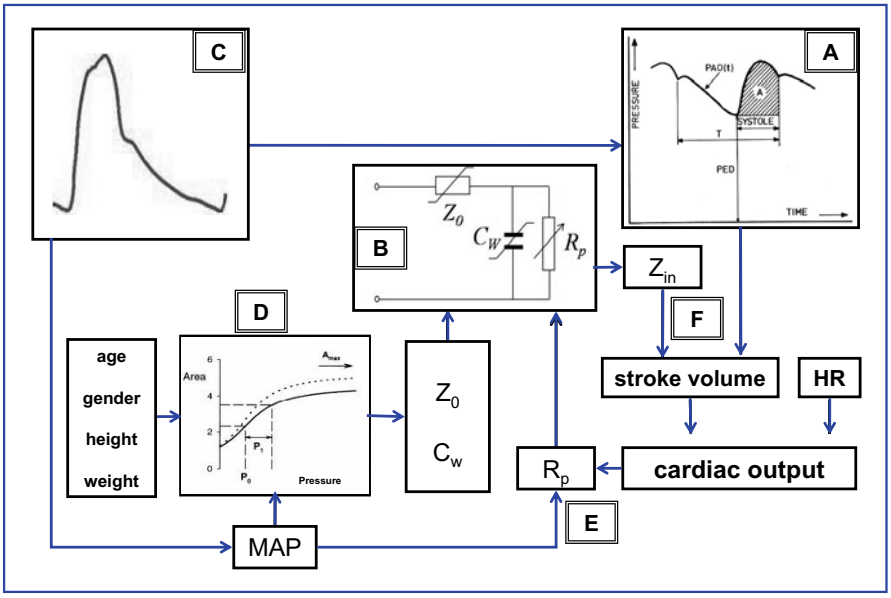

Fig. 4. The Nexfin CO-Trek algorithm integrates the systolic pressure-time integral (A) of the brachial arterial pressure waveform (C). The heart's afterload is calculated from the three-element Windkessel model (B), with Zo (characteristic impedance) and Cw (arterial compliance) derived from the aortic pressure-diameter relationship using age, gender, height and weight as input parameters (D). The total peripheral resistance (Rp) is time-dependent and is an outcome of the model computations (E).

integrates the systolic pressure-time integral similar to the cZ method (**Fig. 4A**), but in doing so it uses the reconstructed brachial arterial pressure waveform as a close substitute for aortic pressure as pressure input (**Fig. 4C**). The heart's afterload is calculated from the three-element Windkessel model (**Fig. 4B**), with Zo (characteristic impedance) and Cw (arterial compliance) derived from the aortic pressure-diameter relationship using age, gender, height and weight as input parameters (**Fig. 4D**). With the individual input of these parameters for each patient, the components of the three-element Windkessel afterload are individualized, can be computed for any arterial pressure level, and can further be used for SV computation. The total peripheral resistance (Rp) is time-dependent and is an outcome of the model computations (**Fig. 4E**). Beat-to-beat SV is calculated by dividing the pressure-time integral by the resulting Zin (**Fig. 4F**), so that SV = 1 / Zin * $\int$ [P(t) – Pd]dt.

Validation of the Nexfin HD

Since 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 cardiac output, which was measured by an automated series of 4 thermodilution injections equally spread over the ventilatory cycle for better accuracy [8]. 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 cardiac output were obtained using the Modelflow method [9]. The results were found to be better than those of Wesseling's cZ method, and of the LiDCO and PiCCO algorithms. In a more recent study from 2009, the same group of de Wilde et al. studied another small group of patients within 2 h of arrival in the intensive care unit (ICU) following cardiac surgery [10]. The values of cardiac output measured by the FloTrac device, the Modelflow method and the transesophageal ultrasonic HemoSonic system (Arrow), were compared with accurately performed thermodilution as the reference. Cardiac output values were measured during and after four interventions: (i) an increase in tidal volume by 50 %; (ii) a 10 cmH_2O increase in positive end-expiratory pressure (PEEP); (iii) passive leg raising; (iv) head-up position. The cardiac output values measured by Modelflow were found to have the best precision (0.69 l/min) and smallest limits of agreement (-1.08, +1.68 l/min, 26 %), compared with the FloTrac (-1.47, +2.13 l/min, 34 %) and the Hemosonic (-2.62, +1.80 l/min, 44 %) systems. The authors concluded that only the Modelflow yielded limits of agreement (26 %) that were below the 30 % criteria for a theoretically acceptable alternative to thermodilution cardiac output. The FloTrac was found to overestimate changes in cardiac output, although directional changes in thermodilution cardiac output were detected with a high score by all three methods [10].

In another recent study [11], the authors observed a good correlation between cardiac output values measured by a PAC and by the Nexfin HD, with an r^2 = 0.83, a bias of 0.23 l/min, and two SD of ± 2.1 l/min, and a percentage of error of 29 %. These findings are even more impressive if one takes into account that the study was done in severely ill patients (4 patients were post-lung transplant,

4 patients were post-liver transplant, and 2 had severe acute respiratory distress syndrome [ARDS]), all of whom were receiving norepinephrine at the time of the study. Moreover, data were analyzed retrospectively using hourly Nexfin HD cardiac output measurements, rather than simultaneously measured cardiac output 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 a safe use of the Nexfin HD system. In addition, the authors noted that the Nexfin HD, being quick to install and easy to use, could offer a quick initial hemodynamic overview and allow to bridge the time until a longer-lasting invasive monitoring could be installed in the case of a deteriorating patient [11].

Clinical Applications

The totally non-invasive nature of the Nexfin HD allows the measurement of continuous cardiac output in a much wider variety of patients than was hitherto possible. Originally, the Nexfin HD was introduced in cardiology clinics for the performance of tilt-test for the detection of orthostatic hypotension. Indeed, a recent study using finger pressure-derived continuous cardiac output has shown that the early postoperative postural cardiovascular response is impaired after radical prostatectomy with a risk of orthostatic intolerance, limiting early postoperative mobilization [12]. Both the tilt test and the sit-stand test take advantage of the fact that the Nexfin HD provides real-time continuous cardiac output, 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 cardiac output measurement may be more useful and provide more accurate information about the changes in cardiac output than intermittent cardiac output measurements by thermodilution 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 recognized that a small group of patients account for the majority of perioperative morbidity and mortality. These 'high-risk' patients have a poor outcome because of 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 hemodynamic and oxygen transport goals at any point during the perioperative period, the outcome of these patients can be improved. Most studies on perioperative optimization have used repetitive fluid challenges in order to maximize the cardiac output. Cardiac output was measured in most of these studies by esophageal Doppler or by FloTrac. However, esophageal Doppler can be used only after induction of anesthesia and for a limited period, while the FloTrac necessitates the presence of an arterial line. Indeed, finger pressure derived continuous cardiac output has already been used for this purpose [13]. The non-invasive nature of the Nexfin HD and its semi-disposable finger sensor make this monitor fit ideally in this important setting. In fact, the Nexfin is perfectly suitable for any patient who is sick or at risk enough to warrant the need for continuous real-time hemodynamic monitoring, but who is not sick enough to warrant the use of invasive lines and catheters with their associated complications.

There are some limitations to the use of the Nexfin HD. Because of the continuous variable inflation of the finger cuff, the approved duration of continuous measurement is restricted to 8 hours. In addition, the Nexfin HD may not perform well in the presence of strong vasoconstriction or very edematous fingers. Currently the device does not provide measures of pulse pressure (PPV) or stroke volume (SVV) variations, which should be an integral part of any continuous cardiac output monitor. The additional benefits of the Nexfin HD include a semi-disposable finger cuff which can be used for many patients, a user-friendly touch screen, and instant data retrieval with a USB flash drive. The second version of the monitor, the ccNexfin, includes pulse oximetry and non-invasive hemoglobin (Masimo Rainbow SET technology) making all elements of DO_2 available at the bedside in a non-invasive manner.

Conclusion

The monitoring of continuous cardiac output offers important information that cannot be reliably obtained from clinical examination and conventional monitoring alone. The new generation of uncalibrated continuous cardiac output monitors that are based on pulse contour analysis has made this measurement more prevalent in the care of high-risk and critically ill patients. The Nexfin monitor provides uncalibrated continuous cardiac output in a totally non-invasive manner with a finger cuff being the only interface with the patient. The non-invasive nature of this device allows quick and easy measurement of continuous cardiac output in patients without the need for sedation or arterial cannulation. The Nexfin HD can, therefore, be used as a short-term (up to 8 hours) continuous cardiac output monitor in patients who are not sick enough to warrant more invasive and advanced monitoring, or to offer an initial hemodynamic overview until a longer-lasting invasive monitoring can be installed. The Nexfin HD seems most suitable for the perioperative period, where the ability to track hemodynamic events with sort time constants has been shown to improve outcome.

References

1. Wo CCJ, Shoemaker WC, Appel PL, Bishop MH, Kram HB, Hardin E (1993) Unreliability of blood pressure and heart rate to evaluate cardiac output in emergency resuscitation and critical illness. Crit Care Med 21: 218–223
2. Meregalli A, Oliveira RP, Friedman G (2004) Occult hypoperfusion is associated with increased mortality in hemodynamically stable, high-risk, surgical patients. Crit Care 8: R60-R65
3. Veale WN Jr, Morgan JH, Beatty JS, Sheppard SW, Dalton ML, Van de Water JM (2005) Hemodynamic and pulmonary fluid status in the trauma patient: are we slipping? Am Surg 71: 621–625
4. Grissom CK, Morris AH, Lanken PN, et al (2009) Association of physical examination with pulmonary artery catheter parameters in acute lung injury. Crit Care Med 37: 2720–2726
5. Camporota L, Beale R (2010) Pitfalls in hemodynamic monitoring based on the arterial pressure waveform. Crit Care 14: 124
6. Wesseling KH, de Wit B, Weber JA, Smith NT (1983) A simple device for continuous measurement of cardiac output. Adv Cardiovasc Phys 5: 16–52
7. Wesseling KH, Jansen JRC, Settels JJ, Schreuder JJ (1993) Computation of aortic flow from pressure in humans using a nonlinear, three-element model. J Appl Physiol 74: 2566–2573
8. Jansen JRC, Schreuder JJ, Mulier JP, Smith NT, Settels JJ, Wesseling KH (2001) A compari-

son of cardiac output derived from the arterial pressure wave against thermodilution in cardiac surgery patients. Br J Anaesth 87: 212 – 222
9. de Wilde RBP, Schreuder JJ, van den Berg PCM, Jansen JR (2007) An evaluation of cardiac output by five pulse contour techniques during cardiac surgery. Anaesthesia 62: 760 – 768
10. de Wilde RBP, Geerts BF, Cui J, van den Berg PCM, Jansen JRC (2009) Performance of three minimally invasive cardiac output monitoring systems. Anaesthesia 64: 762 – 769
11. Stover JF, Stocker R, Lenherr R, Neff TA, Cottini SR, Zoller B, Béchir M (2009) Noninvasive cardiac output and blood pressure monitoring cannot replace an invasive monitoring system in critically ill patients. BMC Anesthesiology 9:6
12. Bundgaard-Nielsen M, Jørgensen CC, Jørgensen TB, Ruhnau B, Secher NH, Kehlet H (2009) Orthostatic intolerance and the cardiovascular response to early postoperative mobilization. Br J Anaesth 102: 756 – 762
13. Bundgaard-Nielsen M, Ruhnau B, Secher NH, Kehlet H (2007) Flow-related techniques for preoperative goal-directed fluid optimization. Br J Anaesth 98: 38 – 44

Cardiac Output Monitoring: An Integrative Perspective

J.A. Alhashemi, M. Cecconi, and C.K. Hofer

Introduction

Cardiac output monitoring in the critically ill patient is standard practice in order to ensure tissue oxygenation [1] and has been traditionally accomplished using the pulmonary artery catheter (PAC). In recent years, however, the value of PAC has been questioned with some suggesting that its use might not only be unnecessary but also potentially harmful [1]. This notion, together with the availability of new less invasive cardiac output measuring devices, has markedly decreased the widespread use of the PAC [2]. Today, various devices are available to measure or estimate cardiac output using different methods. Some of these less invasive devices track stroke volume (SV) continuously and provide dynamic indices of fluid responsiveness, others allow assessment of volumetric preload variables, and some also provide continuous measurement of central venous saturation via the use of proprietary catheters that are attached to the same monitor. All these variables – together with cardiac output – may result in an improved hemodynamic assessment of the critically ill patient. However, it is important to appreciate that each device has its inherent limitations and that no cardiac output monitoring device can change patient outcome unless its use is coupled with an intervention that by itself has been associated with improved patient outcomes. Therefore, the concept of hemodynamic optimization is increasingly recognized as a cornerstone in the management of critically ill patients and has been shown to be associated with improved outcome in the perioperative [3] and in the intensive care unit (ICU) [4] setting.

The aim of this article is to provide a systematic up-date of the currently available and most commonly used cardiac output monitoring devices. In addition, an integrated approach for the use of these different devices in critically ill patients will be presented taking into consideration the devices' technical characteristics, their performance and typical limitations, and also any additional hemodynamic variables they may offer.

Overview of Cardiac Output Monitoring Devices

When selecting a cardiac output monitoring device for clinical use, different factors play a role (**Table 1**): Institutional factors may largely limit the choice of the available devices. On the other hand important device-related factors, e.g., invasiveness (**Fig. 1**), may restrict the area of application. Moreover, patient specific conditions may dictate the use of an invasive or a particular minimally- or non-invasive device.

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Factor groups	Examples
Institution	Type of institution Availability of monitoring techniques Level of standardization Potential of integration into existing monitoring systems Level of experience
Devices	Invasiveness Handling Technical limitations Validity, accuracy & repeatability Availability of additional hemodynamic information
Patient	Severity of specific diseases Heart rhythm Contraindications Type of intervention Type of treatment protocol

Table 1. Factors affecting selection of cardiac output monitoring devices

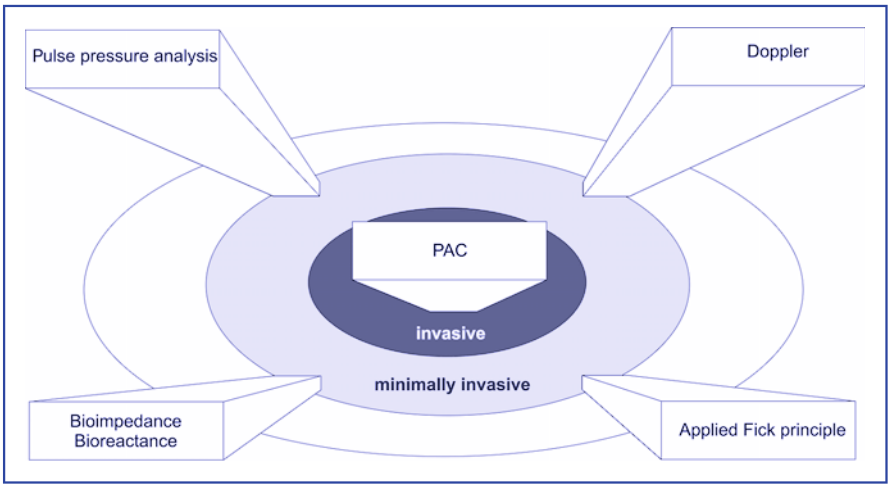

Fig. 1. Overview of cardiac output monitoring techniques. PAC: pulmonary artery catheter

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Invasive Cardiac Output Monitoring

The PAC was the clinical standard for cardiac output monitoring for more than 20 years and the technique has been extensively investigated. Its complications are well known and despite developments in recent years, the PAC has a distinct role in patient care. An in-depth review is beyond the scope of this article, but some technical aspects and limitations need to be noted: Cardiac output measurement by intermittent pulmonary artery thermodilution, which is based on the Stewart-Hamilton principle, is considered to be the 'reference cardiac output monitoring standard' against which all new cardiac output measuring devices are compared. However, operator dependence, various patient conditions (e.g., mitral or tricuspid valve insufficiency, shunt) or misplacement of the PAC may influence reliable cardiac output assessment [6]. In contrast, continuous cardiac output assessment

may overcome some of these limitations. Intermittent thermal filament heating induces pulmonary artery temperature changes that are measured via a distal thermistor and matched with the input signal. Based on the cross correlation of in- and output signals intermittent cardiac output values are produced from a thermodilution wash-out curve. These values are then averaged for the display of continuous cardiac output readings, which results in a delayed response time of several minutes after induction of cardiac output changes (e.g., for Opti-Q™, Abbott, Abbott Park, IL and Vigilance™ catheters, Edwards LifeSiences, Irvine, CA) [7]. A so-called fast response continuous cardiac output catheter (truCCOMS™, Omega Critical Care, East Klibride, GB) allows a more synchronized continuous cardiac output monitoring [8]. The additional hemodynamic variables that can be assessed via PAC and are most often used are conventional filling pressures, pulmonary artery pressures, and mixed venous oxygen saturation (SvO_2). Therefore, the PAC is still indicated when additional monitoring of pulmonary artery pressures and SvO_2 is desirable. It is also indicated in situations where less invasive techniques are contraindicated or fail to provide accurate cardiac output values.

Minimally Invasive Cardiac Output Monitoring

Minimally invasive cardiac output monitoring devices use one of four main principles to measure cardiac output: Pulse contour analysis, pulsed Doppler technology, applied Fick principle, and bioimpedance/bioreactance. Furthermore, devices that use pulse contour analysis can also be classified into calibrated and uncalibrated systems.

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Pulse pressure analysis

Pulse pressure analysis is based on the principle that SV can be continuously estimated by analyzing the arterial pressure waveform obtained from an arterial line. The characteristics of the arterial pressure waveform are affected by the interaction between SV and individual vascular compliance, aortic impedance and peripheral arterial resistance. For reliable cardiac output measurement using all devices that employ pulse pressure analysis technology, optimal arterial waveform signal (i.e., eliminating damping or increased tubing resonance) is a prerequisite. Moreover, it cannot be overemphasized that severe arrhythmias may reduce the accuracy of cardiac output measurement, and that the use of an intraaortic balloon pump precludes adequate performance of the device. Furthermore, pulse pressure analysis may be of limited accuracy during periods of hemodynamic instability, i.e., rapid changes in vascular resistance. This may especially be a problem for uncalibrated pulse pressure analysis. In contrast, calibrated pulse pressure analysis may require frequent re-calibration for accurate cardiac output estimation in these situations. A growing number of calibrated and uncalibrated devices that measure the cardiac output based on the pulse pressure analysis method are available.

PiCCO*plus*™ system (Pulsion Medical Systems, Munich, Germany): The PiCCO™ system uses a dedicated thermistor-tipped catheter, which is typically placed in the femoral artery, in order to assess SV on a beat-to-beat basis. Alternatively a radial or brachial catheter may be employed, but these catheters have to be longer than the femoral one for the adequate assessment of the aortic arterial pressure

wave signal. Cardiac output calibration via transpulmonary thermodilution requires the insertion of a central venous line. The calibration process is also used for the adjustment of individual aortic impedance and needs to be repeated every eight hours in hemodynamically stable patients. However, during situations of hemodynamic instability, calibration needs to be done more frequently (eventually every hour) [9]. Nevertheless, a variety of studies have successfully validated the PiCCO*plus*™ system in different patient populations [10, 11].

The launch of an uncalibrated device from Pulsion Medical Systems, the PulsioFlex™ system, can be expected in 2011. The system will require a specific additional sensor, which can be connected to a regular invasive arterial pressure monitoring set.

LiDCO™*plus* and LiDCO™*rapid system*: The LiDCO™plus and LiDCO™rapid systems (LiDCO Ltd, London, UK) use the same pulse pressure algorithm (PulseCO™) to track continuous changes in SV. This algorithm is based on the assumption that the net power change in the system in a heartbeat is the difference between the amount of blood entering the system (SV) and the amount of blood flowing out peripherally. It uses the principle of conservation of mass (power) and assumes that following correction for compliance there is a linear relationship between netpower and netflow. Therefore, the LiDCO systems should be considered as pulse power analysis techniques. The LiDCO™*plus* requires calibration using the transpulmonary lithium indicator dilution technique, which can be performed via a peripheral venous line [12]. In contrast, the LiDCO™*rapid* uses nomograms for cardiac output estimation. Clinical studies have demonstrated reliable estimation of cardiac output using PulseCO as long as no major hemodynamic changes are observed [13]. Regarding the LiDCO™*plus*, the reliability of the lithium calibration system may be negatively affected by high peak doses of muscle relaxants, which cross-react with the lithium sensor. This can be tackled if the lithium calibration is performed before or 30 minutes after the administration of a muscle relaxant. The LiDCO™*plus* system, in combination with a hemodynamic treatment protocol (targeting an oxygen delivery > 600 ml/min/m^2, was shown to be associated with reduced complications and length of hospital stay in patients after major general surgery [14]. The primary indication for the uncalibrated LiDCO™*rapid* is its perioperative use for SV optimization. Therefore, the LiDCO*rapid* trend analysis is more important than absolute cardiac output values (which may differ when compared with cardiac output assessed by PAC).

FloTrac™/Vigileo™ system: The FloTrac™/Vigileo™ system (Edwards LifeSciences, Irvine, USA) requires a proprietary transducer, the FloTrac™, which is attached to a standard non-proprietary radial or femoral arterial catheter and is connected to the Vigileo™ monitor. The FloTrac™/Vigileo™ system does not require calibration. To estimate cardiac output, the standard deviation of pulse pressure sampled during a time window of 20 seconds is correlated with 'normal' SV based on the patient's demographic data (age, sex, height, and weight) and a built-in database containing information about cardiac output assessed by the PAC in a variety of clinical scenarios. Impedance is also derived from these data, whereas vascular compliance and resistance are determined using arterial waveform analysis. After conflicting results of early validation studies, the cardiac output algorithm has been repeatedly modified in the last 5 years. This has resulted in an improved performance primarily in perioperative setting [15, 16]. Further

software modifications addressed the issue of limited accuracy during hyperdynamic situations and preliminary data showed improved cardiac output measurements under these specific conditions. However, accuracy of the device during rapid hemodynamic changes remains a major concern [17]. Nevertheless, a study using the Flotrac™/Vigileo™ system for intraoperative hemodynamic optimization recently demonstrated a decreased complication rate and a reduced length of hospital stay [18].

A new cardiac output monitoring device based on pulse pressure analysis, which is calibrated by transpulmonary thermodilution – the EV 1000™/VolumeView™ system from Edwards Lifesciences – is currently being tested and will soon be released for its use in daily practice.

Pressure recording analytical method (PRAM): Another method to estimate SV continuously without calibration is the PRAM – MostCare® (Vytech, Padova, Italy), which is based on mathematical assessment of the pressure signal obtained from an arterial line without calibration. PRAM has been validated so far in a porcine model under various hemodynamic states [19] and in humans undergoing cardiac surgery [20]. Similar to other devices that use pulse contour analysis, the accuracy of PRAM-derived cardiac output is affected by the quality of the pressure signal and by factors that interfere with the ability to detect a pressure signal.

Nexfin™: The Nexfin™ HD (BMEYE B.V, Amsterdam, Netherlands) is a completely non-invasive pulse pressure analysis device that assesses pulse pressure using photoelectric plethysmography in combination with a volume-clamp technique (inflatable finger cuff). Cardiac output is derived using the so-called Modelflow method (simulation of a three-element Windkessel model). Regarding validation of the device, only limited published data are available [21].

Doppler cardiac output monitoring devices

Cardiac output can be estimated non-invasively using esophageal or transthoracic Doppler probes. Esophageal Doppler devices measure blood flow in the descending aorta and estimate cardiac output by multiplying the cross sectional area of the aorta by blood flow velocity. The aortic diameter is obtained from a built-in nomogram or by direct measurement using M-mode echocardiography. Several esophageal Doppler probes are available commercially: ODM II™ (Abbott, Maidenhead, UK), CardioQ™ (Deltex Medical Ltd, Chichester, Sussex, UK), and HemoSonic100™ (Arrow, Reading, PA, USA). The latter device is a combination of a Doppler and an M-mode probe, the production of which has been stopped recently. There are several limitations for the use of esophageal Doppler devices. First, the device measures blood flow in the descending aorta and makes an assumption of a fixed partition between flow to the cephalic vessels and to the descending aorta. Although this may be valid in healthy volunteers, this relationship may change in patients with co-morbidities and under conditions of hemodynamic instability. Second, Doppler probes are smaller than conventional transesophageal echocardiography probes and position may change unintentionally, thus limiting continuous cardiac output assessment. Since probe position is crucial to obtaining an accurate measurement of aortic blood flow, this device is operator-dependent and studies have shown that 10 – 12 insertions are required to obtain accurate measurements [22] with an intra- and inter-observer variability of 8 – 12 % [23]. Moreover, aortic cross-sectional area is not constant but rather

dynamic in any individual patient. Thus, the use of a nomogram may result in less accurate cardiac output estimation. Despite some limitations of esophageal Doppler devices, their utility appears to be confirmed by several perioperative hemodynamic optimization studies that have consistently demonstrated a reduction in complication rates and hospital length of stay [24].

Alternatively to the esophageal route, the transthoracic approach may be used to assess cardiac output, albeit intermittently. The USCOM™ device (USCOM, Sidney, Australia) targets the pulmonary and aortic valves accessed via the parasternal and suprasternal windows in order to assess cardiac output completely non-invasively. Validation studies have revealed conflicting results, which could be explained primarily by the inherent problem of variable signal detection [25, 26].

Applied Fick principle

Partial CO_2 rebreathing: The NICO™ system (Novametrix Medical Systems, Wallingford, USA) applies Fick principle to carbon dioxide (CO_2) in order to obtain cardiac output measurement in intubated, sedated, and mechanically ventilated patients using a proprietary disposable re-breathing loop that is attached to the ventilator circuit. The NICO™ system consists of a mainstream infrared sensor to measure CO_2, a disposable airflow sensor, and a pulse oximeter. CO_2 production is calculated as the product of CO_2 concentration and airflow during a breathing cycle, whereas arterial CO_2 content is derived from end-tidal CO_2 and its corresponding dissociation curve. Every three minutes, a partial re-breathing state is generated using the attached re-breathing loop, which results in an increased end-tidal CO_2 and reduced CO_2 elimination. Assuming that cardiac output does not change significantly between normal and re-breathing states, the difference between normal and re-breathing ratios are used to calculate cardiac output. There are several limitations to this device including the need for intubation and mechanical ventilation with fixed ventilator settings and minimal gas exchange abnormalities [27]. Variations in ventilator settings, mechanically-assisted spontaneous breathing, the presence of increased pulmonary shunt fraction, and hemodynamic instability have been associated with decreased accuracy [28]. Thus, this technique may be applied in a precisely defined clinical setting to mechanically ventilated patients only.

Pulsed dye densitometry: The DDG-330® analyzer (Nihon Kohden, Tokyo, Japan) allows intermittent cardiac output measurement based on transpulmonary dye dilution with transcutaneous signal detection adapted from pulse oximetry (pulsed dye densitometry): The concentration of indocyanine green (ICG) is estimated in the arterial blood flow by optical absorbance measurements after its venous injection. Cardiac output is calculated from the dye dilution curve according to the Stewart-Hamilton principle. Unfortunately a variety of factors, e.g., vasoconstriction, interstitial edema, movement or ambient light artefacts, may limit reliable intermittent cardiac output assessment [29].

Bioimpedance and bioreactance

Electrical bioimpedance uses electric current stimulation for identification of thoracic or body impedance variations induced by cyclic changes in blood flow caused by the heart beating. Cardiac output is continuously estimated using skin electrodes (BioZ®, CardioDynamics, San Diego, USA) or electrodes mounted on an endotracheal tube (ECOM™, Conmed Corp, Utica, USA) by analyzing the

occurring signal variation with different mathematical models. Despite many adjustments of the mathematical algorithms, clinical validation studies continue to show conflicting results [30, 31].

Recently, however, Bioreactance® (NICOM®, Cheetah Medical Ltd, Maidenhead, Berkshire, UK) a modification of thoracic bioimpedance, has been introduced [32]. In contrast to bioimpedance, which is based on the analysis of transthoracic voltage amplitude changes in response to high frequency current, the Bioreactance® technique analyzes the frequency spectra variations of the delivered oscillating current. This approach is supposed to result in a higher signal-to-noise ratio and thus in an improved performance of the device. In fact, initial validation studies reveal promising results [32, 33].

Additional Hemodynamic Variables

Apart from SV and cardiac output, hemodynamic monitoring devices provide various additional hemodynamic variables (**Table 2**); namely, static preload variables, functional hemodynamic variables, and continuous central venous oxygen saturation ($ScvO_2$).

Static Preload Variables

Various cardiac output monitoring devices require a central venous line for calibration of the system. Thus, central venous pressure (CVP) is briefly reviewed here. CVP is traditionally assessed as an estimate of cardiac preload since true preload, which is defined as end-diastolic myocardial fiber tension, cannot be measured at the bedside. Several factors, however, affect CVP readings including impaired right ventricular (RV) function, and severe pulmonary or valvular heart disease. Although the majority of physicians use CVP in order to guide fluid therapy [34], several studies have shown lack of correlation between CVP and SV [35, 36]. Moreover, absolute CVP cannot be used to assess preload responsiveness. Therefore, the utility of CVP is limited and changes in trend over time and cyclic changes induced by mechanical ventilation are more important than absolute numbers. In contrast to the pressure preload variables, the so-called volumetric preload variables are considered to be superior indicators of preload. Global end-diastolic volume (GEDV) and extravascular lung water (EVLW) are static volumetric parameters that are assessed by transpulmonary thermodilution, which is required for the calibration of the PiCCO*plus* device and the up-coming EV1000/VolumeView device. Different studies have shown a better correlation between GEDV and SV than between the latter and static pressure preload [35]. GEDV could thus be used to better guide perioperative fluid therapy than pressure preload parameters [37]. EVLW on the other hand can be used to differentiate between cardiac versus non-cardiac pulmonary edema, and has been identified as an independent predictor of survival in critically ill patients [38]. It may, therefore, be of value in tailoring therapy in patients with acute respiratory distress syndrome (ARDS).

Functional Hemodynamic Variables

Pulse pressure analysis devices provide an automated quantification of SV variation (SVV) and some also allow the determination of pulse pressure variation

Table 2. Overview of hemodynamic monitoring techniques

Groups	Examples	Features	Invasiveness	Continuous CO	Additional variables		
					Static	Dynamic	$SvO_2/ScvO_2$
PAC							
	Vigilance™	Right heart catheterization	■■■	Response time up to 12 minutes	CVP PCWP	–	Specific catheter for continuous measurement available
Pulse wave analysis							
Calibrated	PiCCO*plus*™	Thermistor-tipped arterial catheter Central venous line	■■	Response time 3 seconds	CVP GEDV EVLW	SVV PPV	Specific catheter for continuous measurement available
	LiDCO*plus*™	Lithium dilution set	■□	Beat-by-beat	–	SVV PPV	–
	EV1000™/ VolumeView™*	Thermistor-tipped arterial catheter Central venous line	■■	NA	CVP GEDV EVLW	SVV	Specific catheter for continuous measurement available
Uncalibrated	FloTrac/Vigileo™	Specific arterial pressure sensor	■	Response time 20 seconds	–	SVV	Specific catheter for continuous measurement available
	LiDCO*rapid*™	Regular arterial line	■	Beat-by-beat	–	SVV PPV	–
	PulsioFlex™*	Regular arterial line Specific sensor	■	NA	–	SVV PPV	Specific catheter for continuous measurement available
	PRAM MostCare®	Specific arterial kit	■	Beat-by-beat	–	SVV PPV	–
	Nexfin™ HD	Specific pressure sensors	□	Beat-by-beat	–	–	–

Table 2. (*continued*)

Groups	Examples	Features	Invasiveness	Continuous CO	Additional variables		
					Static	Dynamic	$SvO_2/ScvO_2$
Doppler							
TE	CardioQ™	Esophageal Flowprobe	■	Limitation: probe positioning	–	–	–
TT	USCOM™	Flowprobe	□	Intermittent	–	–	–
Applied Fick principle							
Partial CO_2 rebreathing	NiCO™	Rebreating loop	■	Up-date every 3′	–	–	–
Dye dilution	DDG analyzer®	Specific sensor	■	Intermittent	–	–	–
Bioimpedance/Bioreactance							
Endotracheal bioimpedance	ECOM™	Specific endotracheal tube, arterial line	■	Continuous	–	–	–
Thoracic/whole body bioimpedance	BioZ®	Specific electrodes	□	Continuous	–	–	–
Thoracic bioreactance	NICOM™	Specific electrodes	□	Continuous	–	SVV	–

CO: cardiac output; CVP: central venous pressure; EVLW: extravascular lung water; GEDV: global end-diastolic volume; NA: technical specifications not yet available; PAC: pulmonary artery catheter; PAOP: pulmonary artery occlusion pressure; PPV: pulse pressure variation; SvO_2: mixed venous oxygen saturation; $ScvO_2$; central venous oxygen saturation; SVV; stroke volume variation; TE: transesophageal; TT: transthoracic; *not yet available.

(PPV). The basis of these functional variables is cyclic changes in intrathoracic pressure during positive pressure ventilation which induce changes in SV and pulse pressure as a result of a reduction in preload. The different functional hemodynamic variables have been shown to be able to predict fluid responsiveness in various studies [39], whereas static preload variables have not [40]. Nonetheless, it has to be emphasized that cardiovascular and ventilatory limitations, such as arrhythmias, right heart failure, spontaneous breathing activity, and low tidal volume (< 8 ml/kg body weight) affect the reliability of these dynamic indices of fluid responsiveness. Under these circumstances, 'passive leg raising' could be employed to assess fluid responsiveness as it results in an internal fluid shift from the legs to the central compartment caused by the modified Trendelenburg position. This technique has been demonstrated to reliably determine fluid responsiveness in critically ill patients [41].

Central Venous Oxygen Saturation

$ScvO_2$ is used as a global marker of the balance between systemic oxygen supply and demand [42]. It can be easily measured by obtaining a blood sample drawn from a central venous catheter, compared with SvO_2, which requires placement of a PAC and the withdrawal of blood from the distal port of the catheter. In addition to intermittent measurements using a blood sample and a blood gas analyzer, both $ScvO_2$ and SvO_2 can be measured continuously using proprietary central venous and pulmonary artery catheters, respectively. There are no outcome studies that compare intermittent versus continuous measurements of $ScvO_2$ or SvO_2; however, the only study that showed a survival benefit using $ScvO_2$ as a resuscitation endpoint employed continuous measurement [43]. Using proprietary catheters, continuous measurements of $ScvO_2$ can be obtained from both the Vigileo™ and the PiCCO™ systems. As far as its clinical utility is concerned, $ScvO_2$ has been used as a resuscitation endpoint in patients with severe sepsis and septic shock [43]. It is important to realize that absolute $ScvO_2$ and SvO_2 values may differ considerably in different clinical situations; however, a strong correlation of their trends over time has been demonstrated [44].

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Integrative Concept

Considering the technical features and the typical limitations of the different cardiac output monitoring techniques it is obvious that no single device can comply with all clinical requirements. Therefore, different devices may be used in an integrative concept along a typical clinical patient pathway (**Fig. 2**) based on the invasiveness of the devices and the available additional hemodynamic variables (**Table 2**). Bioreactance may be used on the ward or in the emergency department to assess cardiac output initially in order to confirm a preliminary diagnosis. Its use may be expanded in the perioperative and ICU setting. Partial CO_2-rebreathing requires an intubated and mechanically ventilated patient for cardiac output estimation. Thus, this technique may be primarily used during an operation. Uncalibrated pulse pressure analysis devices may be the primary choice in a perioperative setting as they provide functional hemodynamic variables and thus allow comprehensive hemodynamic management. In contrast, calibrated systems may be required when postoperative complications or hemodynamic

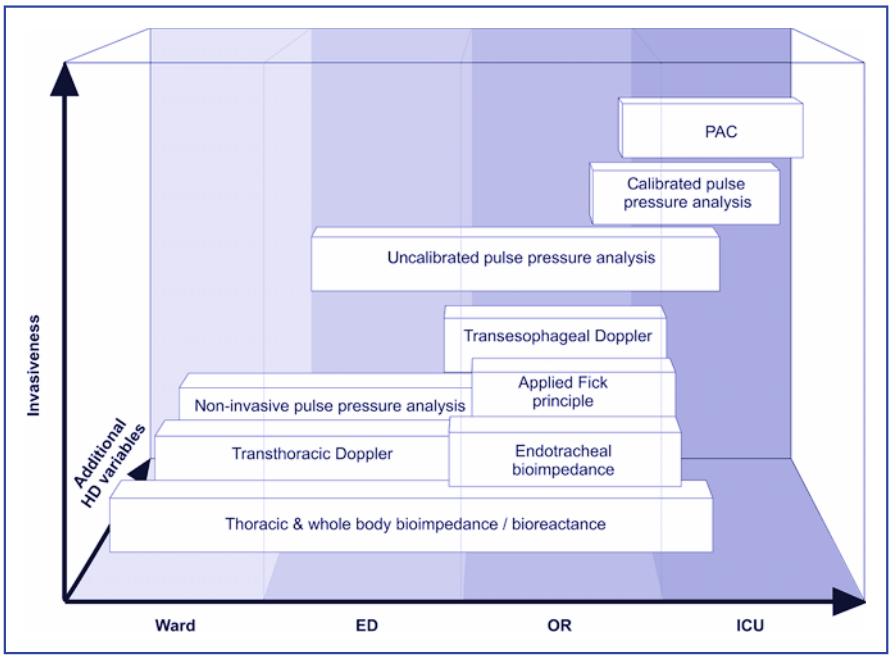

Fig. 2. Integrative concept for the use of cardiac output monitoring devices. ED: emergency department; HD: hemodynamic; ICU: intensive care unit; OR: operating room; PAC: pulmonary artery catheter

instability occur and increased device accuracy or volumetric variables are needed for improved patient management. In the presence of factors that affect the accuracy of all minimally invasive cardiac output monitoring devices, or when pulmonary artery pressure monitoring or right heart failure treatment is required, PAC insertion may be required for patient specific therapy.

Conclusion

Various devices that allow continuous cardiac output measurement in the critically ill patient are commercially available today. Their presence does not completely preclude but does increasingly limit the use of the PAC. A variety of factors (institutional, device related, and patient specific) influence the selection of a cardiac output monitoring device and clinicians need to understand the underlying principles and the inherent limitations of these devices. A selection of these techniques may be used in an integrative approach along a patient pathway. In combination with $ScvO_2$ measurements, the assessment of volumetric preload variables and the functional hemodynamic variables that they provide may obviate the need for a PAC in the treatment of critically ill patients.

References

1. Connors AF Jr, Speroff T, Dawson NV, et al (1996) The effectiveness of right heart catheterization in the initial care of critically ill patients. SUPPORT Investigators. JAMA 276: 889 – 897
2. Harvey S, Stevens K, Harrison D, et al (2006) An evaluation of the clinical and cost-effectiveness of pulmonary artery catheters in patient management in intensive care: a systematic review and a randomised controlled trial. Health Technol Assess 10: 1 – 133
3. Lees N, Hamilton M, Rhodes A (2009) Clinical review: Goal-directed therapy in high risk surgical patients. Crit Care 13: 231
4. Funk D, Sebat F, Kumar A (2009) A systems approach to the early recognition and rapid administration of best practice therapy in sepsis and septic shock. Curr Opin Crit Care 15: 301 – 307
5. Harvey S, Harrison DA, Singer M, et al (2005) Assessment of the clinical effectiveness of pulmonary artery catheters in management of patients in intensive care (PAC-Man): a randomised controlled trial. Lancet 366: 472 – 477
6. Nishikawa T, Dohi S (1993) Errors in the measurement of cardiac output by thermodilution. Can J Anaesth 40: 142 – 153
7. Aranda M, Mihm FG, Garrett S, Mihm MN, Pearl RG (1998) Continuous cardiac output catheters: delay in in vitro response time after controlled flow changes. Anesthesiology 89: 1592 – 1595
8. Leather HA, Vuylsteke A, Bert C, et al (2004) Evaluation of a new continuous cardiac output monitor in off-pump coronary artery surgery. Anaesthesia 59: 385 – 389
9. Hamzaoui O, Monnet X, Richard C, et al (2008) Effects of changes in vascular tone on the agreement between pulse contour and transpulmonary thermodilution cardiac output measurements within an up to 6-hour calibration-free period. Crit Care Med 36: 434 – 440
10. Button D, Weibel L, Reuthebuch O, et al (2007) Clinical evaluation of the FloTrac/Vigileo system and two established continuous cardiac output monitoring devices in patients undergoing cardiac surgery. Br J Anaesth 99: 329 – 336
11. Della Rocca G, Costa MG, Coccia C, et al (2003) Cardiac output monitoring: aortic transpulmonary thermodilution and pulse contour analysis agree with standard thermodilution methods in patients undergoing lung transplantation. Can J Anaesth 50: 707 – 711
12. Cecconi M, Fawcett J, Grounds RM, Rhodes A (2008) A prospective study to evaluate the accuracy of pulse power analysis to monitor cardiac output in critically ill patients. BMC Anesthesiol 8: 3
13. Cecconi M, Dawson D, Grounds RM, Rhodes A (2009) Lithium dilution cardiac output measurement in the critically ill patient: determination of precision of the technique. Intensive Care Med 35: 498 – 504
14. Pearse R, Dawson D, Fawcett J, Rhodes A, Grounds RM, Bennett ED (2005) Early goal-directed therapy after major surgery reduces complications and duration of hospital stay. A randomised, controlled trial [ISRCTN38797445]. Crit Care 9: R687 – 693
15. Mayer J, Boldt J, Poland R, Peterson A, Manecke GR Jr (2009) Continuous arterial pressure waveform-based cardiac output using the FloTrac/Vigileo: a review and meta-analysis. J Cardiothorac Vasc Anesth 23: 401 – 406
16. Senn A, Button D, Zollinger A, Hofer CK (2009): Assessment of cardiac output changes using a modified FloTrac/Vigileo algorithm in cardiac surgery patients. Crit Care 13: R32
17. Camporota L, Beale R (2010) Pitfalls in haemodynamic monitoring based on the arterial pressure waveform. Crit Care 14: 124
18. Mayer J, Boldt J, Mengistu AM, Rohm KD, Suttner S (2010) Goal-directed intraoperative therapy based on autocalibrated arterial pressure waveform analysis reduces hospital stay in high-risk surgical patients: a randomized, controlled trial. Crit Care 14: R18
19. Scolletta S, Romano SM, Biagioli B, Capannini G, Giomarelli P (2005) Pressure recording analytical method (PRAM) for measurement of cardiac output during various haemodynamic states. Br J Anaesth 95: 159 – 165
20. Giomarelli P, Biagioli B, Scolletta S (2004) Cardiac output monitoring by pressure recording analytical method in cardiac surgery. Eur J Cardiothorac Surg 26: 515 – 520
21. Stover JF, Stocker R, Lenherr R, et al (2009) Noninvasive cardiac output and blood pres-

sure monitoring cannot replace an invasive monitoring system in critically ill patients. BMC Anesthesiol 9: 6
22. Lefrant JY, Bruelle P, Aya AG, et al (1998) Training is required to improve the reliability of esophageal Doppler to measure cardiac output in critically ill patients. Intensive Care Med 24: 347 – 352
23. Valtier B, Cholley BP, Belot JP, et al (1998) Noninvasive monitoring of cardiac output in critically ill patients using transesophageal Doppler. Am J Respir Crit Care Med 158: 77 – 83
24. Abbas SM, Hill AG (2008) Systematic review of the literature for the use of oesophageal Doppler monitor for fluid replacement in major abdominal surgery. Anaesthesia 63: 44 – 51
25. Chan JS, Segara D, Nair P (2006) Measurement of cardiac output with a non-invasive continuous wave Doppler device versus the pulmonary artery catheter: a comparative study. Crit Care Resusc 8: 309 – 314
26. Thom O, Taylor DM, Wolfe RE, et al (2009) Comparison of a supra-sternal cardiac output monitor (USCOM) with the pulmonary artery catheter. Br J Anaesth 103: 800 – 804
27. Gueret G, Kiss G, Rossignol B, et al (2006) Cardiac output measurements in off-pump coronary surgery: comparison between NICO and the Swan-Ganz catheter. Eur J Anaesthesiol 23: 848 – 854
28. Tachibana K, Imanaka H, Takeuchi M, Takauchi Y, Miyano H, Nishimura M (2003) Noninvasive cardiac output measurement using partial carbon dioxide rebreathing is less accurate at settings of reduced minute ventilation and when spontaneous breathing is present. Anesthesiology 98: 830 – 837
29. Hofer CK, Buhlmann S, Klaghofer R, Genoni M, Zollinger A (2004) Pulsed dye densitometry with two different sensor types for cardiac output measurement after cardiac surgery: a comparison with the thermodilution technique. Acta Anaesthesiol Scand 48: 653 – 657
30. Ball TR, Culp BC, Patel V, et al (2010) Comparison of the endotracheal cardiac output monitor to thermodilution in cardiac surgery patients. J Cardiothorac Vasc 24: 762 – 766
31. Gujjar AR, Muralidhar K, Banakal S, et al (2008) Non-invasive cardiac output by transthoracic electrical bioimpedence in post-cardiac surgery patients: comparison with thermodilution method. J Clin Monit Comput 22: 175 – 180
32. Squara P, Denjean D, Estagnasie P, Brusset A, Dib JC, Dubois C (2007): Noninvasive cardiac output monitoring (NICOM): a clinical validation. Intensive Care Med 33: 1191 – 1194
33. Raval NY, Squara P, Cleman M, Yalamanchili K, Winklmaier M, Burkhoff D (2008) Multicenter evaluation of noninvasive cardiac output measurement by bioreactance technique. J Clin Monit Comput 22: 113 – 119
34. Boldt J, Lenz M, Kumle B, Papsdorf M (1998) Volume replacement strategies on intensive care units: results from a postal survey. Intensive Care Med 24: 147 – 151
35. Hofer CK, Furrer L, Matter-Ensner S, et al (2005) Volumetric preload measurement by thermodilution: a comparison with transoesophageal echocardiography. Br J Anaesth 94: 748 – 755
36. Kumar A, Anel R, Bunnell E, et al (2004) Pulmonary artery occlusion pressure and central venous pressure fail to predict ventricular filling volume, cardiac performance, or the response to volume infusion in normal subjects. Crit Care Med 32: 691 – 699
37. Goepfert MS, Reuter DA, Akyol D, et al (2007) Goal-directed fluid management reduces vasopressor and catecholamine use in cardiac surgery patients. Intensive Care Med 33: 96 – 103
38. Sakka SG, Klein M, Reinhart K, Meier-Hellmann A (2002) Prognostic value of extravascular lung water in critically ill patients. Chest 122: 2080 – 2086
39. Marik PE, Cavallazzi R, Vasu T, Hirani A (2009) Dynamic changes in arterial waveform derived variables and fluid responsiveness in mechanically ventilated patients: a systematic review of the literature. Crit Care Med 37: 2642 – 2647
40. Marik PE, Baram M, Vahid B (2008) Does central venous pressure predict fluid responsiveness? A systematic review of the literature and the tale of seven mares. Chest 134: 172 – 178
41. Monnet X, Teboul JL (2008) Passive leg raising. Intensive Care Med 34: 659 – 663
42. Marx G, Reinhart K (2006) Venous oximetry. Curr Opin Crit Care 12: 263 – 268

43. Rivers E, Nguyen B, Havstad S, et al (2001) Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med 345: 1368 – 1377
44. Dueck MH, Klimek M, Appenrodt S, Weigand C, Boerner U (2005) Trends but not individual values of central venous oxygen saturation agree with mixed venous oxygen saturation during varying hemodynamic conditions. Anesthesiology 103: 249 – 257

XI Perioperative Medicine

Perioperative Hemodynamic Optimization

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Introduction

Each year, 234 million major surgical procedures are performed worldwide. Despite the overall low risk of death and complications, there is a specific high-risk subgroup, representing over 80 % of postoperative deaths [1]. In the surgical population, poor outcome seems to be determined, among others, by derangements in global oxygen delivery (DO_2) and oxygen consumption (VO_2) derived by a complex interplay between surgical-induced inflammatory response and patient status [2, 3]. Systemic inflammatory response is associated with an increase in oxygen demand [4] that sometimes fails to be matched by an adequate increase of DO_2 promoting hypoperfusion and tissue hypoxia. The consequences of tissue hypoxia are complicated and far reaching and include activation of endothelium, leading to capillary leak, and pro-inflammatory cytokines, leukocyte and complement cascade, enhancing inflammatory status. If this process is left unabated, postoperative complications, which are often fatal, may develop [5, 6]. The strategy of hemodynamic optimization or goal-directed therapy refers to the monitoring and manipulation of physiological hemodynamic parameters by means of therapeutic interventions based mainly on fluids, red blood cells (RBCs) and inotropic drugs aimed at facing the increase in oxygen demand.

In 1988, Shoemaker et al. [7] were the first to perform an interventional trial of perioperative goal-directed therapy aimed at reaching supranormal values of cardiac output and DO_2 based on physiological values previously observed in survivors after surgery [8]. These perfusion-related targets were cardiac index (CI) > 4.5 l/min/m^2, $DO_2 > 600$ ml/min/m^2 and $VO_2 > 170$ ml/min/m^2. Using this approach, mortality was substantially reduced in comparison to standard care, based on targets such as heart rate, arterial blood pressure and central venous pressure (CVP). This study was criticized for several important methodological flaws, such as poorly defined care in the control and intervention groups and a lack of clear randomization procedures. In 1993, Boyd and colleagues [9] performed a randomized controlled trial (RCT) in which the same treatment goals were reached by means of supplemental oxygen, fluid and blood products. A 75 % reduction in mortality was shown in the goal-directed therapy group, associated with fewer postoperative complications. In the following years, while other groups reported favorable results in general surgical patients [10] and trauma patients [11], others failed to show any benefit from goal-directed therapy [12, 13] and the largest multicenter trial to date, comparing conventional and goal-directed therapy in surgical patients, did not find any significant improvement in mortality [13]. This study, however, raises a number of concerns [14]. Although

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the authors claimed that preoperative optimization was performed, in the vast majority of patients the goals were achieved only postoperatively and, unfortunately, the time from catheter insertion to initiation of surgery was not mentioned. Indeed, the time allocated to achieve optimization is crucial, since insertion of a catheter just before the beginning of surgery may not allow sufficient time to achieve hemodynamic optimization, and the catheter might only be used to observe hemodynamic alterations. Moreover, the low rate of attainment of hemodynamic goals contrasts with previous studies and the protocol used to achieve the hemodynamic end-points is not well defined. The authors used fluids and vasoactive agents, but the type and doses of these agents were not specified. It is likely that these elements varied from one institution to another [15]. Moreover, other conflicting results were obtained when goal-directed therapy was performed in critically ill or septic patients with already established organ failure [16, 17].

The first meta-analysis pooling all RCTs on goal-directed therapy and including 1016 surgical and critically ill patients did not demonstrate any significant overall benefit [18]. A further analysis including surgical, trauma and septic patients, and grouping studies according to the timing of goal-directed therapy, reported lower mortality only when optimization treatment was performed before organ failure occurrence [19]. A subsequent meta-analytic study [20], dividing perioperative and critically ill septic patients, showed that mortality was improved only in the perioperative subgroup. The beneficial effect of goal-directed therapy only in surgical patients may rely on the basis that while in the early stage of systemic inflammatory response syndrome it is possible to prevent the deleterious effects of oxygen debt, when the inflammatory process has advanced and oxygen debt is no longer reversible, increasing oxygen transport is no longer effective. Studies in which hemodynamic optimization, applied in the very early stages of severe sepsis or septic shock [21], reduced mortality fit well with this rationale.

Which Hemodynamic Monitoring Tool and Targets For Goal-directed Therapy?

If we accept the concept of preventing and treating tissue oxygen debt, the most important parameters associated with improved survival should relate to oxygen flux. However, a point of debate in the perioperative optimization issue is by how much DO_2 should increase. At the beginning of its history, goal-directed therapy was performed targeting DO_2 and CI to supranormal values that implied an aggressive use of fluids and cathecolamines, carrying potential complications such as acute pulmonary edema, arrhythmias, or mismatch between myocardial oxygen supply and requirements with the risk of myocardial ischemia. Although this has been the most studied endpoint for the resuscitation, it is by no means clear that it is the 'best' target. Some RCTs have set up hemodynamic targets to physiological values, and recently it has been shown that targeting the optimization to physiological values may be as beneficial as adopting supranormal goals [22].

All the original studies on perioperative optimization used the pulmonary artery catheter (PAC) to monitor DO_2, VO_2 and cardiac output. When this technique ran into controversy, the therapies associated with it were also debated,

confounding the tool and the aims. Although goal-directed therapy is still considered synonymous with a PAC, nowadays there are many alternatives.

Current monitoring techniques include Doppler technologies or arterial pressure waveform analysis, measuring changes in stroke volume or cardiac output. These can be used either to predict whether a patient is likely to respond to a volume challenge or to carefully monitor the response to a fluid bolus, thus providing a sophisticated and sensitive mechanism for titrating therapy to complex patients. A meta-analysis of five RCTs of 420 patients undergoing major abdominal surgery showed fewer complications, less requirement for inotropes, faster return of gastrointestinal function, fewer ICU admissions and shorter hospital stay in patients who received esophageal Doppler monitoring for goal-directed fluid administration (i.e., targeting stroke volume and corrected flow-time to maximize cardiac output) [23]. Esophageal Doppler Monitoring is well tolerated, can be used throughout the entire perioperative period and is characterized by high clinical agreement with PAC for monitoring changes in cardiac output [24]. Esophageal Doppler Monitoring provides measurement of corrected flow time that is inversely proportional to systemic vascular resistance (SVR), is sensitive to changes in left ventricular preload and may be a more sensitive indicator of cardiac filling than pulmonary artery occlusion pressure (PAOP) [25].

The LiDCOplus system (LiDCO Ltd, Cambridge, UK) is also well validated and has been successfully used for goal-directed therapy [26]. Other studies have shown that the PiCCO system (PULSION Medical Systems, Munich, Germany) is also a reliable method of cardiac preload assessment and may actually substitute for the PAC in goal-directed therapy [27]. In patients undergoing elective coronary artery bypass grafting (CABG) surgery, Goepfert and colleagues [27] proposed a goal-directed therapy algorithm based on PiCCO and targeting global end-diastolic volume index > 640 ml/m^2 and CI > 2.5 l/min/m^2. Patients benefited from reduced vasopressor and inotrope requirements, reduced duration of mechanical ventilation, and were ready for ICU discharge earlier than the control group. Intraoperative goal-directed therapy using a protocol based on enhanced hemodynamic variables derived by the Flo-Trac/Vigileo device reduced the length of stay in high-risk patients undergoing major abdominal surgery [28].

Recently, central venous oxygen saturation ($ScvO_2$) has been proposed as a useful tool for goal-directed therapy in surgical patients. Donati et al. [29] observed a reduced number of postoperative complications when using arterial oxygen saturation and $ScvO_2$ to titrate fluids and dobutamine to reach an oxygen extraction ratio < 27 % (value shown to be a predictor of survival in high-risk surgical patients) [8]. Other targets suggested to be useful include serum lactate, mixed venous oxygen saturation (SvO_2), and regional measures of DO_2, such as gastric intramucosal pH (pHi) [30]. Further, large, prospective RCTs are needed to clarify whether these new monitoring tools for hemodynamic optimization will provide advantages over PAC.

At the moment there is no 'best tool or target', and the choice of perioperative hemodynamic monitoring for goal-directed therapy should depend on the surgery-related and the patient-related risk. Basically, patients with cardiac morbidity who are undergoing major surgical procedures associated with fluid shifts and hemodynamic stress would benefit most from more invasive monitoring. Therefore, thermodilution methods and/or continuous cardiac output/oxygen transport monitoring should be chosen in major surgery and high-risk/unstable patients

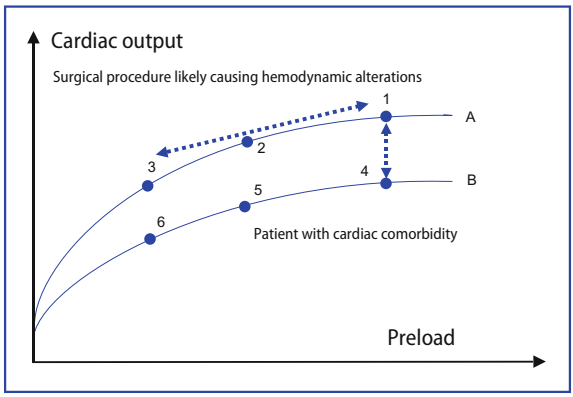

Fig. 1. Potential hemodynamic changes in high-risk, unstable patients undergoing major surgical procedures. Perioperative hemodynamic monitoring for goal-directed therapy should depend on surgery-related and patient-related risk. Patients with cardiac morbidity who are undergoing major surgical procedures associated with fluid shifts and hemodynamic stress may move from point 1 of the Starling curve A either along curve A to point 2 and 3, or shift to point 4 on curve B, or shift to curve B and move to points 5 and 6. Therefore, in major surgery in high-risk/unstable patients, continuous cardiac output/oxygen transport and preload monitoring should be chosen.

(**Fig. 1**), while conventional monitoring or minimally invasive approaches should be used for perioperative optimization of low- to moderate-risk patients [31].

The modular stepwise monitoring concept recently described by Hofer et al. [32] provides an example of a clinical approach to stratification of monitoring levels and targets for therapy. Level I implies that conventional invasive hemodynamic monitoring may be appropriate when a patient presents with predefined values of hemodynamics (heart rate 100 beats/min, mean arterial pressure [MAP] > 65 mmHg, CVP 8–12 mmHg), organ function (lactate 1–2 mmol/l, urine output 1 ml/kg/h) and oxygen transport, such as $ScvO_2$ > 70 % and hemoglobin 8–10 g/dl. The shift to Level II is suggested when the patient fails to improve their organ function following early fluid loading with diuresis < 1 ml/kg/h, lactate > 2 mmol/l and $ScvO_2$ < 70 %. Level II operates less invasive monitoring, namely, transpulmonary thermodilution and continuous $ScvO_2$ targeting CI to more than 2.5 l/min/m^2, global end-diastolic volume index (GEDVI) in the 600–800 ml/m^2 range and extravascular lung water (EVLW) < 7 ml/kg, as well as predictors of fluid responsiveness < 12 %. Level III is recommended in case of left/right heart failure and/or pulmonary hypertension. At this level, a PAC is proposed for CI monitoring in association with PAOP (12–15 mmHg), SvO_2 (> 65 %) and continuous right ventricular end-diastolic volume (110–130 ml/m^2).

XI

How to Achieve the Goals?

The aim of goal-directed therapy is to prevent tissue oxygen debt by maintaining tissue perfusion. Since hypovolemia with consequent hypoperfusion and hypoxia may often coexist with normal values of conventional hemodynamic variables such as MAP, CVP and heart rate, the first and most common step in goal-directed therapy is to ensure that the circulating volume is at an optimal level. Often fluid boluses alone are sufficient to achieve goals of cardiac output and DO_2, and fluid-based goal-directed therapy has been associated with improved outcomes [26, 30, 33, 34]. However, fluid therapy is a double-edge sword, and studies showing benefits from fluid administration seem to conflict with studies

in which patients receiving a perioperative restrictive fluid regimen had fewer postoperative complications than patients receiving a liberal fluid approach [35]. Since the overall volume administered in some goal-directed studies is of a similar amount to the volume administered in both the restricted and the liberal comparative group of fixed-dose studies, the different strategies of fluid loading (goal-directed versus fixed-dose) are hard to compare. Most goal-directed therapy studies with positive outcome had an average positive fluid balance in the goal-directed therapy group of only 500–600 ml [33,34], much less than the difference between restrictive and liberal strategies (almost 2650 ml in a study by Brandstrup et al. [35]). Therefore, a goal-directed therapy group may receive more fluid load than its own control, but less than patients receiving a 'liberal' regimen.

The real major controversy thus seems not to be how much, but how to titrate fluid infusion. A restrictive strategy is based on prefixed volume infusion, regardless of any specific hemodynamic monitoring and target of oxygen debt, and does not consider individual differences, complicating illness, preoperative hydration and duration or severity of surgical insult, all critical factors in determining the amount of fluid infusion. This standardized approach may not be ideal, since some patients may receive too much and others too little fluid, and, interestingly, more postoperative complications can occur even in the 'so-called' restrictive group. A more suitable term than 'restriction' should be 'avoidance of crystalloid excess', which is the key to improving outcomes. Goal-directed therapy and avoidance of crystalloid excess can, therefore, be complementary when a judicious volume of crystalloid is administered (that is, 'restrictive' approach) combined with a stroke volume-targeted amount of colloid ('goal-directed'), depending on the patient and type of surgery. In this context, an individualized, timely fluid 'replacement' therapy, by titration of volume to physiologic flow-related endpoints with appropriate monitoring [36], may be a rational choice during major surgery. Careful crystalloid management, following the 'avoidance of crystalloid excess' principles and accounting for crystalloid needs, is the first important step. Early, simple stroke volume-targeted colloid administration is the second crucial step, guiding both the administration and the pausing of intravenous fluids.

Sometimes, fluids may not be sufficient to achieve hemodynamic goals and, in addition, a positive inotrope or vasodilator is necessary. Lobo and co-workers [37] compared the use of fluids and dobutamine with fluids alone to achieve DO_2 > 600 ml/min/m^2 in high-risk surgical patients. The use of fluid and dobutamine produced better postoperative outcomes with fewer cardiovascular complications than the fluid group. Those patients given dobutamine were more likely to achieve the goals. Dopexamine is a positive inotrope and peripheral vasodilator that improves microcirculatory flow and splanchnic perfusion and oxygenation, and may reduce inflammation secondary to tissue hypoxia and translocation of bacterial products or endotoxin. A recent meta-analysis demonstrated that low-dose dopexamine infusion (1 μg/kg/min) was associated with survival benefit and reduction in hospital stay, while a survival benefit was not seen with higher dosage [38]. Therefore, evidence shows that use of dobutamine or dopexamine after fluid loading may confer significant benefits. It is not possible to state whether the effects of fluid and inotropes are synergistic or if the beneficial effect of one intervention counteracts the adverse effect of the other. A likely explanation may be that in patients with a reduced physiologic reserve, fluids alone may not be sufficient to optimize hemodynamic status and that the additional administration of inotropic drugs is warranted in order to increase DO_2 and counteract systemic hypoperfusion.

What is the Optimal Timing For Goal-directed Therapy?

The timing of commencement of optimization is another point of debate. Goal-directed therapy before surgery has been shown to be effective, but difficult to institute because of resource constraints. Shoemaker et al. [4] observed that if flow and oxygen debts developing at the time of surgical stress are paid back soon after, i.e., within 8 hours, the incidence of postoperative complications may equally decrease, but if they are never paid back, cell dysfunction and death occur. Since there is increasing evidence that both intra- and postoperative optimization work well, these are alternative strategies when preoptimization is not possible, allowing preoperative hemodynamic monitoring to be avoided, difficult to pursue if resources are limited or if time prior to surgery is not sufficient.

Who Should Benefit from Goal-directed Therapy?

Three meta-analyses [19, 20, 22] observed a lower mortality when optimization treatment was perioperatively performed in surgical patients. However, in one meta-analysis [19] formal quality RCT analysis and heterogeneity tests were not performed, while in the others [20, 22] significant statistical heterogeneity and inconsistency were found. Among others, one explanation of this result may derive from variability of study populations. Some RCTs have enrolled patients defined as 'high-risk' [7, 9, 10, 14, 26, 29] on the basis of a perioperative scoring system (POSSUM) or specific risk criteria including age, pre-operative morbidity, ASA classification, extension and duration of surgery, blood loss, or need of emergent surgery. Other studies have focused on elective or specific (e.g., cardiac, abdominal) types of surgery, or have explicitly excluded high risk patients. Therefore, the extreme variability in baseline mortality (ranging from 0 to 50 %) may explain the high statistical heterogeneity of meta-analytic results.

Although high-risk patients represent a small percentage of the surgical population, over 80 % of postoperative deaths occur in this subgroup of patients [1]. Clinical criteria for high-risk surgical patients, i.e., criteria identifying patients at risk for organ failure rather than those who have already developed complications, are defined as patient-related (severe cardiac or respiratory illness resulting in severe functional limitation, age over 70 years with moderate functional limitation of one or more organ systems, expected blood loss > 2.5 l, severe sepsis, shock or severe hypovolemia of any origin, respiratory failure, acute gastrointestinal failure [e.g., intraabdominal compartment syndrome, pancreatitis, perforated viscus, gastrointestinal bleeding], acute renal failure) and surgery-related (extensive non-cardiac surgery [e.g., carcinoma involving bowel anastomosis, pneumonectomy, complex trauma and orthopedic procedures], major/combined cardiovascular surgery [e.g., aortic aneurysm, combined valve repair, coronary surgery and carotid endarterectomy], surgery prolonged > 2 hours, emergency surgery) [31]. These patients are likely to be unable to spontaneously increase cardiac output to the required level, are more prone to hypoperfusion-related complications, and would benefit most from goal-directed therapy.

However, how much higher should the mortality risk be? A high-risk surgical patient can be defined as a patient with an individual mortality risk greater than 5 % or undergoing a procedure carrying a 5 % mortality [39]. The largest RCT comparing conventional and goal-directed therapy in explicitly defined high-risk

surgical patients with a control mortality of nearly 8 % [14] did not find any significant improvement in mortality, whereas goal-directed therapy was shown to be effective when perioperative optimization was performed in patients with a control group mortality > 20 % [19]. The extent of patient risk evaluated as control group mortality may, therefore, be the key factor determining the effectiveness of goal-directed therapy.

In **Figure 2**, a subgroup analysis, based on control mortality rates was applied to all RCTs on perioperative goal-directed therapy. The overall statistical heterogeneity and inconsistency is confirmed, but when analyzing subgroups this result

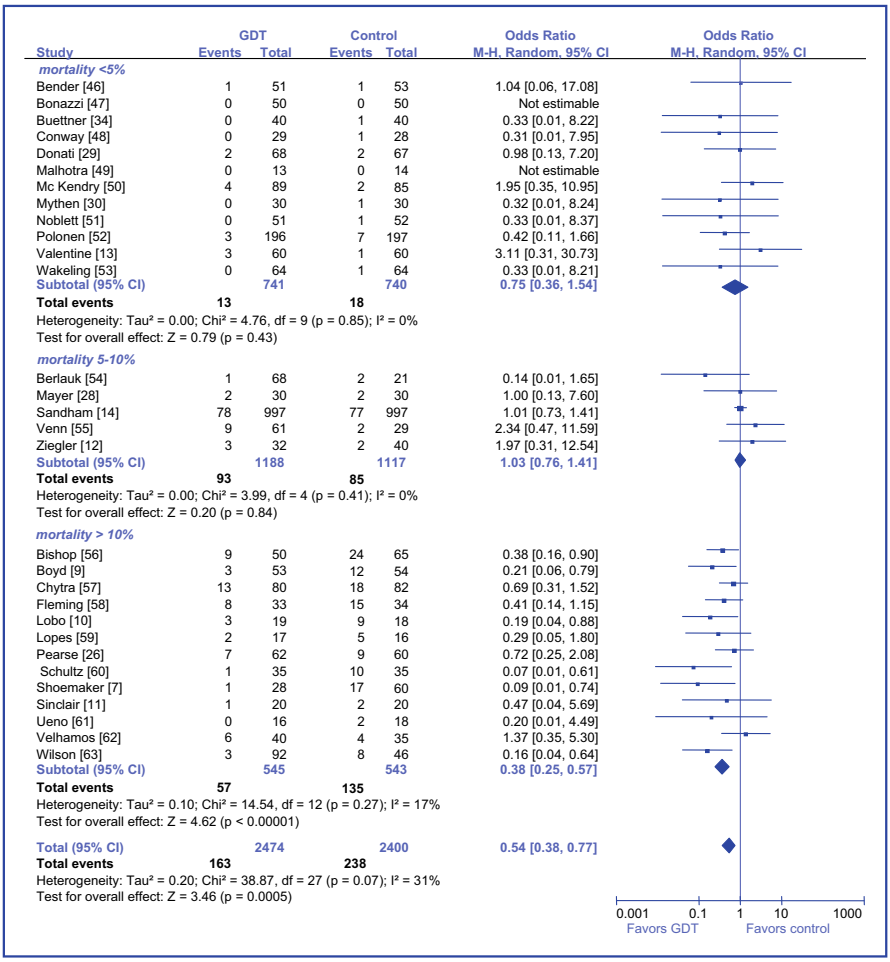

Fig. 2. Rates of postoperative mortality for randomized controlled trials on perioperative goal-directed therapy (GDT) with odds ratios (ORs) and 95 % confidence intervals (CIs). The studies were divided into three subgroups defined on the basis of mortality of control group (< 5 %, 5 – 10 %, > 10 %). The pooled OR and 95 % CI are shown as the total and subtotals. The size of the box at the point estimate of the OR gives a visual representation of the 'weighting' of the study. The diamond represents the point estimate of the pooled OR and the length of the diamond is proportional to the CI.

vanishes, indicating adequate study grouping. Moreover, it is evident that goal-directed therapy seems really effective only in studies with a control mortality > 10 %. In the subgroups of lower risk (0–5 % and 5–10 %) patients no significant difference in mortality is observed. Therefore, these patients may not be ill enough to clearly benefit from hemodynamic improvement, and the risk to benefit ratio of perioperative optimization in such patients should be taken into account.

Goal-directed Therapy and Organ Function

Strategies to maintain DO_2 and minimize splanchnic hypoperfusion have been advocated to improve postoperative morbidity [40]. Gastrointestinal (GI) dysfunction, ranging from mild complications (e.g., postoperative ileus and inability to tolerate enteral nutrition) to more severe surgical complications (ischemic injury), is a very common complication after major surgery and is associated with prolonged hospital stay, high mortality, and substantial costs and resource consumption [41]. Since selective vasoconstriction of mesenteric arterioles, mediated primarily by the renin–angiotensin system, contributes to the maintenance of systemic arterial pressure and the perfusion of non-mesenteric organs, episodes of reduced splanchnic perfusion and oxygenation, related to intraoperative hypotension or occult hypovolemia, are frequent during major surgery [6, 30]. This response often outlasts the period of the hypovolemic insult or low-flow state, promoting abdominal organ damage. Strategies to maintain DO_2 and minimize splanchnic hypoperfusion have been advocated to improve postoperative morbidity [40] and a recent meta-analysis of 16 RCTs (3410 patients) found that both major and minor GI complications were significantly reduced by perioperative goal-directed therapy [42].

Another meta-analysis focused on the protective effect of perioperative goal-directed therapy on kidney function [22]. Postoperative acute kidney injury (AKI) is one of the most serious complications in surgical patients, and markedly increases perioperative morbidity and mortality both in cardiac [43] and non-cardiac surgery [44]. Most cases of postoperative AKI are related to episodes of renal hypoperfusion as a consequence of systemic hypotension, hypovolemia, decreased circulating blood volume, prolonged cardiopulmonary bypass (CPB), and cardiac dysfunction. The kidney normally receives 20–25 % of total cardiac output resulting in the highest tissue perfusion in the body and the medullary portion of the nephrons is especially at risk of hypoperfusion, being physiologically characterized by low blood flow, and high oxygen demand (due to tubular transport activity) and extraction (approaching 90 %). Decreased cardiac output not only directly causes renal hypoperfusion, but also activates neuro-humoral responses which cause renal vasoconstriction. Maintenance of adequate cardiac output under hemodynamic monitoring may reduce the risk of postoperative renal injury by assuring adequate renal blood flow and reducing renal vasoconstriction. The results of this meta-analysis [22], including 20 studies (4220 patients), substantiate this concept, showing that postoperative AKI was significantly reduced by goal-directed therapy. The occurrence of renal dysfunction was reduced when treatment started preoperatively, intraoperatively or postoperatively, when performed in high-risk patients and was obtained by fluids and inotropes. At the moment, perioperative goal-directed therapy is the only evidence-based strategy shown to reduce kidney injury in non-cardiac postoperative patients [45].

Conclusion

Although all RCTs dealing with perioperative goal-directed therapy have the same starting point, i.e., fluid loading, and the same end point, i.e., increasing DO_2, they vary in their approaches to the targets they aim to achieve, the monitoring tools, the timing and the modalities of interventions, and the type of patients enrolled. Notwithstanding this variability, goal-directed therapy has been shown to protect organs particularly at risk of perioperative hypoperfusion, to decrease the incidence of postoperative complications, and to improve survival after major surgery. Since it is highly unlikely that 'one goal fits all', it seems prudent to individualize each patient's target based on his/her specific physiologic profile. Perioperative goal-directed therapy should be early, adequate and, above all, individualized for every patient; therefore, the key question to be addressed in future studies is how to identify the correct hemodynamic monitoring and therapy on the basis of patient- and surgery-related risk category. Despite unfavorable results in patients with advanced sepsis, it is likely that high-risk patients will benefit most from such approaches. A major and more realistic limitation to the adoption of goal-directed therapy is that of limited critical care resources. Many units are unable to admit high-risk patients pre-operatively to institute goal-directed therapy and, similarly, many high-risk patients do not return to a critical care environment following surgery. Improving the outcome of high-risk surgical populations by relatively simple means would be highly desirable from a purely clinical standpoint and also in terms of appropriate resource allocation. Therefore, quality improvement efforts should be focused on prompt identification and treatment of this often underestimated category of surgical patients.

References

1. Jhanji S, Thomas B, Ely A, et al (2008) Mortality and utilisation of critical care resources amongst high-risk surgical patients in a large NHS trust. Anaesthesia 63: 695–700
2. Pearse R, Dawson D, Fawcett J, Rhodes A, Grounds RM, Bennett ED (2005) Changes in central venous saturation after major surgery, and association with outcome. Crit Care 9: R694-R699
3. Shoemaker WC, Appel PL, Kram HB (1992) Role of oxygen debt in the development of organ failure, sepsis and death in high-risk surgical patients. Chest 102: 208–215
4. Shoemaker WC, Appel PL, Kram HB (1993) Haemodynamic and oxygen transport responses in survivors and nonsurvivors of high-risk surgery. Crit Care Med 21: 977–990
5. Peerless JR, Alexander JJ, Pinchak AC, et al (1998) Oxygen delivery is an important predictor of outcome in patients with ruptured abdominal aortic aneurysms. Ann Surg 227: 726–732
6. Kusano C, Baba M, Takao S, et al (1997) Oxygen delivery as a factor in the development of fatal postoperative complications after oesophagectomy. Br J Surg 84: 252–257
7. Shoemaker WC, Appel PL, Kram HB, et al (1988) Prospective trial of supranormal values of survivors as therapeutic goals in high-risk surgical patients. Chest 94: 1176–1186
8. Bland RD, Shoemaker WC, Abraham E, Cobo JC (1985) Haemodynamic and oxygen transport patterns in surviving and nonsurviving patients. Crit Care Med 13: 85–90
9. Boyd O, Grounds RM, Bennett ED (1993) A randomized clinical trial of the effect of deliberate perioperative increase of oxygen delivery on mortality in high-risk surgical patients. JAMA 270: 2699–2707
10. Lobo SM, Salgado PF, Castillo VG, et al (2000) Effects of maximising oxygen delivery on morbidity and mortality in high-risk surgical patients. Crit Care Med 10: 3396–3404
11. Sinclair S, James S, Singer M (1997) Intraoperative intravascular volume optimisation and length of hospital stay after repair of proximal femoral fracture: randomised controlled trial. BMJ 315: 909–912

12. Ziegler DW, Wright JG, Choban PS, Flancbaum L (1997) A prospective randomized trial of preoperative 'optimization' of cardiac function in patients undergoing elective peripheral vascular surgery. Surgery 122: 584–592.
13. Valentine RJ, Duke ML, Inman MH, et al (1998) Effectiveness of pulmonary artery catheters in aortic surgery: a randomized trial. J Vasc Surg 27: 203–211
14. Sandham JD, Hull RD, Brant RF, et al for the Canadian Critical Care Trials Group (2003) A randomized controlled trial of the use of pulmonary artery catheters in high risk surgical patients. N Engl J Med 348: 5–14
15. De Backer D, Jacques Creteur J, Vincent JL (2003) Perioperative optimization and right heart catheterization: what technique in which patient? Crit Care 7: 201–202
16. Hayes TA, Timmins AC, Yau EH, et al (1994) Elevation of systemic oxygen delivery in the treatment of critically ill patients. N Engl J Med 330: 1717–1722
17. Gattinoni L, Brazzi L, Pelosi P, et al (1995) A trial of goal-oriented hemodynamic therapy in critically ill patients. SvO_2 Collaborative Group. N Engl J Med 333: 1025–1032
18. Heyland DK, Cook DJ, King D, Kernerman P, Brun-Buisson (1996) Maximizing oxygen delivery in critically ill patients: a methodologic appraisal of the evidence. Crit Care Med 24: 517–524
19. Kern JW, Shoemaker WC (2002) Meta-analysis of hemodynamic optimization in high-risk patient. Crit Care Med 30: 1686–1692
20. Poeze M, Greve JWM, Ramsay G (2005) Meta-analysis of hemodynamic optimization: relationship to methodological quality. Crit Care 9: R771-R779
21. Rivers E, Nguyen B, Havstad S, et al (2001) Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med 345: 1368–1377
22. Brienza N, Giglio MT, Marucci M, Fiore T (2009) Does perioperative hemodynamic optimization protect renal function in surgical patients? A meta-analytic study. Crit Care Med 37: 2079–2090
23. Abbas SM, Hill AG (2008) Systematic review of the literature for the use of oesophageal Doppler monitor for fluid replacement in major abdominal surgery. Anaesthesia 63: 44–51
24. Dark PM, Singer M (2004) The validity of trans-oesophageal Doppler ultrasonography as a measure of cardiac output in critically ill adults. Intensive Care Med 30: 2060–2066
25. DiCorte CJ, Latham P, Greilich PE, Cooley MV, Grayburn PA, Jessen ME (2000) Esophageal Doppler monitor determinations of cardiac output and preload during cardiac operations. Ann Thorac Surg 69: 1782–1786
26. Pearse R, Dawson D, Fawcett J, Rhodes A, Grounds RM, Bennett ED (2005) Early goal-directed therapy after major surgery reduces complications and duration of hospital stay. A randomised, controlled trial [ISRCTN38797445]. Crit Care 9: R687-R693
27. Goepfert MSG, Ruter DA, Akyol DA, Lamm P, Kilger E, Goetz AE (2007) Goal-directed fluid management reduces vasopressor and catecholamine use in cardiac surgery patients. Intensive Care Med 33: 96–103
28. Mayer J, Boldt J, Mengistu AM, Röhm KD, Suttner S (2010) Goal-directed intraoperative therapy based on autocalibrated arterial pressure waveform analysis reduces hospital stay in high-risk surgical patients: a randomized, controlled trial. Crit Care 14: R18
29. Donati A, Loggi S, Preiser JC, et al (2007) Goal-directed intraoperative therapy reduces morbidity and length of hospital stay in high-risk surgical patients. Chest 132: 1817–1824
30. Mythen MG, Webb A (1995) Perioperative plasma volume expansion reduces the incidence of gut mucosal hypoperfusion during cardiac surgery. Arch Surg 130: 423–429
31. Kirov MY, Kuzkov VV, Molnar Z (2010) Perioperative haemodynamic therapy. Curr Opin Crit Care 16: 384–392
32. Hofer CK, Cecconi M, Marx G, Della Rocca G (2009) Minimally invasive monitoring. Eur J Anaesth 26: 996–1002
33. Gan TJ, Soppitt A, Maroof M, et al (2002) Goal directed intraoperative fluid administration reduces length of hospital stay after major surgery. Anesthesiology 97: 820–826
34. Buettner M, Schummer W, Huettemann E, et al (2008) Influence of systolic pressure-variation-guided intraoperative fluid management on organ function and oxygen transport. Br J Anaesth 101: 194–199
35. Brandstrup B, Tønnesen H, Beier-Holgersen R, et al (2003) Effects of intravenous fluid

restriction on postoperative complications: comparison of two perioperative fluid regimens – a randomized assessor-blinded multicenter trial. Ann Surg 238: 641 – 648
36. Chappell D, Jacob M, Hofmann-Kiefer K, Conzen P, Rehm M (2008) A rational approach to perioperative fluid management. Anesthesiology 109: 723 – 740
37. Lobo SM, Lobo FR, Polachini CA, et al (2006) Prospective, randomized trial comparing fluids and dobutamine optimization of oxygen delivery in high-risk surgical patients [ISRCTN42445141]. Crit Care 10: R72
38. Pearse RM, Belsey JD, Cole JN, Bennett ED (2008) Effect of dopexamine infusion on mortality following major surgery: individual patient data meta-regression analysis of published clinical trials. Crit Care Med 36: 1323 – 1399
39. Boyd O, Jackson N (2005) Clinical review: how is risk defined in high-risk surgical patient management? Crit Care 9: 390 – 396
40. Davies SJ, Wilson RJT (2004) Preoperative optimization of high risk surgical patient. Br J Anaesth 93: 121 – 128
41. Lang M, Niskanen M, Miettinen P, Alhava E, Takala J (2001) Outcome and resource utilization in gastroenterological surgery. Br J Surg 88: 1006 – 1014
42. Giglio MT, Marucci M, Testini M, Brienza N (2009) Goal-directed haemodynamic therapy and gastrointestinal complications in major surgery: a meta-analysis of randomized controlled trials. Br J Anaesth 103: 637 – 646
43. Lassnigg A, Schmid ER, Hiesmayr M, et al (2008) Impact of minimal increases in serum creatinine on outcome in patients after cardiothoracic surgery: Do we have to revise current definitions of acute renal failure? Crit Care Med 36: 1129 – 1137
44. Kheterpal S, Tremper KK, Englesbe MJ, et al (2007) Predictors of postoperative acute renal failure after non cardiac surgery in patients with previously normal renal function. Anesthesiology107: 892 – 902
45. Brienza N, Giglio MT, Marucci M (2010) Preventing acute kidney injury after non-cardiac surgery. Curr Opin Crit Care 16: 353 – 358
46. Bender JS, Smith-Meek MA, Jones CE (1997) Routine pulmonary artery catheterization does not reduce morbidity and mortality of elective vascular surgery: results of a prospective, randomized trial. Ann Surg 226: 229 – 236
47. Bonazzi M, Gentile F, Biasi GM, et al (2002) Impact of perioperative haemodynamic monitoring on cardiac morbidity after major vascular surgery in low risk patients. A randomised pilot trial. Eur J Vasc Endovasc Surg 23: 445 – 451
48. Conway DH, Mayall R, Abdul-Latif MS; Gilligan S, Tackaberry C (2002) Randomized controlled clinical trial investigating the influence of intravenous fluid titration using oesophageal Doppler monitoring during bowel surgery. Anaesthesia 57: 845 – 849
49. Malhotra PK, Kakani M, Chowdhury U, et al (2008) Early goal-directed therapy in moderate to high-riosk cardiac surgery patients. Ann Card Anaesth 11: 27 – 34
50. McKendry M, McGloin H, Saberi D, Caudwell L, Brady AR, Singer M (2004) Randomised controlled trial assessing the impact of a nurse delivered, flow monitored protocol for optimisation of circulatory status after cardiac surgery. BMJ 329: 258
51. Noblett SE, Snowden CP, Shenton BK, Horgan AF (2006) Randomized clinical trial assessing the effect of Doppler-optimized fluid management on outcome after elective colorectal resection. Br J Surg 93: 1069 – 1076
52. Polonen P, Ruokonen E, Hippelainen M, et al (2000) A prospective, randomized study of goal-oriented hemodynamic therapy in cardiac surgical patients. Anesth Analg 90: 1052 – 1059
53. Wakeling HG, McFall MR, Jenkins CS, et al (2005) Intraoperative oesophageal Doppler guided fluid management shortens postoperative hospital stay after major bowel surgery. Br J Anaesth 95: 634 – 642
54. Berlauk JF, Abrams JH, Gilmour IJ, et al (1991) Preoperative optimization of cardiovascular hemodynamics improves outcome in peripheral vascular surgery: a prospective, randomized clinical trial. Ann Surg 214: 289 – 299
55. Venn R, Steele A, Richardson P, et al (2002) Randomized controlled trial to investigate influence of the fluid challenge on duration of hospital stay and perioperative morbidity in patients with hip fractures. Br J Anaesth 88: 65 – 71
56. Bishop MH, Shoemaker WC, Appel P, et al (1992) Prospective, randomized trial of survi-

vor values of cardiac index, oxygen delivery, and oxygen consumption as resuscitation endpoints in severe trauma. Arch Surg 127: 1175–1179
57. Chytra I, Pradl R, Bosman R, Pelnár P, Kasal E, Zidková A (2007) Esophageal Doppler-guided fluid management decreases blood lactate levels in multiple-trauma patients: a randomized controlled trial. Crit Care 11: R24
58. Fleming A, Bishop M, Shoemaker W, et al (1992) Prospective trial of supranormal values as goals of resuscitation in severe trauma. Arch Surg 27: 1175–1179
59. Lopes M, Oliveira M, Pereira V, Lemos IP, Auler JO Jr, Michard F (2007) Goal-directed fluid management based on pulse pressure variation monitoring during high-risk surgery: a pilot randomized controlled trial. Crit Care 11: R100
60. Schultz RJ, Whitfield GF, LaMura JJ, et al (1985) The role of physiologic monitoring in patients with fractures of the hip. J Trauma 25: 309–316
61. Ueno S, Tanabe G, Yamada H, et al (1998) Response of patients with cirrhosis who have undergone partial hepatectomy to treatment aimed at achieving supranormal oxygen delivery and consumption. Surgery 123: 278–286
62. Velmahos GC, Demetriades D, Shoemaker WC, et al (2000) Endpoints of resuscitation of critically injured patients: normal or supranormal? A prospective randomized trial. Ann Surg 232: 409–418
63. Wilson J, Woods I, Fawcett J, et al (1999) Reducing the risk of major elective surgery: Randomised controlled trial of preoperative optimisation of oxygen delivery. BMJ 318: 1099–1103

Perioperative Myocardial Ischemia/reperfusion Injury: Pathophysiology and Treatment

S.G. De Hert and P.F. Wouters

Introduction

When blood flow through the coronary circulation is interrupted, myocardial ischemia and ultimately cell death will occur. Therefore, prompt restoration of blood flow is necessary in order to prevent the development of irreversible myocardial cell dysfunction. However, with restoration of the coronary blood flow to the ischemic area, transient myocardial dysfunction may occur. This phenomenon is known as reperfusion injury and may manifest as arrhythmias, reversible contractile dysfunction (myocardial stunning), endothelial dysfunction, and ultimately irreversible reperfusion injury with myocardial cell death. Therefore, treatment of myocardial ischemia should not only include restoration of the coronary circulation but also the application of measures that limit the extent of the reperfusion injury.

Pathophysiology of Ischemia/reperfusion Injury

The mechanisms involved in the pathogenesis of reperfusion injury are still not fully elucidated. Although the major metabolic abnormality in the stunned myocardium is a reduction of the adenosine triphosphate (ATP) concentration in the cells, ATP depletion as such may not play a major causal role in the development of reperfusion injury. Instead, release of reactive oxygen species (ROS) and the disruption of normal intracellular calcium homeostasis appear to be the major mechanisms involved in the pathogenesis of reperfusion injury. The key component in the development of ischemia/reperfusion injury seems to be the opening of a non-specific pore in the inner mitochondrial membrane, the mitochondrial permeability transition pore (MPTP). In normal conditions this pore is closed, but in conditions of stress, such as reperfusion of the heart after a period of ischemia, the MPTP will open. When this occurs, the mitochondria loose their ATP generating capacity, resulting in loss of ionic homeostasis and ultimately necrotic cell death. Transient opening and subsequent closure of the MPTP may also occur leading to the release of cytochrome c and other pro-apoptotic molecules that initiate the apoptotic cascade [1–3] (**Fig. 1**).

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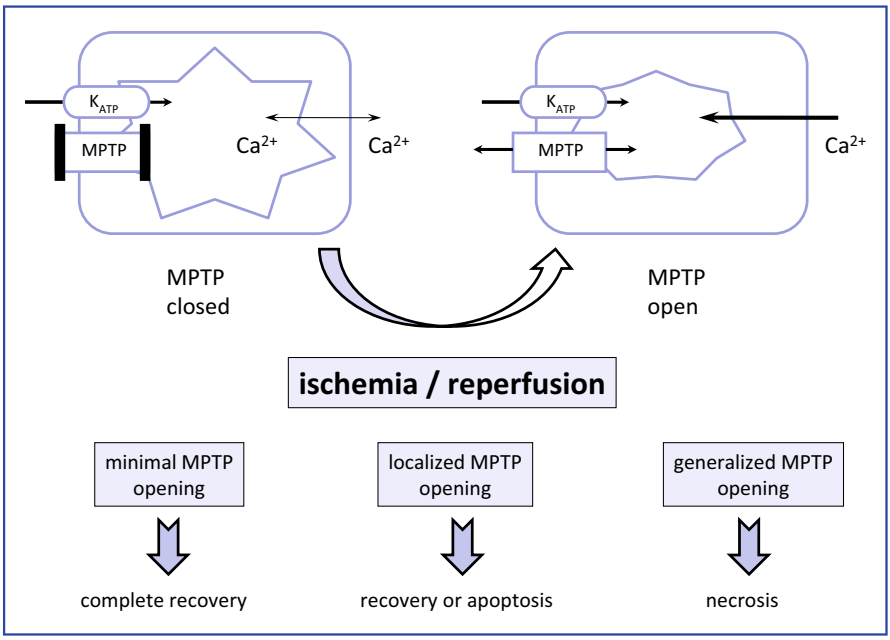

Fig. 1. Schematic representation of the presumed role of the mitochondrial permeability transition pore (MPTP) in the development of ischemia/reperfusion injury. During ischemia/reperfusion injury, cytosolic Ca^{2+} concentration increases with accumulation of inorganic phosphate and reactive oxygen species. This is accompanied by swelling of the intermembrane space, with subsequent shrinkage of the mitochondrial matrix. The MPTP opens and, depending on the extent of MPTP opening, this may ultimately lead to cell death.

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Treatment of Ischemia/reperfusion Injury

Based on the pathophysiology of ischemia/reperfusion injury, the application of potential protective measures can be subdivided into three phases: Measures taken before the period of myocardial ischemia, measures during the ischemic period, and measures instituted after the ischemic period.

Traditionally, the maintenance of a favorable myocardial oxygen balance has been the cornerstone of perioperative myocardial protective strategies. Although this is still true, there is now increasing experimental and clinical evidence that other protective mechanisms, such as preconditioning (protective measures *before* the occurrence of myocardial ischemia) and postconditioning (protective measures *after* the occurrence of myocardial ischemia), may play an important role [4].

Myocardial Oxygen Balance

The intimate relationship between the determinants of myocardial oxygen supply and demand and the occurrence of myocardial ischemia has resulted in the identification of a number of therapeutic approaches that may help in the prevention of perioperative myocardial ischemia. The ultimate goal of such treatment is to reduce the oxygen demand of the myocardium at risk while simultaneously main-

taining or increasing the oxygen supply to this tissue. Myocardial oxygen demand is dependent on heart rate, myocardial contractility and ventricular loading conditions. Myocardial oxygen supply depends on the adequacy with which the blood is able to provide sufficient oxygen to the different regions of the ventricles. To date, β-blocking therapy has been most extensively studied with regard to its potential protective action against the occurrence of perioperative myocardial ischemia. Proposed mechanisms for this protective action include a decrease in myocardial oxygen demand secondary to lower heart rates and a decrease in myocardial contractility, antiarrhythmic effects, coronary plaque-stabilizing effects, anti-inflammatory effects, a shift in energy metabolism, and anti-renin-angiotensin effects [5]. Although several clinical studies have suggested reduced postoperative cardiac morbidity and mortality in the presence of perioperative β-blocking therapy, others have failed to confirm these findings (reviewed in [6]). Based on the recently available data, the ACC/AHA has re-evaluated the recommendations and published an update on the perioperative use of β-blockers [7]. A class I recommendation for the use of perioperative β-blocking therapy is now only given for those patients already receiving β-blockers and in patients undergoing vascular surgery who are at high cardiac risk because of cardiac ischemia on stress testing.

Another type of drug that is receiving wide attention with regard to a potential myocardial protective effect in the perioperative period is statins. Proposed mechanisms for their action include anti-inflammatory and antithrombotic effects, scavenging of ROS, and decreased endothelial cell apoptosis [8].

Protection before Ischemia: Preconditioning

Ischemic preconditioning is a rapid adaptive response to a brief ischemic insult, which slows the rate of cell death and extent of cell dysfunction during a subsequent, prolonged period of ischemia. The protective effect offered by ischemic preconditioning can be divided into two phases: The early phase occurs immediately and induces strong protection but has a limited duration of 1 to 2 hours, whereas the late phase occurs about 24 hours after the initial stimulus, induces less protection, but lasts for as long as 3 days. In addition, this protective action may be present when the stimulus is applied early before the ischemic insult (*early* preconditioning) but may also be active when the preconditioning stimulus has been applied some hours before the actual ischemic insult (*late* preconditioning). Recent data indicate that an ischemic preconditioning stimulus at the level of other organ systems may also have a protective effect at the level of the ischemic myocardium (*remote* preconditioning). A detailed discussion on the mechanisms involved in the phenomenon of preconditioning is beyond the scope of this article and the reader is referred to published reviews on the subject [9–12].

Although ischemic preconditioning has been applied as a therapeutic strategy to limit the extent of ischemia/reperfusion injury in the setting of coronary angioplasty and during coronary surgery, the fact that an additional ischemic burden is applied to an already jeopardized heart has limited its widespread use [13–16].

Ischemic preconditioning can be modulated with pharmacological agents that block or stimulate certain steps in the intracellular cascade of events. The use of such agents might help to mimic the beneficial effects of the ischemic precondition without the drawback of imposing an additional ischemic burden to the

heart. However, the clinical application of this pharmacological preconditioning is hampered by the side-effects of the compounds tested. During recent years, experimental and clinical studies have shown that volatile anesthetics but also opioids demonstrate such pharmacological preconditioning effects. The mechanisms involved in anesthetic preconditioning closely resemble those involved in ischemic preconditioning [10–12].

Protection during Ischemia

Perioperative cardioprotective strategies aim to limit the extent and the consequences of myocardial ischemia/reperfusion injury. The mechanisms behind the ischemia/reperfusion injury are numerous and may be linked. The three main factors involved, however, are free radical formation, calcium overload, and impairment of the coronary vasculature. Protective strategies aim to target one or more of these underlying mechanisms. These include strategies to preserve or replenish myocardial high energy phosphate stores, strategies to modulate electrochemical intracellular gradients, free radical oxygen scavengers and/or antioxidants, inhibitors of the complement systems and neutrophil activation, and many others [17–19]. Whereas most of these approaches (adenosine modulators, cardioplegia solution adjuvants, Na^+/H^+ exchange inhibitors, K_{ATP} channel openers, anti-apopototic agents, and many other drugs with proven or anticipated effects on the complement–inflammation pathways) have been shown to be effective in some experimental and even observational clinical settings, none of them has been unequivocally proven to demonstrate a clinically relevant protective action. Of interest, anesthetic agents have also been claimed to have a direct protective action when administered during ischemia [11, 12].

Protection after Ischemia – during Reperfusion: Postconditioning

After a transient decrease or interruption in blood flow, the subsequent injury results from two components: The direct damage occurring during the ischemia and the subsequent damage related to the reperfusion. Indeed, the restoration of blood flow induces a second series of harmful events that produce additional injury. The goal of protection at this stage is to reduce or prohibit the metabolic, functional and structural changes that occur after restoration of coronary perfusion, by modification of the reperfusion conditions [20].

Targeting the Mitochondrial Permeability Transition Pore

Opening of the MPTP has a pivotal role in the development of ischemia/reperfusion injury. Consequently, targeting the MPTP may attenuate the extent of ischemia/reperfusion injury. In a pilot trial in patients, Piot et al. administered cyclosporine, which inhibits the opening of the MPTP, at the time of percutaneous coronary intervention for acute myocardial infarction. The release of creatine kinase, but not of troponin I, was significantly reduced in the cyclosporine group as compared with the control group. On day 5, the absolute mass of the area of infarcted tissue was significantly reduced in the cyclosporine group compared with the control group [21].

Cardioprotective Strategies in Clinical Practice

The major obstacle to translating experimental observations to a clinical setting is that myocardial ischemia has to be present in a predictable and reproducible manner. This is possibly one of the reasons why promising therapeutic strategies in experimental set-ups did not make it in clinical practice. This is also the reason why studies on clinical applications of cardioprotective strategies are mainly performed in the setting of coronary revascularization because this allows for a more or less standardized ischemic insult.

Among the agents that have been most widely studied in recent years with regard to their cardioprotective properties in the perioperative setting are the volatile anesthetic agents. Experimental data have demonstrated that volatile anesthetic agents confer myocardial protection against ischemia/reperfusion injury by a preconditioning and a postconditioning effect but also by a direct effect during ischemia (for a review on the subject see references [11, 12, 22, 23]. The application of this protective strategy in the clinical setting, however, was associated with less straightforward effects. The first studies that were performed consisted of a protocol where the anesthetic agent was administered before the ischemic episode, as a preconditioning protocol. Highly variable results were obtained with regard to the extent of the cardioprotective effects. Part of the variability between studies can be attributed to differences in protocols, such as choice of the anesthetic agent, duration of administration, inclusion of a washout period, etc. [24] Taken together, it would appear that none of these preconditioning studies, although suggesting some protective action on either a biochemical or a functional variable, unequivocally demonstrated that the use of a volatile anesthetic regimen resulted in a clinical benefit for the patients.

The absence of clinically straightforward data from anesthetic preconditioning studies initiated the question whether the choice of the anesthetic regimen during the surgical procedure would actually influence myocardial outcome. In a first clinical study on the subject [25], the effects of sevoflurane and propofol on myocardial function were compared during and after coronary artery surgery. Before cardiopulmonary bypass (CPB), all hemodynamic variables were comparable between the two anesthetic treatment groups. However, after CPB, patients who received the volatile anesthetic regimen for anesthesia had preserved cardiac performance, which was evident from a preserved stroke volume and dP/dt_{max}, and the preservation of the length-dependent regulation of myocardial function. In addition, need for inotropic support in the early postoperative period was significantly less with the volatile anesthetic, and postoperative plasma concentrations of cardiac troponin I were consistently lower when compared with patients who received the total intravenous anesthetic regimen [25]. These data, therefore, suggested that volatile anesthetics provided a cardioprotective effect that was not observed with the intravenous anesthetic regimen. These cardioprotective effects of a volatile anesthetic regimen during coronary surgery were subsequently confirmed in other reports [26–30]. All these clinical studies clearly indicated that volatile anesthetics protect the myocardium during coronary surgery. Only one study, in patients undergoing off-pump coronary surgery, failed to observe such protective actions of a volatile anesthetic regimen [31]. In this study, however, intra-operative remifentanil concentrations were consistently higher and bispectral index values lower in the propofol group compared to the sevoflurane-treated patients, indicating that there were probably differences in anesthetic depth that may have influenced the results.

These cardioprotective effects were also observed during aortic valve replacement procedures [32] but not in patients undergoing isolated mitral valve replacement [33] or coronary stenting procedures [34]. Data in non-cardiac surgery are lacking. In a recent study in vascular surgery patients, it was observed that patients anesthetized with sevoflurane experienced fewer postoperative cardiovascular complications than patients receiving a total intravenous anesthetic regimen [35].

Perioperative Anesthetic Cardioprotection and Outcome

Despite the fact that most clinical observations clearly indicate a cardioprotective effect of volatile anesthetics, the impact of this phenomenon on postoperative morbidity and clinical recovery remains to be established, mainly related to the fact that the sample sizes of the different studies were too small to address outcome issues. In a study on 320 coronary surgery patients who were randomly assigned to receive either a total intravenous anesthetic regimen or a volatile anesthetic regimen, a significantly lower intensive care unit (ICU) and hospital length of stay was observed in the patients who received a volatile anesthetic regimen [36]. Multiple regression analysis revealed that prolonged length of stay in the ICU in this particular study was related to the following independent predictors of outcome: Occurrence of atrial fibrillation, an increase in postoperative troponin I levels in excess of 4 ng/ml, and the need for prolonged postoperative inotropic support for more than 12 hours. Although the differences in incidence of atrial fibrillation between groups in this study did not reach statistical significance, the number of patients with an increase in postoperative troponin I of more than 4 ng/ml and the number of patients who needed prolonged postoperative inotropic support was significantly lower in the volatile anesthetic groups. This was associated with better myocardial function during the first postoperative hours [36].

A Danish retrospective database analysis on 10,535 patients who had undergone cardiac surgery in 3 cardiac centers with either a volatile or an intravenous anesthetic regimen revealed no difference in 30-day total mortality [37]. Correct interpretation of these data remains difficult because of methodological issues that are inherent to this type of analysis, such as the retrospective design including patients over a period of 6 years, the lack of information on the different surgical and anesthetic techniques, the differences in patient collection between centers, etc. A recent meta-analysis focused on the data obtained with the newer volatile anesthetics desflurane and sevoflurane. Twenty two trials with a total of 1922 patients were included from studies that compared a volatile with an intravenous anesthetic regimen. With the volatile anesthetic regimen, postoperative troponin release was lower, cardiac index was better with less need for inotropic support, the incidence of perioperative myocardial infarction was lower, and mechanical ventilation time, ICU length of stay, and hospital length of stay were shorter [38].

Data on long-term outcome are even scarcer. One study using a sevoflurane preconditioning protocol observed a lower incidence of 1-year postoperative cardiac events [39] whereas another multicenter study observed lower 1-year mortality in coronary surgery patients anesthetized with a volatile anesthetic regimen compared to a total intravenous anesthetic regimen [40]. Both studies however, were underpowered to address long-term outcome issues.

Conclusion

Over the years, various cardioprotective strategies have been developed to help reduce myocardial ischemia/reperfusion and the incidence of perioperative cardiac events. The great majority of these strategies showed promising results in experimental settings but mostly failed to provide a convincing significant clinical effect. Anesthetic cardioprotection, however, seems to be an exception to this with experimentally observed protective effects being shown to translate into clinically measurable benefits. The impact of such effects on mortality, however, remains to be established. Furthermore, the potentially beneficial effects on organ protection of other compounds and drugs, such as levosimendan, need further exploration.

References

1. Halestrap AP, Clarke SJ, Javadov SA (2004) Mitochondrial permeability transition pore opening during myocardial reperfusion – a target for cardioprotection. Cardiovasc Res 61: 372 – 385
2. De Hert S (2008) Myocardial protection from ischemia and reperfusion injury. In: Mebazaa A, Gheorgiade M, Zannad FM, Parrillo JE (eds) Acute Heart Failure. Springer-Verlag, London, pp 70 – 86
3. Hausenloy DJ, Ong SB, Yellon DM (2009) The mitochondrial permeability transition pore as a target for preconditioning and postconditioning. Basic Res Cardiol 104: 189 – 202
4. De Hert SG (2008) Cardioprotection in anesthesia. Minerva Anesthesiologica 74: 259 – 270
5. Schouten O, Bax JJ, Dunkelgrun M, et al (2007) Pro: Beta-blockers are indicated for patients at risk for cardiac complications undergoing noncardiac surgery. Anesth Analg 104: 8 – 10
6. Daumerie G, Fleisher LA (2008) Perioperative β-blocker and statin therapy. Curr Opin Anaesthesiol 21: 60 – 65
7. Fleishmann KE, Beclman JA, Buller CE, et al (2009) 2009 ACCF/AHA update on perioperative beta blockade. J Am Coll Cardiol 54: 2102 – 2128
8. Kersten J, Fleisher LA (2006) Statins: the next advance in cardioprotection? Anesthesiology 105: 1079 – 1080
9. Gross GJ, Kersten JR, Warltier DC (1999) Mechanisms of postischemic contractile dysfunction. Ann Thorac Surg 68: 1898 – 1904
10. Zaugg M, Lucchinetti E, Uecker M, et al (2003) Anaesthetics and cardiac preconditioning: Part I. Signalling and cytoprotective mechanisms. Br J Anaesth 91: 551 – 565
11. De Hert SG (2004) Cardioprotection with volatile anesthetics: clinical relevance. Curr Opin Anaesthesiol 17: 57 – 62
12. De Hert SG, Turani F, Mathur S, Stowe DF (2005) Cardioprotection with volatile anesthetics: mechanisms and clinical implications. Anesth Analg 100: 1584 – 1493
13. Tomai F, Crea F, Gaspardone A, et al (1994) Ischemic preconditioning during coronary angioplasty is prevented by glibenclamide, a selective ATP-sensitive K+ channel blocker. Circulation 90: 700 – 705
14. Jenkins DP, Pygsley WB, Alkhulaifi AM, et al (1997). Ischaemic preconditioning reduces troponin T release in patients undergoing coronary artery bypass surgery. Heart 77: 314 – 318
15. Wu ZK, Iivainen T, Pehkonen E, et al (2002) Ischemic preconditioning suppresses ventricular tachyarrhythmias after myocardial revascularization. Circulation 106: 3091 – 3096
16. Laskey WK, Beach D (2003) Frequency and clinical significance of ischemic preconditioning during percutaneous coronary intervention. J Am Coll Cardiol 42: 998 – 1003
17. Piper HM, Garcia-Dorado D, Ovize M (1998) A fresh look at reperfusion injury. Cardiovasc Res 38: 291 – 300
18. Wang Q, Pernow J, Sjöquist P, Ryden L (2002) Pharmacological possibilities for protection against myocardial reperfusion injury. Cardiovasc Res 55: 25 – 37

19. Piper HM, Abdallah Y, Schäfer C (2004) The first minutes of reperfusion: a window of opportunity for cardioprotection. Cardiovasc Res 61: 365–371
20. Rosenkranz ER, Buckberg GD (1983) Myocardial protection during surgical coronary reperfusion. J Am Coll Cardiol 21: 1235–1246
21. Piot C, Croisille P, Staat P et al (2008) Effect of cyclosporine on reperfusion injury in acute myocardial infarction. N Engl J Med 359: 473–481
22. Weber NC, Preckel B, Schlack W (2005) The effect of anaesthetics on the myocardium-new insights into myocardial protection. Eur J Anaesthesiol 22: 647–657
23. Fräβdorf J, De Hert S, Schlack W (2009) Anaesthesia and myocardial ischaemia-reperfusion injury Br J Anaesth 103: 89–98
24. De Hert SG, Cromheecke S, Van der Linden PJ, et al (2005) Cardioprotective properties of sevoflurane in patients undergoing coronary surgery with cardiopulmonary bypass are related to the modalities of its administration. Anesthesiology 102: 699–700
25. De Hert SG, ten Broecke PW, Mertens E et al (2002) Sevoflurane but not propofol preserves myocardial function in coronary surgery patients. Anesthesiology 97: 42–49
26. De Hert SG, Cromheecke S, ten Broecke PW, et al (2003) Effects of propofol, desflurane, and sevoflurane on recovery of myocardial function after coronary surgery in elderly high-risk patients. Anesthesiology 99: 314–323
27. Conzen PF, Fisher S, Detter C, Peter K (2003) Sevoflurane provides greater protection of the myocardium than propofol in patients undergoing off-pump coronary artery bypass surgery. Anesthesiology 99: 826–833
28. Bein B, Renner J, Caliebe D, et al (2005) Sevoflurane but not propofol preserves myocardial function during minimally invasive direct coronary artery bypass surgery. Anesth Analg 100: 610–616
29. Guarracino F, Landoni G, Tritapepe L, et al (2006) Myocardial damage prevented by volatile anesthetics: A multicenter randomised controlled study. J Cardiothorac Vasc Anesth 20: 477–483
30. Tritapepe L, Landoni G, Guarracino F, et al (2007) Cardiac protection by volatile anaesthetics: a multicentre randomized controlled study in patients undergoing coronary artery bypass grafting with cardiopulmonary bypass. Eur J Anaesthesiol 24: 323–331
31. Law-Koune JD, Raynaud C, Liu N et al (2006) Sevoflurane-remifentanyl versus propofol-remifentanyl anesthesia at a similar bispectral level for off-pump coronary artery surgery: no evidence of reduced myocardial ischemia. J Cardiothorac Vasc Anesth 20: 484–492
32. Cromheecke S, Pepermans V, Hendrickx E, et al (2006) Cardioprotective properties of sevoflurane in patients undergoing aortic valve replacement with cardiopulmonary bypass. Anesth Analg 103: 289–296
33. Landoni G, Calabro MG, Marchetti C, et al (2007) Desflurane versus propofol in patients undergoing mitral valve surgery. J Cardiothorac Vasc Anesth 21: 672–677
34. Landoni G, Zangrillo A, Fochi O, et al (2008) Cardiac protection with volatile anesthetics in stenting procedures. J Cardiothorac Vasc Anesth 22: 543–547
35. Van der Linden PJ, Dierick A, Wilmin S, et al (2010) A randomized controlled trial comparing an intraoperative goal-directed strategy with routine clinical practice in patients undergoing peripheral arterial surgery. Eur J Anaesthesiol 27: 788–793
36. De Hert SG, Van der Linden PJ, Cromheecke S, et al (2004) Choice of primary anesthetic regimen can influence intensive care unit length of stay after coronary surgery with cardiopulmonary bypass. Anesthesiology 101: 9–20
37. Jakobsen CJ, Berg H, Hindsholm KB, et al (2007) The influence of propofol versus sevoflurane anesthesia on outcome in 10,535 cardiac surgical procedures. J Cardiothor Vasc Anesth 21: 664–671
38. Landoni G, Biondi-Zoccai GG, Zangrilla A, et al (2007) Desflurane and sevoflurane in cardiac surgery: a meta-analysis of randomized clinical trials. J Cardiothor Vasc Anesth 21: 502–511
39. Garcia C, Julier K, Bestmann L, et al (2005) Preconditioning with sevoflurane decreases PECAM-1 expression and improves one-year cardiovascular outcome in coronary artery bypass graft surgery. Br J Anaesth 94: 159–165
40. De Hert S, Vlasselaers D, Barbé R, et al (2009) A comparison of volatile and non volatile agents for cardioprotection during on-pump coronary surgery. Anaesthesia 64: 953–960

XII Infection and Sepsis

A New Approach to Ventilator-associated Pneumonia Based on the PIRO System

I. Martin-Loeches, M. Ulldemolins, and E. Diaz

Introduction

Several new scoring systems have been developed over recent years to assess the degree of organ failure (e.g., Acute Physiology and Chronic Health Evaluation [APACHE] II, APACHE III, Sequential Organ Failure Assessment [SOFA], Simplified Acute Physiology Score [SAPS] II, and Multiple Organ Dysfunction Score [MODS]). Most of these were models generated based on the concepts of sepsis, severe sepsis and septic shock. In 2001, an International Sepsis Definition Conference updated these terms in order to facilitate standardized enrolment into clinical trials, but due to their simplicity and easy use physicians rapidly adopted them for daily clinical practice [1].

However, few of these scoring systems are focused on ventilator-associated pneumonia (VAP), the leading cause of nosocomial infection in critically ill patients requiring mechanical ventilation [2]. The approach to VAP severity has been traditionally based on three clinical items: The underlying disease, the time of onset, and the causative microorganism. The VAP-PIRO score (**Table 1**) [3], based on the PIRO system (predisposition, insult, response, organ dysfunction), has been recently developed by our group and endeavors to identify different risk levels for VAP. This score stratifies patients with VAP into mortality risk groups and correlates these with health-care resource use in VAP patients. The PIRO concept, a conceptual framework for understanding sepsis [1], is a classification scheme that could stratify patients based on their predisposing conditions, the nature and extent of the insult, the nature and magnitude of the host response, and the degree of the concomitant organ dysfunction. Conceptually, PIRO was

Table 1. Summary of the main components of the VAP-PIRO scoring system

P	I	R	O
• COPD • Immunocompromised host • Trauma patient • Genetic factors	• Bacteremia • Pathogens – MRSA – *Pseudomonas* spp. – *Aanetobacter* spp. • *Candida* spp. • VAT • Blood transfusions	• Clinical resolution • Biomarkers • Compartimentalization • Shock • Immunoparalysis, macrolides	• Renal failure • ARDS

VAT: ventilator-associated tracheobronchitis; ARDS: acute respiratory distress syndrome; COPD: chronic obstructive pulmonary disease; MRSA: methicillin-resistant *Staphylococcus aureus*

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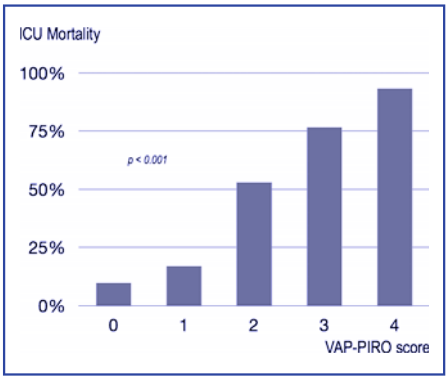

Fig. 1. Intensive care unit (ICU) mortality according to the VAP-PIRO score classification. (adapted from [3])

modeled on the TNM (tumor, nodes, metastases) classification [4] which has been successfully used to define prognostic indicators in clinical oncology. PIRO was introduced as a hypothesis-generating model for future research, but its practical applications were limited. The aim of this chapter is to describe a new approach to the prognosis of VAP based on the PIRO concept focusing in its main components and their relative impact on VAP severity and prognosis.

Figure 1 shows the mortality rate in ICU patients with VAP classified according to the VAP-PIRO score.

Components of the VAP-PIRO Score: Predisposition

Genetic Factors

Despite considerable advances in our understanding of the biology of pneumonia, improvements in clinical outcomes have been sporadic and, with few notable exceptions, because of improvements in supportive care rather than specific therapies. As a result, morbidity, mortality, and costs remain high.

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Although it is clear that gene sequencing and manipulation of experimental models have provided a better approach for insight into the biology of the inflammatory response to infection, these technologies and their application to the study of naturally occurring human genetic variation have yet to provide the same insight or clinical benefit. Variations in genes encoding important components of the inflammatory response and the microbial recognition system are likely to be involved in the development of pneumonia. In contrast to entities such as community-acquired pneumonia (CAP) or meningitis where 'the genetic approach' is being developed with some success, there are still scarce data that link VAP to genetic variability [5–9].

In addition, genetics may explain the wide variation in the individual response to infection that has puzzled clinicians for long. VAP phenotypes can range from septic shock to a very well compartmentalized consolidation on x-ray accompanied by low grade hypoxemia. Fortunately, novel therapeutic strategies are currently being developed in experimental models to modulate the inflammatory response in the host and may be available at the bedside in the near future.

Underlying Diseases

Chronic obstructive pulmonary disease

Chronic obstructive pulmonary disease (COPD) is a risk factor for nosocomial lower respiratory tract infections. The incidence of VAP in intubated COPD patients has been estimated to range between 6 and 33 % [10]. Tracheo-bronchial colonization, local and systemic immunosuppression and frequent antibiotic treatment are factors predisposing to VAP in these patients. However, the impact of COPD on VAP mortality remains controversial. Our group [11] demonstrated that COPD was associated with higher mortality rates in patients with VAP. However, after adjustment for confounding factors, COPD was not independently associated with mortality in these patients. In contrast, Nseir et al. [12] reported that VAP was associated with higher mortality rates and longer duration of mechanical ventilation and intensive care unit (ICU) stay in COPD patients, and was independently associated with ICU mortality.

Immunocompromised host

A huge number of immunocompromised patients are admitted to the ICU and immunosuppression has been recognized as an independent risk factor for infectious morbidity and mortality [13]. In addition, immunosuppression represents a risk factor for multidrug-resistant pathogens in VAP and should be considered in treatment decisions. As has been described by Nseir et al. [12], a significantly greater proportion of immunosuppressed patients received antibiotic therapy before and during ICU admission, being more likely to be colonized and/or infected by multidrug resistant organisms. However, despite the evidence available, current guidelines for treatment of VAP and or hospital-acquired pneumonia (HAP)/VAP do not consider patients who are known to be immunosuppressed because of human immunodeficiency virus (HIV) infection, hematologic malignancy, chemotherapy-induced neutropenia or organ transplantation [14], factors likely to determine prognosis.

Trauma patients

Trauma deaths have a classic trimodal distribution. Late death (3 days to 3 weeks postinjury) occurs in more than 25 % of the patients, in whom infection is the principal cause of death and is associated with high rates of extracranial complications, like pneumonia, that determine the final outcome. In fact, Bronchard et al. [15], in trauma patients, described that for patients developing pneumonia there was a higher risk of secondary cerebral injury, increased intra-cranial pressure, hypotension, fever and hypoxemia that would worsen outcomes in such patients. Therefore, in trauma patients, early identification of subjects at a high risk of developing VAP reduces morbidity and costs.

Trauma patients exhibit greater incidences of early-onset VAP, which accounts for 30 – 40 % of cases [15]. Most reports regarding microorganisms indicate that methicillin-sensitive *Staphylococcus aureus* (MSSA) is the predominant pathogen in multiple-trauma patients in coma, and nasal MSSA colonization at the time of severe injury may increase the risk of MSSA pneumonia [16]. As length of stay increases, causal pathogens are likely to switch to antibiotic-resistant bacteria. Rangel et al. [17] reported that the presence of multi-drug resistance (*Pseudomonas aeruginosa, Acinetobacter baumannii, Stenotrophomonas maltophilia*, and methicillin-resistant *S. aureus* [MRSA]) in respiratory isolates increased from

27 % to 52 % after 5 days of admission. Therefore, in comatose patients, coverage with a beta-lactam active against MSSA is mandatory when early VAP is suspected, however treatment of late onset VAP should be based on local bacteriologic patterns and antimicrobial susceptibility.

Components of the VAP-PIRO Score: Insult

Bacteremia

In HAP, bacteremia occurs in 8 to 20 % of the episodes [18] and is associated with high mortality rates [19], but because many of these studies were not designed to investigate attributable mortality, little is known regarding its real impact on VAP patients. Agbaht et al. [20] found that bacteremic-VAP was independently associated with increased ICU mortality. Moreover bacteremic episodes occurred later during the ICU stay and were more frequent in previously hospitalized patients. MRSA was found to be an independent risk factor for bacteremia and Depuydt et al. [21] reported a high mortality rate in MRSA bacteremia associated with nosocomial pneumonia,

Pathogens

Consideration of the particularities of each ICU's ecology should provide a more rational basis for selecting initial therapy for VAP patients before culture results are available. As we reported [22], the observed differences in pathogen etiology across institutions reflected differences in antibiotic use and local patterns of resistance, which prompted the development of a more patient specific antibiotic management.

The impact of multidrug resistant pathogens, including *P. aeruginosa* and MRSA, causing nosocomial infection is ever-increasing and is now recognized as a major health problem. Multidrug resistant pathogens have been recognized as contributing to unfavorable clinical outcome and increased resource utilization [23]. The greater associated hospital mortality has been attributed to the virulence of these bacteria and the increased occurrence of inadequate initial antibiotic treatment of VAP due to the presence of antibiotic resistance. However, the impact of multidrug resistance is difficult to assess because of the presence of multiple patient characteristics that may confound uniform analysis.

P. aeruginosa, MRSA and *A. baumannii* represent the three most important microorganisms in VAP.

Pseudomonas aeruginosa

P. aeruginosa represents the most prevalent microorganism in VAP in different series and is associated with high mortality rates [24]. Some surface factors, by either injecting cytotoxin to damaged epithelial cells or by rupturing epithelial integrity or by mechanisms like the type III secretion system, increase *P. aeruginosa*'s virulence, particularly exoU. The type III secretion system induces the translocation of toxins from the bacterial cytoplasm into the cytosol of host cells directly. *P. aeruginosa* strains producing type III secreted proteins are linked with worse outcome [25].

Zhuo et al. [26] reported that patients with large burdens of *P. aeruginosa* had an increased risk of death and possessed more virulent strains. Therefore, a high

burden of *P. aeruginosa* may be a marker of inadequate host defense and its presence may also further compromise target host immune cells, for example, macrophages and neutrophils, allowing organisms to evade the immune response and often reducing the number of viable host defense cells.

Staphylococcus aureus

S. aureus is the most important Gram-positive pathogen in VAP. In the recent European multicenter study [27], EUVAP, the most common isolate was *S. aureus* in 32.3 % of cases; 16.3 % were MSSA and 16.0 % MRSA. Virulence and therapy-related factors, such as inappropriate antibiotic prescription, have been consistently associated with increased mortality. There are several factors linked with MRSA isolation in VAP episodes: Administration of antibiotics before the development of VAP [28] and length of hospital stay, rather than the period of mechanical ventilation, were strongly associated with MRSA isolation [29]. Vidaur et al. [30] found that MRSA VAP treated with appropriate therapy resolved more slowly than VAP due to *Haemophilus influenzae*, MSSA, and *P. aeruginosa* treated with appropriate therapy. The risk of death in MRSA episodes is 20 times higher than in episodes caused by MSSA strains treated with beta-lactams [31] and a recent report showed that MRSA-VAP episodes were independently associated with prolonged hospitalization and higher costs than MSSA VAP episodes, even when therapy was appropriate [32].

Acinetobacter baumannii

Several studies have investigated the attributable mortality of *A. baumannii* and found controversial results. Fagon et al. [33] reported higher mortality in cases with VAP caused by *A. baumannii* and *P. aeruginosa* than in controls with bronchial colonization. In contrast, Garnacho-Montero et al. [34], found that VAP due to *A. baumannii* was not associated with worse outcomes than other causes of VAP in a matched case-control study. *A. baumannii* exhibits intrinsic resistance to multiple antimicrobial agents and generates continuing controversy about whether VAP caused by this microorganism increases morbidity and mortality independently of the effects of other confounding factors in ICU setting.

Candida species

In immunocompetent mechanically ventilated patients, isolation of *Candida* spp. from the respiratory tract is relatively common. Olaechea et al. [35] found an association with *Candida* spp. isolation and longer ICU and hospital stays and resource utilization. Azoulay et al. [36] reported that *Candida* spp. colonization was associated with an increased risk of *P. aeruginosa* VAP. *Candida* spp. and *P. aeruginosa* were among the most common microorganisms retrieved from endotracheal tube biofilm and tracheal secretions in patients with VAP. This can be explained because both microorganisms have identical functional enzymes, such as 2' phosphotransferase, acting in concert with ligase to splice transfer RNA molecules. Preemptive treatment with local or systemic therapy has been proposed in order to reduce the incidence of *P. aeruginosa* VAP [37].

Ventilator-associated Tracheobronchitis (VAT) as an Intermediate Insult for VAP

VAT might represent an intermediate process between colonization and VAP [38] and probably is a continuum between bronchitis and pneumonia in mechanically

ventilated patients. Host defenses can be overwhelmed by a large aspirated inoculum or an inherently virulent organism and the main reason for developing infection in the upper airways is the imbalance between host defenses and excess of mucus. Recent studies have shown that bronchial/tracheal epithelial cells are functionally different and represent a first step of injury [39]. VAT represents an interesting target for treatment since it may prevent the progression to VAP, shorten the use of antibiotics that reduce cost and minimize the selective pressure on ICU ecology [40].

Blood Transfusion

The majority of critically ill patients require a transfusion of packed red blood cells (RBCs) at some point during their ICU stay. The incidence of blood transfusion during the ICU stay has been reported to be as frequent as 37.0 % [42]. Nevertheless, transfusion of packed RBCs is not without risk since it represents an insult to the host's immune system with enhancement of cytokine response. Anti-inflamatory (interleukin [IL]-10) and pleiotropic (IL-6) cytokines are increased during transfusion of packed RBCs. Blood transfusion has been associated with nosocomial infection-like surgical site infections and potentiates the risk for catheter-related blood stream infection but also increases the risk of developing VAP.

Shorr et al. [42] reported that transfusion was independently associated with an increased risk for VAP, the effect of transfusion on late-onset VAP being more pronounced and dose-response dependent. Therefore, blood transfusion needs to be considered cautiously in critical care patients in order to evaluate potential adverse events and to acknowledge that the burden of proof is shifting to suggest that transfusion avoidance may be the safer paradigm [43].

Components of the VAP-PIRO Score: Response

Clinical Resolution

Early clinical recognition of therapeutic failure is of paramount importance if corrective measures are to be taken. While this will intuitively make sense to clinicians, data available on this issue are very limited. Several studies have suggested that improvement in oxygenation is the most reliable criteria to distinguish patients who are responding to antibiotic treatment from those who are not. Luna et al. [44] evaluated the performance of the Clinical Pulmonary Infection Score (CPIS) in identifying which patients with VAP respond to therapy. These authors discovered that only the PaO_2/FiO_2 ratio could distinguish survivors from non-survivors, as early as day 3 of therapy for VAP. Moreover they reported that the PaO_2/FiO_2 ratio improved above 250 mmHg in survivors, and this improvement happened before improvement in the other components of the score (white blood cell count, fever, secretions, and radiographic abnormalities). Thus, the PaO_2/FiO_2 ratio may represent a very accurate and rapid measure of the patient's response to therapy and can help tailor appropriate duration of therapy. However, Vidaur et al. [45] reported that improvement in oxygenation was unreliable in patients with the acute respiratory distress syndrome (ARDS), and only fever was delayed compared with non-ARDS patients. At days 7–8 of treatment, when antibiotics for VAP are commonly discontinued [46], Chastre et al. reported that more than 35 % of ARDS patients with VAP remain febrile.

Clinical patterns, such as fever and hypoxemia, are clinical variables that can be easily followed at the bedside of the patient simply by physical examination to monitor clinical response and to individualize and shorten the duration of antibiotic therapy.

Use of Biomarkers to Quantify the Response to VAP

Several biomarkers have been proposed as the most promising candidates, such as leukocyte count, C-reactive protein (CRP) and procalcitonin (PCT), for correlating with the prognosis of VAP [47]. Seligman et al. [48] reported that decreases in either serum PCT or CRP levels between onset and the fourth day of treatment could predict survival of VAP patients. Similarly, Luyt et al. [49] reported different procalcitonin levels as strong predictors of unfavorable outcome (death, recurrent VAP or development of extrapulmonary infection) by a point-of-care test at days 1, 3 and 7 in patients with VAP. However, neither PCT nor CRP threshold values nor their kinetics could predict the development of septic shock in VAP patients [50].

Recently, other biomarkers such us midregional pro-atrial natriuretic peptide (MR-proANP) and copeptin have been suggested and tested as prognostic markers, but their function in VAP resolution is still unproven [51, 52].

Compartmentalization

The response to VAP may vary from compartmentalized forms that account for a local response with minor systemic compromise to systemic spillover or escape of inflammation leading to septic shock and uninfected multiorgan failure.

Cytokines are the key factors in the pathogenesis of pneumonia and add complexity of signaling during VAP development. Millo et al. [53] reported that the production of cytokines and cytokine inhibitors was compartmentalized within the lungs in patients who developed VAP. They reported a significant increase in concentration of tumor necrosis factor (TNF)-α, soluble TNF-α receptors [sTNFaRI], IL-1α, and IL-1β in non-directed bronchoalveolar lavage (BAL) fluid.

Similarly, VAP is characterized by a shift in the local hemostatic balance to the procoagulant side, which precedes the clinical diagnosis of VAP. Fibrin deposits enhance inflammatory responses by increasing vascular permeability, activating endothelial cells to produce pro-inflammatory mediators, and eliciting recruitment and activation of neutrophils; eventually, these effects will disrupt normal gas exchange by creating intrapulmonary shunts and ventilation-perfusion mismatches.

As has been reported by Schultz et al. [54], patients with VAP, before the clinical manifestation, had a dramatic increase in procoagulant activity, increased BAL levels of thrombin-antithrombin III complex (TAT), and decreased fibrinolysis, as reflected by a gradual fall in BAL levels of plasminogen activator activity.

Shock

The inflammatory response of the host to an infection is associated with increased circulating levels of pro-inflammatory cytokines, such as IL-6 and IL-8. The clinical presentation of VAP varies widely, from a relatively benign illness to

a devastating illness resulting in septic shock. The incidence of septic shock among VAP patients can be as high as 50 % in reported series [48]. Bonten et al. [55] reported that high circulating levels of IL-6 and IL-8 were associated with higher mortality rates and with a clinical presentation of severe sepsis or septic shock. Moreover soluble triggering receptor expressed on myeloid cells (sTREM)-1 is particularly increased on evolution from sepsis or severe sepsis to septic shock in patients with VAP. Its sustained increase might be an indicator for poor outcome [56].

Our group reported that septic shock was an independent variable associated with ICU mortality (OR 4.40 CI 2.71 – 7.15) [3]. The early stages of VAP may be accompanied by circulatory insufficiency resulting from hypovolemia, myocardial depression, increased metabolic rate, and vasoregulatory perfusion abnormalities. As a consequence, a variety of hemodynamic combinations create a systemic imbalance between tissue oxygen supply and demand, leading to global tissue hypoxia and shock. Early correction of septic shock is crucial for patient outcomes, for which reason consensus guidelines now recommend early goal-directed therapy [57] for the first six hours of sepsis resuscitation.

Immunoparalysis

In the past, immodulatory therapies in sepsis were driven by the assumption that the adverse outcomes were related to an overly exuberant inflammatory response. However, over the last few years, new evidence on cytokine production in response to bacterial antigens, lymphocyte proliferation in response to recall antigens, or new antigen presentation as a marker of immune function has been released. For example, low HLA-DR expression has been correlated with the development of nosocomial infections, and persistence of abnormally low levels of HLA-DR in the late phase of septic shock (day 5 – 7) has been linked to death [58]. New studies based on HLA-DR modulation in patients with VAP might improve the understanding of the response to VAP.

XII

Immunomodulatory Effects of Macrolides

Compelling evidence has shown that appropriate antibiotic therapy is the cornerstone of success in the treatment of patients with VAP [59]. However, despite early diagnosis and prompt initiation of antibiotics, mortality remains high in severe sepsis [60]. Recent studies suggest that macrolides may have beneficial effects for patients at risk of certain infections due to their immunomodulatory effects rather than their antimicrobial properties [61]. Based on favorable results in experimental models of sepsis caused by Gram-negative organisms, Giamarellos-Bourboulis et al. [62] conducted a randomized controlled trial (RCT) in 200 patients with VAP who were randomly assigned to receive either placebo or clarithromycin. They showed that despite no differences in 28-day mortality rates between the two groups, clarithromycin accelerated the resolution of VAP and weaning from mechanical ventilation in surviving patients and delayed death in those who died of sepsis. The explanation can be based on the regulation of leukocyte function and production of inflammatory mediators, control of mucus hypersecretion, resolution of inflammation, and modulation of host defense mechanisms or on bacterial quorum sensing in *P. aeruginosa* infections. Moreover, some evidence suggests that macrolides might facilitate the killing of micro-

organisms in acute respiratory infections through the stimulation of neutrophil activation, whereas blood monocytes release lower amounts of TNF-α without any change in tissue bacterial load [63].

Components of the VAP-PIRO Score: Organ Dysfunction

Renal Failure

VAP is a risk factor for the development of acute renal failure. The incidence of acute renal failure for the population at risk has been reported to be around 38 % [64]. In this study, VAP caused by multidrug resistant pathogens and sepsis were independent risk factors for the development of acute renal failure. However, there is not yet enough evidence in the published data to explain the relationship between multidrug resistant infections and the development of acute renal failure.

Acute Respiratory Distress Syndrome

Nosocomial pneumonia is a frequent complication of ARDS and *vice versa*. Epidemiologic studies have reported that VAP was present in 20 – 75 % of patients dying of ARDS [65]. Fibrin deposition within the air space is one of the hallmarks of ARDS. Alveolar fibrin deposits appear to contribute to the magnitude of the inflammatory response by virtue of the ability of their cleavage and degradation products to promote chemotaxis, to increase vascular permeability, and to exert modulatory effects on various immune cells. In addition, fibrin may participate in the resolution phase of ARDS, possibly contributing to lung fibrosis by providing a matrix for macrophage migration and by promoting angiogenesis and collagen deposition [66].

Conclusion

Despite recent advances in VAP management, VAP cannot yet be prevented. Some risk factors for developing VAP are not modifiable and the etiology of each episode varies markedly according to the time to pneumonia onset and underlying diseases in the host. The VAP-PIRO approach takes into account these risk factors and the consideration of predisposing conditions, the nature and extent of insult, the nature and magnitude of the host response; in addition, the degree of concomitant organ dysfunction provides a useful and novel approach to VAP. The VAP-PIRO approach may improve the understanding of the natural history and the stratification of patients according to severity of each VAP episode. VAP-PIRO could be useful both for benchmarking and for balancing sickness severity in future randomized clinical trials.

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References

1. Levy MM, Fink MP, Marshall JC, et al (2003) 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. Crit Care Med 31: 1250 – 1256
2. American Thoracic Society and Infectious Diseases Society of America (2005) Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. Am J Respir Crit Care Med 171: 388 – 416
3. Lisboa T, Diaz E, Sa-Borges M, et al (2008) The ventilator-associated pneumonia PIRO score: a tool for predicting ICU mortality and health-care resources use in ventilator-associated pneumonia. Chest 134: 1208 – 1216
4. Sellers A (1960) The staging of breast cancer, trial of the TNM method. Can J Surg 4: 116 – 117
5. Waterer GW, Quasney MW, Cantor RM, Wunderink RG (2001) Septic shock and respiratory failure in community-acquired pneumonia have different TNF polymorphism associations. Am J Resp Crit Care Med 163: 1599 – 1604
6. Gallagher PM, Lowe G, Fitzgerald T, et al (2003) Association of Il-10 polymorphism with severity of illness in community acquired pneumonia. Thorax 58: 154 – 156
7. Wattanathum A, Manocha S, Groshau HS, Russel JAI, Walley KR (2005) Interleukin-10 haplotype associated with increased mortality in critically ill patients with sepsis from pneumonia but not in patients with extrapulmonary sepsis. Chest 128: 1690 – 1698
8. Brouwer MC, de Gans J, Heckenberg SG, Zwinderman AH, van der Poll T, van de Beek D (2009) Host genetic susceptibility to pneumococcal and meningococcal disease: a systematic review and meta-analysis. Lancet Infect Dis 9: 31 – 44
9. Texereau J, Chiche JD, Taylor W, Choukroun G, Comba B, Mira JP (2005) The importance of Toll-like receptor 2 polymorphisms in severe infections. Clin Infect Dis 41 (Suppl 7): S408 – 415
10. Rello J, Rodriguez A, Torres A, et al (2006) Implications of COPD in patients admitted to the intensive care unit by community-acquired pneumonia. Eur Respir J 27: 1210 – 1216
11. Rello, J, Ausina, V, Ricart, M, et al (1993) Impact of previous antimicrobial therapy on the etiology and outcome of ventilator-associated pneumonia. Chest 104: 1230 – 1235
12. Nseir S, Di Pompeo C, Soubrier S, et al (2005) Impact of ventilator-associated pneumonia on outcome in patients with COPD. Chest 128: 1650 – 1656
13. Ibrahim EH, Tracy L, Hill C, Fraser VJ, Kollef MH (2001) The occurrence of ventilator-associated pneumonia in a community hospital: risk factors and clinical outcomes Chest 120: 555 – 561
14. Torres A, Ewig S, Lode H, Carlet J (2009) Defining, treating and preventing hospital acquired pneumonia: European perspective. Intensive Care Med 35: 9 – 29
15. Bronchard R, Albaladejo P, Brezac G, et al (2004) Early onset pneumonia: risk factors and consequences in head trauma patients. Anesthesiology 100: 234 – 239
16. Sirgo G, Bodí M, Díaz E, Rello J (2002) Pneumonia in head-injured and severe trauma patients.. Semin Respir Crit Care Med 23: 435 – 441
17. Rangel EL, Butler KL, Johannigman JA, Tsuei BJ, Solomkin JS (2009) Risk factors for relapse of ventilator-associated pneumonia in trauma patients. J Trauma 67: 91 – 95
18. Taylor GD, Buchanan-Chell M, Kirkland T, et al (1995) Bacteremic nosocomial pneumonia. A 7-year experience in one institution. Chest 108: 786 – 788
19. DeRyke CA, Lodise TP Jr, Rybak MJ, et al (2005) Epidemiology, treatment, and outcomes of nosocomial bacteremic Staphylococcus aureus pneumonia. Chest 128: 1414 – 1422
20. Agbaht K, Diaz E, Muñoz E, et al (2007) Bacteremia in patients with ventilator-associated pneumonia is associated with increased mortality: a study comparing bacteremic vs non-bacteremic ventilator associated pneumonia. Crit Care Med 35: 2064 – 2070
21. Depuydt P, Benoit D, Vogelaers D, et al (2006) Outcome in bacteremia associated with nosocomial pneumonia and the impact of pathogen prediction by tracheal surveillance cultures Intensive Care Med 32: 1773 – 1781
22. Rello J, Sa-Borges M, Correa H, Leal SR, Baraibar J (1999) Variations in etiology of ventilator-associated pneumonia across four treatment sites: implications for antimicrobial prescribing practices. Am J Respir Crit Care Med 160: 608 – 613
23. Depuydt PO, Vandijck DM, Bekaert MA, et al (2008) Determinants and impact of multidrug antibiotic resistance in pathogens causing ventilator-associated-pneumonia. Crit Care 12: R142

24. Rello J, Jubert P, Vallés J, Artigas A, Rué M, Niederman MS (1996) Evaluation of outcome for intubated patients with pneumonia due to P aeruginosa aeruginosa. Clin Infect Dis 23: 973 – 978
25. Roy-Burman A, Savel RH, Racine S, et al (2001) Type III protein secretion is associated with death in lower respiratory and systemic P aeruginosa aeruginosa infections. J Infect Dis 183: 1767 – 1774
26. Zhuo H, Yang K, Lynch SV, et al (2008) Increased mortality of ventilated patients with endotracheal P aeruginosa aeruginosa without clinical signs of infection Crit Care Med 36: 2495 – 2503
27. Koulenti D, Lisboa T, Brun-Buisson C, et al (2009) Spectrum of practice in the diagnosis of nosocomial pneumonia in patients requiring mechanical ventilation in European intensive care. Crit Care Med 37: 2360 – 2368
28. Trouillet J, Chastre J, Vuagnat A, et al (1998) Ventilator- associated pneumonia caused by potentially drug-resistant bacteria. Am J Respir Crit Care Med 157: 531 – 539
29. Ibrahim EH, Ward S, Sherman G, et al (2000) A comparative analysis of patients with earlyonset vs late-onset nosocomial pneumonia in the ICU setting. Chest 117: 1434 – 1442
30. Vidaur L, Planas K, Sierra R, et al (2008) Ventilator-associated pneumonia: impact of organisms on clinical resolution and medical resources utilization. Chest 133: 625 – 632
31. Rello J, Torres A, Ricart M, et al (1994) Ventilatorassociated pneumonia by Staphylococcus aureus. Comparison of methicillin-resistant and methicillin-sensitive episodes. Am J Respir Crit Care Med 150: 1545 – 1549
32. Shorr AF, Tabak YP, Gupta V, et al (2006) Morbidity and cost burden of methicillin-resistant Staphylococcus aureus in early onset ventilator-associated pneumonia. Crit Care 10: R97
33. Fagon JY, Chastre J, Hance AJ, Montravers P, Novara A, Gibert C (1993) Nosocomial pneumonia in ventilated patients: a cohort study evaluating attributable mortality and hospital stay. Am J Med 94: 281 – 288
34. Garnacho J, Sole-Violan J, Sa-Borges M, Diaz E, Rello J (2003) Clinical impact of pneumonia caused by A A baumannii baumannii in intubated patients: a matched cohort study. Crit Care Med 31: 2478 – 2482
35. Olaechea PM, Palomar M, León-Gil C, et al (2004) Economic impact of Candida colonization and Candida infection in the critically ill patient. Eur J Clin Microbiol Infect Dis 23: 323 – 330
36. Azoulay E, Timsit JF, Tafflet M, et al (2006) Candida colonization of the respiratory tract and subsequent pseudomonas ventilator-associated pneumonia. Chest 129: 110 – 117
37. Nseir S, Jozefowicz E, Cavestri B, et al (2007) Impact of antifungal treatment on Candida-Pseudomonas interaction: a preliminary retrospective case-control study. Intensive Care Med 33: 137 – 142
38. Craven DE, Chroneou A, Zias N, Hjalmarson KI (2009) Ventilator-associated tracheobronchitis: the impact of targeted antibiotic therapy on patient outcomes. Chest 135: 521 – 528
39. Seki N, Shirasaki H, Kikuchi M, Himi T (2007) Capsaicin induces the production of IL-6 in human upper respiratory epithelial cells. Life Sci 80: 1592 – 1597
40. Martin-Loeches I, Pobo A (2010) What's new in ventilator-associated tracheobronchitis. Clin Pulm Med 17: 117 – 121
41. Vincent JL, Sakr Y, Sprung C, et al (2008) Are blood transfusions associated with greater mortality rates? Results of the Sepsis Occurrence in Acutely Ill Patients study. Anesthesiology. 108: 31 – 39
42. Shorr AF, Duh MS, Kelly KM, Kollef MH; CRIT Study Group (2004) Red blood cell transfusion and ventilator-associated pneumonia: A potential link? Crit Care Med 32: 666 – 674
43. Zilberberg MD, Carter C, Lefebvre P, et al (2007) Red blood cell transfusions and the risk of acute respiratory distress syndrome among the critically ill: a cohort study. Crit Care 11: R63
44. Luna CM, Blanzaco D, Niederman MS, et al (2003) Resolution of ventilator-associated pneumonia: Prospective evaluation of the clinical pulmonary infection score as an early clinical predictor of outcome. Crit Care Med 31: 676 – 682
45. Vidaur L, Gualis B, Rodriguez A, et al (2005) Clinical resolution in patients with suspicion of ventilator-associated pneumonia: A cohort study comparing patients with and without acute respiratory distress syndrome. Crit Care Med 33: 1248 – 1253

46. Chastre J, Wolff M, Fagon JY, et al (2003) Comparison of 8 vs 15 days of antibiotic therapy for ventilator-associated pneumonia in adults: A randomized trial. JAMA 290: 2588–2598
47. Boucher BA, Hanes SD (1999) Searching for simple outcome markers in sepsis: an effort in futility? Crit Care Med 27: 1390–1391
48. Seligman R, Meisner M, Lisboa TC, et al (2006) Decreases in procalcitonin and C-reactive protein are strong predictors of survival in ventilator-associated pneumonia. Crit Care 10: R125
49. Luyt CE, Guerin V, Combes A, et al (2005) Procalcitonin kinetics as a prognostic marker of ventilatorassociated pneumonia. Am J Respir Crit Care Med 171: 48–53
50. Hillas G, Vassilakopoulos T, Plantza P, Rasidakis A, Bakakos P (2010) C-reactive protein and procalcitonin as predictors of survival and septic shock in ventilator-associated pneumonia. Eur Respir J 35: 805–811
51. Seligman R, Papassotiriou J, Morgenthaler NG, Meisner M, Teixeira PJ (2008) Copeptin, a novel prognostic biomarker in ventilator-associated pneumonia. Crit Care 12: R11
52. Seligman R, Papassotiriou J, Morgenthaler NG, Meisner M, Teixeira PJ (2008) Prognostic value of midregional pro-atrial natriuretic peptide in ventilator-associated pneumonia. Intensive Care Med 34: 2084–2091
53. Millo JL, Schultz MJ, Williams C, et al (2004) Compartmentalisation of cytokines and cytokine inhibitors in ventilator-associated pneumonia. Intensive Care Med 30: 68–74
54. Schultz MJ, Millo J, Levi M, et al (2004) Local activation of coagulation and inhibition of fibrinolysis in the lung during ventilator associated pneumonia. Thorax 59: 130–135
55. Bonten MJ, Froon AH, Gaillard CA, et al (1997) The systemic inflammatory response in the development of ventilator-associated pneumonia. Am J Respir Crit Care Med 156: 1105–1113
56. Routsi C, Giamarellos-Bourboulis EJ, Antonopoulou A, et al (2005) Does soluble triggering receptor expressed on myeloid cells-1 play any role in the pathogenesis of septic shock? Clin Exp Immunol 142: 62–67
57. Rivers E, Nguyen B, Havstad S, et al (2001) Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med 345: 1368–1377
58. Finck ME, Elmenkouri N, Debard AL, et al (2003) Preliminary results in standardization of flow cytometry protocols for monocytic HLA-DR measurement and their application in the follow up of septic shock. Ann Biol Clin 61: 441–448
59. Clec'h C, Timsit JF, De Lassence A, et al (2004) Efficacy of adequate early antibiotic therapy in ventilator-associated pneumonia: influence of disease severity. Intensive Care Med 30: 1327–1333
60. Dellinger RP, Levy MM, Carlet JM et al (2008) Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. Crit Care Med 36: 296–327
61. Parnham MJ (2005) Immunomodulatory effects of antimicrobials in the therapy of respiratory tract infections. Curr Opin Infect Dis 18: 125–131
62. Giamarellos-Bourboulis EJ, Tziortzioti V, Koutoukas P, et al (2006) Clarithromycin is an effective immunomodulator in experimental pyelonephritis caused by pan-resistant Klebsiella pneumoniae. J Antimicrob Chemother 57: 973–944
63. Giamarellos-Bourboulis EJ (2008) Immunomodulatory therapies for sepsis: unexpected effects with macrolides. Int J Antimicrob Agents 32 (Suppl 1): S39–43
64. Gursel G, Aydogdu M, Ozyilmaz E, Ozis TN (2008) Risk factors for treatment failure in patients with ventilator-associated pneumonia receiving appropriate antibiotic therapy. J Crit Care 23: 34–40
65. Markowicz P, Wolff M, Djedaïni K, et al (2000) Multicenter prospective study of ventilator-associated pneumonia during acute respiratory distress syndrome. Incidence, prognosis, and risk factors. ARDS Study Group. Am J Respir Crit Care Med 161: 1942–1948
66. Bastarache JA, Fremont RD, Kropski JA, Bossert FR, Ware LB (2009) Procoagulant alveolar microparticles in the lungs of patients with acute respiratory distress syndrome. Am J Physiol Lung Cell Mol Physiol 297: L1035–1041

Selective Decontamination of the Digestive Tract and Antibiotic Resistance

E. de Jonge and E.H.R. van Essen

Introduction: Infections in Intensive Care Unit Patients

Infections occur frequently during stays in intensive care units (ICUs) and contribute to the high mortality in critically ill patients. Respiratory tract infections in patients undergoing mechanical ventilation (ventilator-associated pneumonia [VAP]) may develop in up to 67 % of ICU patients [1]. Some studies have estimated that one-third to one-half of all VAP-associated deaths are a direct result of infection [2] and attributable mortality by VAP may be up to 50 % [1, 3]. That infections directly contribute to mortality in ICU patients is also supported by the finding that early and appropriate treatment of infections is associated with improved outcome [4].

ICU-acquired respiratory tract infections have a typical etiological distribution. Most infections in ICU patients are endogenous; they are caused by bacteria that have already colonized the patient's digestive tract prior to infection. Silvestri and co-authors reported that 60 % of infections in ICU patients were caused by bacteria colonizing the patient on admission (primary endogenous), 23 % by bacteria acquired during ICU-stay and leading to colonization before infection (secondary endogenous), and 17 % by bacteria introduced from the ICU environment leading to infection without prior colonization (exogenous) [5]. Oropharyngeal colonization is much more important than gastric colonization in endogenous infections. If the stomach is colonized prior to the development of VAP, then the bacteria causing pneumonia are also found in the mouth in virtually all cases [6, 7].

Infections occurring within the first days of mechanical ventilation and hospital stay are most frequently caused by commensal bacteria of the respiratory tract, such as *Streptococcus pneumoniae*, *Haemophilus influenzae*, and methicillin-susceptible *Staphylococcus aureus* (MSSA). In most patients, colonization of the airways with these commensal bacteria is replaced during the first week of stay in the ICU by colonization with Gram-negative enteric bacteria, such as *Escherichia coli* and *Klebsiella pneumoniae*, *Pseudomonsa aeroginosa*, *Acinetobacter species* and methicillin-resistant *Staphylococcus aureus* (MRSA). Interestingly, this shift in colonizing bacteria also occurs in patients not treated with antibiotics [8].

Selective Decontamination of the Digestive Tract

The fact that most infections in ICU patients are caused by bacteria already present in the oropharynx and stomach well before the onset of infection means that eradicating the potentially pathogenic bacteria from the digestive tract may pre-

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vent infectious complications in critically ill patients. Selective decontamination of the digestive tract (SDD) is an infection prevention measure, introduced for ICU patients in 1983 by Chris Stoutenbeek and coworkers [9]. For SDD, non-absorbable antibiotics are applied in the oropharynx and stomach to eradicate potentially pathogenic microorganisms from the digestive tract, while relatively preserving the indigenous anaerobic flora to prevent overgrowth with resistant bacteria. For this, the antibiotics should fulfill the following criteria: (a) Their spectrum should cover aerobic Gram-negative bacteria, including enterobacteriaceae and *P. aeruginosa*; (b) they should be non-absorbable to achieve high intraluminal levels; (c) they should have minimal inactivation by fecal material; and (d) any acquired resistance to these antibiotics should be rare. The regimen most often used consists of tobramycin, polymyxin E and amphotericin B. In addition, a short course of intravenous antibiotics, most often cefotaxime, is used at the start of SDD to treat early infections that may occur before the topical antibiotics have eradicated pathogenic bacteria from the gut.

Currently, 15 randomized clinical trials have investigated the influence of SDD with the combination of topical and systemic antibiotics on mortality of ICU patients [10–24]. The three largest studies all showed improved survival in SDD treated patients. In the study conducted by Krueger and coworkers [11], mortality was reported to be lower in a subgroup of 237 surgical patients who had APACHE II scores in the midrange stratum (APACHE II score of 20–29 at ICU admission). Analysis of their entire study population yielded a non-significant reduction in mortality by Cox proportional hazards modeling. Interestingly, had the data been analyzed on a strict intention-to-treat basis, the reduction in mortality would have been significant (relative risk of 0.69, 95 % confidence interval [CI] 0.51–0.95). In a single center study in 934 patients conducted in Amsterdam, treatment with SDD was associated with lower hospital mortality (odds ratio 0.71, 95 % CI 0.53–0.94) and shorter length of stay in the ICU [10]. The improved survival was found in both medical and surgical patients. Recently a very large multicenter study in 5939 patients in the Netherlands showed that SDD resulted in a 13 % relative decrease in risk-adjusted 28-day mortality rate with a 3.5 % absolute survival benefit [24]. Moreover, SDD treated patients had significantly fewer ICU-acquired bacteremias.

Selective Oropharyngeal Decontamination

Almost all nosocomial pneumonias in ICU patients are preceded by orapharyngeal colonization with the same bacteria that cause the pneumonia [6, 7]. Selective oropharyngeal decontamination (SOD) consists of the same antibiotics as used by SDD applied to the mouth, but without administration of antibiotics to the stomach. Furthermore, systemic antibiotics are not prescribed routinely but only on clinical indication. Until a few years ago, the influence of SOD on outcome in ICU patients had been studied in small populations only and none of these studies found increased survival in SOD-treated patients [25–28]. However, in 2009 de Smet and co-workers published the results of their large multicenter trial comparing SOD versus SDD versus no prophylaxis [24]. They found that not only SDD but also SOD improved survival (absolute survival benefit 2.9 %, SOD versus no prophylaxis).

SDD/SOD and Antibiotic Resistance

Antibiotics that are part of the SDD and SOD regimens are mostly active against aerobic Gram-negative bacteria. SDD leads to a shift in the microbial flora with an overgrowth of microorganisms that are already intrinsically resistant to the antibiotics used. Thus, SDD may select for colonization and infections with Gram-positive bacteria, such as *Enterococcus faecalis* and *Staphylococcus epidermidis* [29]. It is generally assumed that these bacteria have low virulence, but they may lead to infections in critically ill patients. SOD does not include antibiotics applied to the stomach and SOD, therefore, has fewer effects on the fecal flora [30].

Until recently, it was generally assumed that the widespread use of prophylactic antibiotics during SDD and SOD would lead to increased resistance. Worldwide, infections by highly resistant microorganisms are more and more common and are associated with high costs and worse outcome [31]. Despite the numerous randomized trials that reported increased survival of ICU patients treated with SDD, the probable threat of increasing resistance was arguably the most important reason not to introduce SDD in many ICUs. However, there is conflicting evidence on the influence of SDD on resistance. Increasing methicillin resistance in *S. aureus* after introduction of SDD has been reported, but in contrast to common beliefs, SDD did not lead to increased but rather decreased resistance in aerobic Gram-negative bacteria.

Enterobacteriaceae and *P. aeruginosa*

Three randomized trials studied the effects of SDD on resistance [10, 11, 24] and one of these trials also studied the effects of SOD [24]. All three studies found a decreased incidence of (multi)resistant Gram-negative bacteria in SDD-treated patients. In Germany, Krueger and co-workers compared SDD, using gentamicin, polymyxin B and a short intravenous treatment with ciprofloxacin, with standard care. They observed an almost 50 % reduction in resistance to these antibiotics of enterobacteriaceae, *P. aeruginosa* and *Acinetobacter* spp. [11]. Recently, the same study group reported that long-term resistance remained stable over a 5-year period with lower resistance in aerobic Gram-negative bacteria in ICUs that used SDD compared with ICUs without SDD [32]. In a single-center study in Amsterdam (**Fig. 1**), we showed that colonization of aerobic Gram-negative bacteria resis-

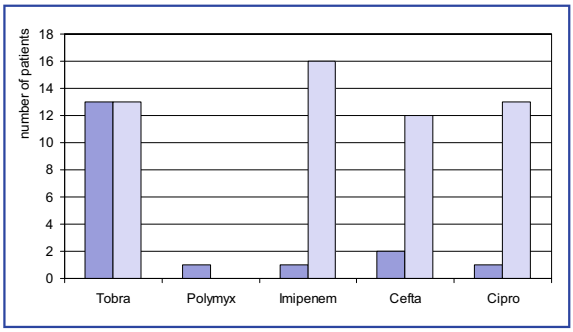

Fig. 1. Acquired colonization with bacteria resistant against tobramycin (tobra), polymyxin E (polymyx), imipenem, ceftazidime (cefta) or ciprofloxacin (cipro) during standard treatment (n = 468, light blue bars) or selective decontamination of the digestive tract (SDD, n = 466, dark blue bars) reported by de Jonge and co-workers [10]. Colonization was assessed from rectal swabs and endotracheal aspirates taken twice weekly.

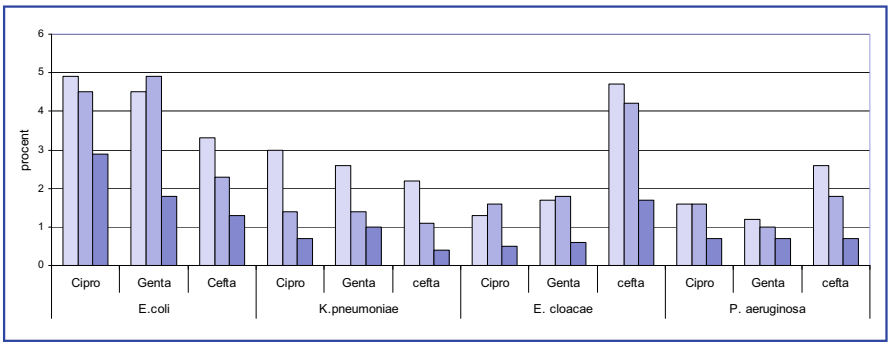

Fig. 2. Rectal colonization (percentage of patients studied) with bacteria resistant against ciprofloxacin (cipro), gentamicin (genta) and ceftazidime (cefta) during standard treatment (light blue bars), selective oropharyngeal decontamination (SOD, middle blue bars) and selective decontamination of digestive tract (SDD, dark blue bars) in study by de Smet and co-workers [24]. Rectal colonization was assessed in a monthly point-prevalence survey.

tant to imipenem, ceftazidime, ciprofloxacin, tobramycin or polymyxin E occurred in 16 % of SDD-patients compared to 26 % of control patients [10]. In the multicenter study by de Smet and co-workers, the proportion of patients with Gram-negative bacteria in rectal swabs that were not susceptible to ciprofloxacin, gentamicin or ceftazidime was lower with SDD than with standard care or SOD (**Fig. 2**) [24]. Compared to standard care, resistance was not increased during SOD; for some antibiotic-bacteria combinations it was actually decreased. Multiresistance was also less frequent during SDD.

In their analysis of the same data from the study by de Smet, Oostdijk and coworkers suggested that a rebound effect was present with increasing ceftazidime-resistance rates after discontinuation of SDD [33]. The prevalence of ceftazidime-resistance in Gram-negative bacteria was higher after discontinuation of SDD than before SDD was used. Although in normal situations, ICUs will not discontinue SDD, this may still be an important observation, as it points to some unwanted ecological effect of SDD. However, it must be recognized that the design of this study did not allow a real comparison between 'before SDD' and 'after SDD'. In fact, data presented as 'before SDD' were from different ICUs than data presented as 'after SDD'. Thus, ICU-related factors other than SDD itself, may have contributed to the higher prevalence of resistance found after discontinuation of SDD.

Randomized studies on the long-term effects of SDD or SOD on resistance have never been performed. However, in a 5-year prospective observational cohort study from Germany, aminoglycoside- and beta-lactam-resistant Gram-negative rods did not increase during SDD use. Aminoglycoside resistance of *P. aeruginosa* was 50 % below the mean value in ICUs not using SDD [32].

As reviewed above, controlled studies have repeatedly showed that resistance of aerobic Gram-negative bacteria decreased during the use of SDD. However, these observations were based on rectal cultures. It cannot be completely ruled out that some resistant strains remain present and that antibiotics present in the faeces in low quantities prevent their growth in cultures. If this were true, rapid recolonization with resistant bacteria could occur after discontinuation of SDD. Presently, there are no data that support this hypothesis. Controlled trials that

study the effects of SDD and SOD on recolonization with resistant bacteria are ongoing; results are expected to be reported within a few years.

Resistance in Gram-positive Bacteria

The antibiotics used for SDD and SOD are mostly inactive against Gram-positive bacteria. MSSA is covered by tobramycin, but no protection is to be expected against enterococci, vancomycin-resistant enterococcus (VRE), or MRSA. In areas with low prevalence of MRSA, no increase in resistance of Gram-positive bacteria with SDD has been found. Krueger et al. found unchanged resistance against gentamicin, ciprofloxacin or oxacillin in *S. aureus*, coagulase-negative staphylococci and *Enterococcus* spp. [11]. In the studies by de Jonge and coworkers [10] and by de Smet at al. [24], the incidence of MRSA was 0 % in all groups; the incidence of VRE was low (0.2 to 1.5 %) and similar in SDD and control patients.

The situation may be different if SDD is given in populations with high MRSA prevalence. Seven controlled trials on the use of SDD have been conducted in areas where MRSA was endemic [22, 34–39]. Important increases in MRSA during SDD were reported in Belgium and Austria [22, 40]. Cerda and co-workers studied the effects of adding vancomycin to the SDD-antibiotics to control MRSA [41] in burn patients. They found that during a 4-year period with SDD (polymyxin E, tobramycin and amphotericin B) and additional vancomycin applied to the nose, oropharynx and stomach, incidence densities of acquired colonization with MRSA were reduced by approximately 75 % compared to a 5-year period without prophylaxis. VRE was very rare and did not increase during SDD-vancomycin. Earlier, the same authors reported the results of a similar study in a mixed medical/surgical ICU. In this study, MRSA was also decreased by the use of SDD with vancomycin. Notably, during this study, the use of vancomycin/SDD was associated with one VRE-outbreak in 13 patients [42]. These data suggest that the spread of MRSA may well be suppressed by the use of vancomycin-containing SDD. An alternative for the use of vancomycin is the combination of SDD with nasal mupirocin and chlorhexidine bodywashing. In a French study, Camus and co-workers found an increase in MRSA infections in SDD treated patients that could be completely prevented by adding mupirocin and chlorhexidine to this regimen [43].

The effects of SDD on the spread of VRE are largely unknown. In VRE-naïve-settings, SDD had no effect on colonization with VRE [10, 24]. SDD has not been studied in settings with endemic VRE.

Conclusion

Over the last 20 years of research, the use of SDD to treat patients in ICUs has been a highly controversial issue. From many randomized trials, we now know that SDD lowers mortality of ICU patients when given in settings with low prevalence of MRSA and VRE. SOD may be as effective as SDD, but its benefits have been reported in one study only.

All available evidence points to a reduction in resistance of aerobic Gram-negative bacteria when SDD is used. This reduction may be caused by the very high fecal concentrations of antibiotics killing all aerobic Gram-negative bacteria, even when minimum inhibitory concentration (MIC) values are moderately increased.

Monitoring of resistance remains necessary, but to date no signs of emerging resistance after long-term use have been reported. One of the most important remaining questions is the role of SOD, particularly with respect to effects on resistance. The only study performed so far showed that resistance during SOD was higher than during the use of SDD.

Resistance against methicillin in *S. aureus* may be increased during SDD and probably also during use of SOD. This has only been shown in areas with a high prevalence of MRSA. In studies in areas where MRSA is rare, the incidence did not increase after introduction of SDD. In areas where MRSA is endemic, SDD may have to be adapted, e.g., by adding vancomycin or mupirocin and chlorexidine bodywashing. Research in these settings is urgently needed. Unfortunately, despite all evidence that the concept of enteral administration of non-absorbable antibiotics may substantially lower mortality in ICU patients, and that it may lower resistance in Gram-negative bacteria, in most countries SDD is still an 'elephant in the room', a controversial issue that is obvious, but which is being ignored or unaddressed, generally because it causes embarrassment or is taboo [44].

References

1. Chastre J, Fagon JY (2002) Ventilator-associated pneumonia. Am J Respir Crit Care Med 165: 867–903
2. Bonten MJ, Kollef MH, Hall JB (2004) Risk factors for ventilator-associated pneumonia: from epidemiology to patient management. Clin Infect Dis 38: 1141–1149
3. Burgmann H, Hiesmayr JM, Savey A, Bauer P, Metnitz B, Metnitz PG (2010) Impact of nosocomial infections on clinical outcome and resource consumption in critically ill patients. Intensive Care Med 36: 1597–1601
4. Iregui M, Ward S, Sherman G, Fraser VJ, Kollef MH (2002) Clinical importance of delays in the initiation of appropriate antibiotic treatment for ventilator-associated pneumonia. Chest 122: 262–268
5. Silvestri L, Monti BC, Milanese M, et al (1999) Are most ICU infections really nosocomial? A prospective observational cohort study in mechanically ventilated patients. J Hosp Infect 42: 125–133
6. Garrouste-Org, Chevret S, Arlet G, et al (1997) Oropharyngeal or gastric colonization and nosocomial pneumonia in adult intensive care unit patients. A prospective study based on genomic DNA analysis. Am J Respir Crit Care Med 156: 1647–1655
7. Bonten MJ, Gaillard CA, van Tiel FH, Smeets HG, van der Geest S, Stobberingh EE (1994) The stomach is not a source for colonization of the upper respiratory tract and pneumonia in ICU patients. Chest 105: 878–884
8. Bonten MJ (2006) Selective digestive tract decontamination--will it prevent infection with multidrug-resistant gram-negative pathogens but still be applicable in institutions where methicillin-resistant Staphylococcus aureus and vancomycin-resistant enterococci are endemic? Clin Infect Dis 43 (Suppl 2): S70-S74
9. Stoutenbeek CP, van Saene HK, Miranda DR, Zandstra DF (1983) A new technique of infection prevention in the intensive care unit by selective decontamination of the digestive tract. Acta Anaesthesiol Belg 34: 209–221
10. de Jonge E, Schultz MJ, Spanjaard L, et al (2003) Effects of selective decontamination of digestive tract on mortality and acquisition of resistant bacteria in intensive care: a randomised controlled trial. Lancet 362: 1011–1016
11. Krueger WA, Lenhart FP, Neeser G, et al (2002) Influence of combined intravenous and topical antibiotic prophylaxis on the incidence of infections, organ dysfunctions, and mortality in critically ill surgical patients: A prospective, stratified, randomized, double-blind, placebo-controlled clinical trial. Am J Respir Crit Care Med 166: 1029–1037
12. Abele-Horn M, Dauber A, Bauernfeind A, et al (1997) Decrease in nosocomial pneumonia

in ventilated patients by selective oropharyngeal decontamination (SOD). Intensive Care Med 23: 187 – 195
13. Aerdts SJ, van Dalen R, Clasener HA, Festen J, van Lier HJ, Vollaard EJ (1991) Antibiotic prophylaxis of respiratory tract infection in mechanically ventilated patients. A prospective, blinded, randomized trial of the effect of a novel regimen. Chest 100: 783 – 791
14. Blair P, Rowlands BJ, Lowry K, Webb H, Armstrong P, Smilie J (1991) Selective decontamination of the digestive tract: a stratified, randomized, prospective study in a mixed intensive care unit. Surgery 110: 303 – 309
15. Cockerill FR, III, Muller SR, Anhalt JP, et al (1992) Prevention of infection in critically ill patients by selective decontamination of the digestive tract. Ann Intern Med 117: 545 – 553
16. Jacobs S, Foweraker JE, Roberts SE (1992) Effectiveness of selective decontamination of the digestive tract in an ICU with a policy encouraging a low gastric pH. Clin Intensive Care 3: 52 – 58
17. Kerver AJ, Rommes JH, Mevissen-Verhage EA, et al (1988) Prevention of colonization and infection in critically ill patients: a prospective randomized study. Crit Care Med 16: 1087 – 1093
18. Palomar M, Alvarez-Lerma F, Jorda R, Bermejo B (1997) Prevention of nosocomial infection in mechanically ventilated patients: selective digestive decontamination versus sucralphate. Clin Intensive Care 8: 228 – 235
19. Rocha LA, Martin MJ, Pita S, et al (1992) Prevention of nosocomial infection in critically ill patients by selective decontamination of the digestive tract. A randomized, double blind, placebo-controlled study. Intensive Care Med 18: 398 – 404
20. Sanchez Garcia M, Cambronero Galache JA, Lopez DJ, et al (1998) Effectiveness and cost of selective decontamination of the digestive tract in critically ill intubated patients. A randomized, double-blind, placebo-controlled, multicenter trial. Am J Respir Crit Care Med 158: 908 – 916
21. Ulrich C, Harinck-de Weerd JE, Bakker NC, Jacz K, Doornbos L, de Ridder VA (1989) Selective decontamination of the digestive tract with norfloxacin in the prevention of ICU-acquired infections: a prospective randomized study. Intensive Care Med 15: 424 – 431
22. Verwaest C, Verhaegen J, Ferdinande P, et al (1997) Randomized, controlled trial of selective digestive decontamination in 600 mechanically ventilated patients in a multidisciplinary intensive care unit. Crit Care Med 25: 63 – 71
23. Winter R, Humphreys H, Pick A, MacGowan AP, Willatts SM, Speller DC (1992) A controlled trial of selective decontamination of the digestive tract in intensive care and its effect on nosocomial infection. J Antimicrob Chemother 30: 73 – 87
24. de Smet AM, Kluytmans JA, Cooper BS, et al (2009) Decontamination of the digestive tract and oropharynx in ICU patients. N Engl J Med 360: 20 – 31
25. Rodriguez-Roldan JM, Altuna-Cuesta A, Lopez A, et al (1990) Prevention of nosocomial lung infection in ventilated patients: use of an antimicrobial pharyngeal nonabsorbable paste. Crit Care Med 18: 1239 – 1242
26. Bergmans DC, Bonten MJ, Gaillard CA, et al (2001) Prevention of ventilator-associated pneumonia by oral decontamination: a prospective, randomized, double-blind, placebo-controlled study. Am J Respir Crit Care Med 164: 382 – 388
27. Pugin J, Auckenthaler R, Lew DP, Suter PM (1991) Oropharyngeal decontamination decreases incidence of ventilator-associated pneumonia. A randomized, placebo-controlled, double-blind clinical trial. JAMA 265: 2704 – 2710
28. Laggner AN, Tryba M, Georgopoulos A, et al (1994) Oropharyngeal decontamination with gentamicin for long-term ventilated patients on stress ulcer prophylaxis with sucralfate? Wien Klin Wochenschr 106: 15 – 19
29. Bonten MJ, Kullberg BJ, van Dalen R, et al (2000) Selective digestive decontamination in patients in intensive care. The Dutch Working Group on Antibiotic Policy. J Antimicrob Chemother 46: 351 – 362
30. Benus RF, Harmsen HJ, Welling GW, et al (2010) Impact of digestive and oropharyngeal decontamination on the intestinal microbiota in ICU patients. Intensive Care Med 36: 1394 – 1402
31. Roberts RR, Hota B, Ahmad I, et al (2009) Hospital and societal costs of antimicrobial-

resistant infections in a Chicago teaching hospital: implications for antibiotic stewardship. Clin Infect Dis 49: 1175 – 1184
32. Heininger A, Meyer E, Schwab F, Marschal M, Unertl K, Krueger WA (2006) Effects of long-term routine use of selective digestive decontamination on antimicrobial resistance. Intensive Care Med 32: 1569 – 1576
33. Oostdijk EA, de Smet AM, Blok HE, et al (2010) Ecological effects of selective decontamination on resistant gram-negative bacterial colonization. Am J Respir Crit Care Med 181: 452 – 457
34. Gastinne H, Wolff M, Delatour F, Faurisson F, Chevret S (1992) A controlled trial in intensive care units of selective decontamination of the digestive tract with nonabsorbable antibiotics. The French Study Group on Selective Decontamination of the Digestive Tract. N Engl J Med 326: 594 – 599
35. Hammond JM, Potgieter PD, Saunders GL, Forder AA (1992) Double-blind study of selective decontamination of the digestive tract in intensive care. Lancet 340: 5 – 9
36. Ferrer M, Torres A, Gonzalez J, et al (1994) Utility of selective digestive decontamination in mechanically ventilated patients. Ann Intern Med 120: 389 – 395
37. Wiener J, Itokazu G, Nathan C, Kabins SA, Weinstein RA (1995) A randomized, double-blind, placebo-controlled trial of selective digestive decontamination in a medical-surgical intensive care unit. Clin Infect Dis 20: 861 – 867
38. Lingnau W, Berger J, Javorsky F, Lejeune P, Mutz N, Benzer H (1997) Selective intestinal decontamination in multiple trauma patients: prospective, controlled trial. J Trauma 42: 687 – 694
39. de la Cal MA, Cerda E, Garcia-Hierro P, et al (2005) Survival benefit in critically ill burned patients receiving selective decontamination of the digestive tract: a randomized, placebo-controlled, double-blind trial. Ann Surg 241: 424 – 430
40. Lingnau W, Berger J, Javorsky F, Fille M, Allerberger F, Benzer H (1998) Changing bacterial ecology during a five-year period of selective intestinal decontamination. J Hosp Infect 39: 195 – 206
41. Cerda E, Abella A, de la Cal MA, et al (2007) Enteral vancomycin controls methicillin-resistant Staphylococcus aureus endemicity in an intensive care burn unit: a 9-year prospective study. Ann Surg 245: 397 – 407
42. de la Cal MA, Cerda E, van Saene HK, et al (2004) Effectiveness and safety of enteral vancomycin to control endemicity of methicillin-resistant Staphylococcus aureus in a medical/surgical intensive care unit. J Hosp Infect 56: 175 – 183
43. Camus C, Bellissant E, Sebille V, et al (2005) Prevention of acquired infections in intubated patients with the combination of two decontamination regimens. Crit Care Med 33: 307 – 314
44. Elephant in the room. Definition, available at http://en.wikipedia.org/wiki/Elephant_in_the_room. Accessed Nov 2010

New Treatment Options against Gram-negative Organisms

M. Bassetti, F. Ginocchio, and M. Mikulska

Introduction

In recent years, infections caused by multi-drug resistant (MDR) pathogens have become a serious problem, especially in the nosocomial setting. The World Health Organization (WHO) has identified antimicrobial resistance as one of the three most important problems for human health. Some authors have summarized this phenomenon with the word 'ESKAPE', to include the most frequent MDR microorganisms: *Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa* and *Enterobacter* spp. [1]. Resistance to the current library of antibacterial drugs is a serious problem in all parts of the world including the Asia-Pacific region, Latin America, Europe, and North America.

Numerous classes of antimicrobials are currently available for physicians to use in the treatment of patient with infections; however, the pace of antibiotic drug development has slowed during the last decade (**Fig. 1**). In particular, the pharmaceutical pipeline of antibiotics active against MDR Gram-negative bacteria is very limited. New antibiotics that have been discovered and introduced into clinical practice in the last few years are active mostly against Gram-positive organisms, whereas when targeting resistant Gram-negative bacteria, clinicians are forced to rediscover old drugs, such as polymixins and fosfomycin. Among new antibacterials active against Gram-negative microorganisms that are already on the market, tigecycline, the first Food and Drug Administration (FDA)-approved representative of the glycylcyclines, and doripenem, a new carbapenem, seem the most promising.

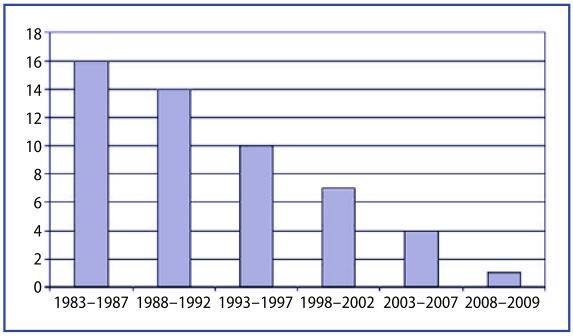

Fig. 1. New antibacterial agents approved in the United States, 1983–2009. From [3] with permission

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Since 2001, different agencies and societies have tried to draw attention to the significant lack of new antibiotics for Gram-negative pathogens. In fact, in 2004 the Infectious Diseases Society of America (IDSA) issued their report, "Bad Bugs, No Drugs: As Antibiotic Discovery Stagnates, A Public Health Crisis Brews," which proposed incentives to reinvigorate pharmaceutical investment in antibiotic research and development [2]. In 2007, the IDSA and the FDA repeated their call for an increase in new antibacterial research to develop next-generation drugs [3]. Recently, the IDSA supported an initiative of developing 10 new systemic antibacterial drugs through the discovery of new drug classes, as well as exploring possible new molecules from existing classes of antibiotics (the "10 x '20" initiative, endorsed by the American Academy of Pediatrics, American Gastroenterological Association, Trust for America's Health, Society for Healthcare Epidemiology of America, Pediatric Infectious Disease Society, Michigan Antibiotic Resistance Reduction Coalition, National Foundation for Infectious Diseases, and European Society of Clinical Microbiology and Infectious Diseases) [4].

The profile of resistance to currently used antimicrobial agents and the development of new anti-Gram-negative agents, with a particular attention to cephalosporins, β-lactamase inhibitors and carbapenems will be discussed.

Mechanism of Resistance to Currently used Antimicrobial Agents in Multi-Drug Resistant Gram-Negative Bacteria

β-lactamase-mediated resistance is the most important and efficient method of β-lactam resistance for Gram-negative bacteria. The origin of β-lactamases is presumably ancient and their development evolved to combat natural β-lactams. However, resistance has been heavily influenced over the years by the widespread administration of these antibiotics in clinical practice. For example, the rapid increase in resistance to the widely-used ampicillin in the early 1960s turned out to be due to a plasmid-mediated β-lactamase, one of the first described in Gram-negative bacteria, known as TEM (the TEM 1 enzyme was originally found in *Eschericihia coli* isolated from a patient named Temoniera, hence named TEM). The further selection of resistant mutants led to the appearance of extended-spectrum β-lactamases (ESBLs) that now compromise the use of even third-generation cephalosporins. In the 1990s, the pharmaceutical industry introduced carbapenems, which are extremely stable to degradation by β-lactamases. However, a variety of β-lactamases that are capable of hydrolyzing these antibiotics, including imipenemase (IMP), Verona integron-encoded MBL (VIM), *K. pneumoniae* carbapenemase (KPC) and oxacillinase (OXA) are being increasingly seen in Gram-negative bacterial isolates.

Different classifications of β-lactamases have been proposed, but the Ambler classification is the most widely used and divides β-lactamases into four classes (A, B, C and D) based upon their amino acid sequences (**Table 1**) [5, 6]. Briefly, class A enzymes are plasmid-mediated penicillinases, constitutively expressed and susceptible to inhibition by β-lactamase inhibitors; representative enzymes include TEM and sulfhydryl reagent variable (SHV) subclasses. Some evolved class A β-lactamases accept extended-spectrum cephalosporins as substrates and are known as ESBLs, even if there are ESBL enzymes belonging to other classes as well. Class B enzymes are metallo-β-lactamases (MBL) with broad substrate specificity that includes not only penicillins and cephalosporins, but also carbape-

Table 1. Classification schemes for bacterial β-lactamases.

Bush-Jacoby group (2009)	Molecular class (subclass)	Distinctive substrate(s)	Defining characteristic(s)	Representative enzyme(s)
1	C	Cephalosporins	Greater hydrolysis of cephalosporins than benzylpenicillin; hydrolyzes cephamycins	*E. coli* AmpC, P99, ACT-1, CMY-2, FOX-1, MIR-1
1e	C	Cephalosporins	Increased hydrolysis of ceftazidime and often other oxyimino-β-lactams	GC1, CMY-37
2a	A	Penicillins	Greater hydrolysis of benzylpenicillin than cephalosporins	PC1
2b	A	Penicillins, early cephalosporins	Similar hydrolysis of benzylpenicillin and cephalosporins	TEM-1, TEM-2, SHV-1
2be	A	Extended-spectrum cephalosporins, monobactams	Increased hydrolysis of oxyimino-β-lactams (cefotaxime, ceftazidime, ceftriaxone, cefepime, aztreonam)	TEM-3, SHV-2, CTX-M-15, PER-1, VEB-1
2br	A	Penicillins	Resistance to clavulanic acid, sulbactam, and tazobactam	TEM-30, SHV-10
2ber	A	Extended-spectrum cephalosporins, monobactams	Increased hydrolysis of oxyimino-β-lactams combined with resistance to clavulanic acid, sulbactam, and tazobactam	TEM-50
2c	A	Carbenicillin	Increased hydrolysis of carbenicillin	PSE-1, CARB-3
2ce	A	Carbenicillin, cefepime	Increased hydrolysis of carbenicillin, cefepime, and cefpirome	RTG-4
2d	D	Cloxacillin	Increased hydrolysis of cloxacillin or oxacillin	OXA-1, OXA-10
2de	D	Extended-spectrum cephalosporins	Hydrolyzes cloxacillin or oxacillin and oxyimino-β-lactams	OXA-11, OXA-15
2df	D	Carbapenems	Hydrolyzes cloxacillin or oxacillin and carbapenems	OXA-23, OXA-48
2e	A	Extended-spectrum cephalosporins	Hydrolyzes cephalosporins. Inhibited by clavulanic acid but not aztreonam	CepA
2f	A	Carbapenems	Increased hydrolysis of carbapenems, oxyimino-β-lactams, cephamycins	KPC-2, IMI-1, SME-1
3a	B (B1)	Carbapenems	Broad-spectrum hydrolysis including carbapenems but not monobactams	IMP-1, VIM-1, CcrA, IND-1
	B (B3)			L1, CAU-1, GOB-1, FEZ-1
3b	B (B2)	Carbapenems	Preferential hydrolysis of carbapenems	CphA, Sfh-1
NI	Unknown			

Adapted from [5].

nems. Class C enzymes are primarily chromosomally encoded cephalosporinases and are often referred to as AmpC β-lactamases resistant to inhibition by β-lactamase inhibitors. Finally, class D β-lactamases have a substrate preference for oxacillin and are therefore called oxacillinases. This class diversity is a crucial aspect for antimicrobial therapy. Recently, a new plasmid MBL, the New Delhi MBL (NDM-1) was identified in *K. pneumoniae* and *E. coli* recovered from a Swedish patient who was admitted to hospital in New Delhi, India [7]. Of particular concern is that NDM enzymes are present in *E. coli*, the most common cause of community-associated urinary tract infections. The NDM-producing bacteria are resistant to many groups of antibiotics, including fluoroquinolones, aminoglycosides, and β-lactams (especially carbapenems), and are susceptible only to colistin and tigecycline [7]. Nevertheless, even these two agents might lose their activity.

The target of the antimicrobial action of colistin is the bacterial cell membrane and studies on colistin-resistant *P. aeruginosa* strains have reported alterations at the outer membrane of the cell, leading to resistance [8]. Thus, colistin might not be a long-standing treatment option for MDR Gram-negative bacteria. As far as resistance to tigecycline is concerned, low concentrations attained in the serum are probably the driving force for the development of resistance while on treatment, particularly when the minimum inhibitory concentrations (MICs) of the targeted pathogen exceed the Cmax of the drug, which is almost the rule for all targeted *A. baumannii* strains [9]. The genetic basis of development of resistance has been investigated with molecular studies and efflux pumps seem to be the most important mechanism of decreased susceptibility. Various efflux pumps have been reported in *E. coli, E. cloacae*, *K. pneumoniae* and *A. calcoaceticus-A. baumannii* [10].

Gram-negative Resistant Bacteria and Drug Development Needs

Given the continuous increase in antibiotic resistance, the IDSA's Antimicrobial Availability Task Force identified development needs for the ESKAPE pathogens, including Gram-negatives such as *E. coli*, *Klebsiella* spp., *Enterobacter* spp., *P. aeruginosa* and *Acinetobacter* spp. [1, 11].

In *Enterobacteriaceae*, the main resistance problems stem from production of ESBL, inducible chromosomal cephalosporinases and carbapenemases, including *K. pneumoniae* carbapenemase (KPC)-hydrolyzing β-lactamases [12]. Infections due to ESBL-producing *E. coli* and *Klebsiella* spp. continue to increase in frequency and severity. In an interesting meta-analysis of 16 studies, bacteremias caused by ESBL-producing pathogens were significantly associated with delayed initiation of effective therapy and increased crude mortality [13]. Additionally, *Enterobacter* causes an increasing number of health care-associated infections and is increasingly resistant to multiple antibacterials [12]. *Enterobacter* infections, especially bloodstream infections, are associated with significant morbidity and mortality [14]. Unfortunately, drugs in late stage development, as well as the recently approved doripenem, offer little advantage over already existing carbapenems for treating infections due to ESBL-producing bacteria. Moreover, carbapenem-resistant *Enterobacteriaceae* are increasingly recognized as the cause of sporadic infections and outbreaks worldwide [15, 16]. Thus, tigecycline and the polymyxins, including colistin, have been used with variable success rates and there

are currently no antibacterials in advanced development for these highly resistant pathogens [17]. Aggressive infection-control practices are required to abort epidemic outbreaks.

Rates of infection by resistant *P. aeruginosa* continue to increase in the United States and globally, as does resistance to β-lactams, quinolones, aminoglycosides, and carbapenems [18]. Resistance of *P. aeruginosa* to polymyxins has also been reported. Patients at risk include those in the intensive care unit (ICU), particularly if they are ventilator dependent, and individuals with cystic fibrosis. To date, no drug in clinical development addresses the issue of MDR or offers a less toxic alternative to the polymyxins for treating *P. aeruginosa*.

Last but not least, the incidence of infections due to MDR *Acinetobacter* spp. continues to increase globally [19]. Unfortunately, no agents against *Acinetobacter* spp. are under development and infections caused by this pathogen are emblematic of the mismatch between unmet medical needs and the current antimicrobial research and development pipeline.

New β-lactamase Inhibitors

In β-lactam agent/β-lactamase inhibitor combinations, the latter agent potentates the action of the former by protecting it from enzymatic hydrolysis. Currently used β-lactam/β-lactamase inhibitor compounds are highly active against class A and various ESBLs, whereas activity against class C and class D enzymes is poor [20, 21].

Several compounds are now under investigation as potential β-lactamase inhibitors, in different stages of pre-clinical and clinical studies. They can be classified as β-lactams and non-β-lactams according to their molecular structure. Their main advantage over the older β-lactamase inhibitors is conferred by their ability to inhibit class C and D enzymes. Thus, the MICs of various currently used β-lactams, such as piperacillin or ceftazidime, is decreased when administered together with a novel β-lactam inhibitor, and these antibiotics become active

Table 2. Old and new β-lactamase inhibitors and specific activity against different classes of β-lactamases

Inhibitor	Class A	Class B	Class C	Class D	FDA Status
Inhibitors with β-lactam structure					
Clavulanic acid	++	–	+	+	Approved
Tazobactam	++	–	+	+	Approved
Sulbactam	++	–	+	+	Approved
BLI-489	++	UA	++	++	Pre-clinical
Ro 48 – 1220	+++	UA	++	UA	Pre-clinical
4-phenyl cyclic phosphate	+++	UA	++	UA	Pre-clinical
C3-methylene-modified group penicillin sulfone	UA	UA	++	UA	Pre-clinical
BAL 30376	UA	+	++	UA	Pre-clinical
LK-157	++	UA	UA	UA	Pre-clinical
Oxapenems	++	UA	++	++	Pre-clinical
Inhibitors without β-lactam structure					
NXL104	+++	+	++	++	Phase II
ME1071	UA	++	UA	UA	Pre-clinical

UA, unknown activity; FDA: Food and Drug Administration

against ESBL-producing strains. Moreover, their combined use with carbapenems, makes the latter active against MBL-producing strains.

Although the results of studies on the clinical usefulness of new β-lactam inhibitors are not yet available, they seem particularly promising as therapeutic agents. Details of new β-lactam inhibitors are outlined in **Table 2**.

Inhibitors with a β-lactam Structure

Imidazole-substituted 6-methylidene-penem molecules
The unique structure of these compounds (they contain byciclic or triciclic substituents connected by a methydilene linkage to the 6 position of the β-lactam ring) imparts potent activity against class A and C β-lactamases, such as the AmpC enzyme, which is not observed with the currently used inhibitors. Several novel compounds demonstrated excellent *in vitro* inhibition of the TEM-1 enzyme (class A β-lactamases) and AmpC enzyme with significantly higher activity compared with tazobactam [22]. *In vitro* tests showed synergistic activity of these compounds when combined with piperacillin with susceptibility of 90 % of the tested organisms; animal models confirmed the synergistic effect with piperacillin [22, 23]. Among these agents, BLI-489 is the compound with the most promising clinical data. It has shown activity against molecular class A, C and D enzymes, including ESBL as well as class C β-lactamases; some strains that were class C or ESBL producers, classified as non-susceptible to piperacillin/tazobactam, were found to be susceptible to piperacillin/BLI-489 [24].

2β-alkenyl penam sulfones
2β-alkenyl penam sulfones, another group of inhibitors with β-lactam structure, inhibit most of the common types of β-lactamases, with a level of activity depending strongly on the nature of the substituent in the 2β-alkenyl group. Richter et al. demonstrated that Ro 48-1220, the most active inhibitor from this class of compounds, enhanced the action of ceftriaxone against a broad selection of organism producing β-lactamases, including strains of cephalosporinase-producing *Enterobacteriaceae* [25]. In a different study, Ro 48-1220 was at least 15 times more effective than tazobactam against the class C enzymes and reduced the MIC values of ceftriaxone and ceftazidime against the class A plasmid-mediated β-lactamases; less potency was exerted towards SHV-type β-lactamases [26].

4-phenyl cyclic phosphate
4-phenyl cyclic phosphate is a monocyclic acyl phosphonate. It has an irreversible reaction with *E. Cloacae* P99 β-lactamase (Class C). This compound also bound TEM-2 and P99 β-lactamases non-covalently. Similar to other novel inhibitors, it is effective against class A and class C enzymes [27].

C3-modified penicillin sulfones
Buynak et al. reported that C3-methylene-group penicillin sulfones were 10-fold more active against class C β-lactamases compared to sulbactam [28].

Monobactam-based structure compounds
BAL 30376 is a β-lactamase inhibitor and is a combination of BAL 0019764 (a siderophore monobactam), BAL 0029880 (a bridged monobactam which is a class C inhibitor), and clavulanic acid [24]. Page et al. [29] demonstrated the *in vitro*

activity of BAL 30376 against various Gram-negative bacteria. MICs were observed in a range of ≤ 0.06 – 4 mg/l, including most carbapenem-resistant strains. Higher MICs were observed for a few strains of *Acinetobacter* spp., *Enterobacter* spp. and *P. aeruginosa*.

Tricyclic carbapenem inhibitors
LK-157 is a tricyclic carbapenem inhibitor of serine β-lactamases [24]. LK-157 decreased the MICs of aztreonam, ceftazidime, and cefuroxime for *B. fragilis* and a wide range of β-lactamases-producing *Enterobacteriaceae* members. However, LK-157 did not affect the MICs of aztreonam, ceftazidime or cefuroxime against CTX-M producing members of *Enterobacteriaceae* [24].

Oxapenems
Four β-lactamase inhibitors, members of the oxapenems, are being developed (AM-112 – AM-115) and express activity against class A, C, and D enzymes [30]. AM-114 and AM-115 displayed the most potent activity against class A enzymes, comparable to that of clavulanic acid. Activity against class C and class D enzymes was similar to that of AM-112 and AM-113 and was superior to that of clavulanic acid. A synergistic activity of ceftazidime with the oxapenems was demonstrated against SHV- and TEM-producing *E. coli*. Enhanced activity of oxapenems in combination with ceftazidime was also noted against *Pseudomonas* strains and MRSA [31].

Inhibitors with no β-lactam Structure

NXL104
NXL104 is a non-β-lactam compound which inhibits β-lactamases through the formation of a stable covalent carbamoyl linkage. In combination with ceftazidime and cefotaxime against *Enetrobacteriaceae* producing CTX-M ESBLs, it showed a 4 to 8000-fold potentiation of the cephalosporins, with MIC values ≤ 1 for all organisms irrespective of CTX-M type [24]. Against P99, NXL104 showed a stronger inhibition than tazobactam, whereas clavulanic acid was inactive. Another study showed that combination with NXL104 restored the activity of ceftazidime and cefotaxime against isolates producing class A carbapenemases [24]. NXL104/ceftazidime combination is currently undergoing Phase II clinical trials in patients admitted for complicated intra-abdominal and complicated urinary tract infections [32].

Maleic acid derivates
ME1071, previously known as CP3242, is a metallo β-lactamase inhibitor that competitively inhibits IMP-1 and VIM-2. It significantly lowered the MICs of biapenem in a concentration-dependent manner against MBL-producing *P. aeruginosa*. MIC lowering by ME1071 was also shown for IMP- or VIM-producing *E. coli*, *S. marcescens*, *A. baumanii* and *K. pneumoniae* [24].

New Cephalosporins

New cephalosporins are very resistant to penicillinases and two of them have demonstrated anti-methicillin resistant *S. aureus* (MRSA) activity in animal mod-

els of infections. Some of these compounds also showed potent anti-Gram-negative activity. However, there is no evidence of better activity against MDR Gram-negative bacteria compared to older cephalosporins.

Ceftobiprole

Ceftobiprole (formerly BAL-9141) is the active component of the prodrug ceftobiprole medocaril (formerly BAL-5788), and represents a novel cephalosporin with expanded activity against Gram-positive bacteria. It has been engineered to bind highly to penicillin binding protein 2a (PBP2a). Ceftobiprole is stable against some enzymes (non-ESBL class A), but is hydrolyzed by ESBLs and carbapenemases [33]. A study published in 2008 reported that ceftobiprole monotherapy was as effective as vancomycin combined with ceftazidime for treating patients with a broad range of complicated skin and skin-structure infections and infections due to Gram-positive and Gram-negative bacteria [32]. Ceftobiprole is an effective anti-MRSA agent that also has activity against important Gram-negative bacteria, but there is no evidence that ceftobiprole has better activity against class A and class C β-lactamase-producing Gram-negative bacteria compared to ceftazidime.

Ceftaroline

Ceftaroline is a novel semisynthetic anti-MRSA cephalosporin with broad-spectrum activity, which is currently undergoing Phase III clinical trials [35]. Ceftaroline maintains good activity against Gram-negative pathogens: MIC values were 0.06 – 0.5 for *E. coli*, *Klebsiella* spp., *M. morganii* and *Proteus*, and 0.12 – 1 mg/l for *Enterobacter*, *Serratia* and *Citrobacter* spp. MIC value rose to 1 – 2 mg/l for many *Enterobacteriaceae* with classical TEM β-lactamases and were much higher for those with ESBL, hyperproduced AmpC or K1 enzymes. Ceftaroline selected AmpC-derepressed *Enterobacter* mutants. Similar to cefotaxime in single-step experiments, in multistep procedures it selected ESBL variants of TEM [36]. Another study showed that ceftaroline was synergistic with the β-lactamase inhibitor, tazobactam, (up to 500-fold) against MDR Gram-negative pathogens such as ESBL-producing *E. coli* and *K. pneumoniae* [37].

Despite being active against resistant Gram-positive bacteria, ceftaroline was less active than currently used antimicrobial agents against Gram-negatives. A combination of vancomycin plus aztreonam demonstrated higher favorable microbiological response rates than did ceftaroline monotherapy against Gram-negative infections. The efficacy of ceftaroline against non-ESBL-producing *E. coli* and *K. pneumoniae* was comparable to that of aztreonam; however, the efficacy of aztreonam against *P. aeruginosa* and *Proteus mirabilis* infection was better than that of ceftaroline [38].

New Carbapenems

Carbapenems are a class of broad-spectrum β-lactams identified in the late 1970s. The main advantage of this class of antibiotics is their stability to hydrolysis by many ESBLs. At present, meropenem and imipenem/cilastatin are widely used and are recommended for treatment of several nosocomial infections such as

Table 3. FDA status and pharmacokinetic characteristics of new carbapenems.

Drug	FDA status	Dose	Administration	Half-life (h)	Active against			
					P. aeruginosa	MRSA	VRE	PRP
Ertapenem	Approved	1 g qd	i.v.	4	–	–	–	–
Doripenem	Approved	500 mg tid	i.v.	1	+	–	–	+
Biapenem	Phase II	300 mg bid	i.v.	1.03	+	–	–	+
Panipenem	Approved in Japan, China and Korea	0,5/0,5 g bid	i.v.	1.10 – 0.7	–	–	–	+
Tebipenem	Phase II	4 or 6 mg/kg bid	oral	U	–	–	U	+
Tomopenem	Phase II	700 mg	i.v.	1.7	+	+		
Razupenem	Phase II	U	i.v.	U	+	+	+	
Trinems		U	U	U	–	U	+/–	–

i.v.: intravenous; MRSA: methicillin-resistant *S. aureus*; PRP: penicillin-resistant pneumococci; U: unknown; VRE: vancomycin-resistant enterococci; +: active; –: non active; +/–: data only on small number of strains

pneumonia (if MRSA is excluded), complicated urinary tract infections, complicated intra-abdominal infections, febrile neutropenia, septicemia, complicated skin and skin-structure infections and meningitis. Imipenem is hydrolyzed by renal dehydropeptidase I (DHP-I) and this process produces a nephrotoxic compound; consequently cilastatin, the DHP-I inhibitor without antibacterial activity, is always co-administered with imipenem in a 1:1 ratio. Other carbapenems do not require DHP-1 inhibitors.

Three mechanisms of acquired resistance to carbapenems are known: 1) structural changes in PBPs; 2) carbapenemases; and 3) changes in membrane permeability through the loss of specific porins [39].

Over ten novel compounds are reported in different phases of clinical development; two of them are currently marketed and available (ertapenem and doripenem), others are in phase II clinical trials while several are still being investigated in pre-clinical studies (**Table 3**). Of note, two of the novel carbapenems are developed to be administered orally.

Ertapenem

Ertapenem was licensed in the US in 2001 and in Europe in 2002. Its main indications include: Intra-abdominal infections, complicated skin and skin-structure infections, complicated urinary tract infections, acute pelvic infections and community acquired pneumonia. The most important pharmacokinetic feature of this drug is due to its net negative charge that increases its binding to plasma proteins (95 %), which results in a long half-life permitting once-daily administration [40]. The main limitation of ertapenem is its limited activity against non-fermenting

Gram-negative bacteria, such as *P. aeruginosa, Acinetobacter* spp. and *B. cepacia* [40]. Even though its activity against Gram-negative ESBL-producers seems to be lower than other carbapenems, ertapenem is approved for the treatment of infections caused by these bacteria. All three above-mentioned mechanisms of acquired resistance to carbapenems have been reported for ertapenem [40]. The role of ertapenem in the treatment of ventilator-associated pneumonia (VAP) was investigated in a pilot study, which reported that ertapenem was useful for treating early-onset VAP due to ESBL-producers, with clinical success achieved in 80 % of patients and microbiological success in 75 % of cases [41].

Doripenem

Doripenem is a new broad-spectrum, parenteral carbapenem with a chemical structure that confers β-lactamase stability and resistance to inactivation by renal DHP-I. It is as active as imipenem or ertapenem against Gram-positive cocci (methicillin-susceptible *S. aureus* [MSSA] and coagulase negative staphylococci), but anti-Gram-negative activity is similar to that of meropenem, and two to three fold superior to imipenem [42]. However, doripenem has no activity against MRSA, *E. fecium*, some strains of *Burkholderia* spp. and *Stenotrophomonas maltophilia* [42]. In an extensive study, in which the activity of 24 antibiotics was tested against 394 strains, doripenem was fully active against AmpC and other ESBL-producing *Enterobacteriaceae* [43]. Additionally, doripenem was found to be more active against *Acinetobacter* spp. and *P. aeruginosa* when the same susceptible and intermediate concentrations were used for imipenem and meropenem. Other strains that remained inhibited by doripenem concentrations ≤ 4 microg/ml were penicillin-resistant streptococci, *H. influenzae* with all resistance patterns tested, and many *Enterobactericeae* resistant to other carbapenems because of outer membrane protein alterations, hyperexpression of AmpC or acquisition of a Bush group 2f carbapenemase [43]. At a dose of 500 mg every 8 h, doripenem is effective against strains with a MIC < 2 mg/l and dose adjustment is required only when creatinine clearance is < 30 ml/min. *In vivo* animal studies demonstrated that the incidence of seizures with doripenem was lower than with other carbapenems and at the recommended dosage the most frequent adverse events are nausea (3.7 %) and diarrhea (2.5 %).

Biapenem

Biapenem is a new parenteral agent that was approved in Japan in 2002 and it is currently undergoing phase II clinical studies in the USA. The prominent feature of this new carbapenem is related to its high concentration in respiratory tissue and other body fluids. Biapenem has a broad spectrum of activity including against Gram-positive bacteria such as *S. pneumoniae* (also penicillin-resistant strains), MSSA and Gram-negatives including *A. baumannii*, ESBL-producing *Enterobacteriaceae*, *E. cloacae*, *S. marcescens* and *Citrobacter freundii*. Moderate activity with median MIC of 8 mg/l was found against *P. aeruginosa* [44]. Biapenem has a mean plasma half-life of one hour and it is recommended at a dosage of 300 mg twice daily. It requires an adjustment in case of reduced glomerular filtration rate. Biapenem is generally well tolerated and clinical trials reported the incidence of adverse events ranging from 1.9 % to 3.4 % with nausea, skin eruption, vomiting and diarrhea as the most common side effects [45].

Panipenem/betamipron

The combination of panipenem with betamipron, like imipenem/cilastatin, is necessary because betamipron inhibits the renal uptake of panipenem. This combination is approved in Japan, China and Korea for the treatment of lower respiratory tract infections, urinary tract infections, obstetric/gynecological infections, and surgical infections at a dosage of 0.5/0.5 g twice daily as an intravenous infusion over 30–60 mins. The clinical efficacy of panipenem/betamipron was demonstrated in three large, randomized, phase III clinical trials comparing this drug with imipenem/cilastatin in adults with respiratory and urinary tract infections [46–48]. Panipenem's spectrum of activity includes *Enterobacteriaceae* and common respiratory tract pathogens, although meropenem remains the most active carbapenem against *H. influenzae* [49]. Panipenem is not active against *E. faecium* and *S. maltophilia*, and *P. aeruginosa* seems to be resistant, showing MIC90 values of 12.5–25 mg/l [49].

Tebipenem

Tebipenem pivoxil is a prodrug of an oral carbapenem with a high degree of stability to DHP-I and absorption of the active metabolite into the blood from the intestine. While tebipenem is inactive against MBL-producing pathogens and MRSA, good activity against penicillin-susceptible and penicillin-resistant *S. pneumoniae, S. pyogenes, H. influenzae, K. pneumoniae, M. catarrhalis* and *E. coli* has been reported. It is likely to become a specific antibiotic for the treatment of persistent otitis media, upper respiratory infection and bacterial pneumonia in pediatric patients [50]. Phase II clinical studies are being conducted in Japan.

Tomopenem

Tomopenem is a novel 1-methyl carbapenem which inhibits the activity of PBP and disrupts bacterial cell wall peptidoglycan biosynthesis. Tomopenem seems to have a very low rate of spontaneous emergence of resistance. *In vitro* activity against β-lactam susceptible and resistant strains, including MRSA, ceftazidime-resistant *P. aeruginosa* and ESBL-producing *Enterobacteriaceae* has been demonstrated [51].

Other New Carbapenems

Several novel compounds, still in pre-clinical phases of evaluation, are mentioned below, highlighting the results of *in vitro* studies aimed to define the activity spectrum of these new molecules.

1. The group of 2-(thyazol-2-ylthio)-1β-methyl carbapenems includes SM-197436, SM-232721 and SM-232724. These molecules are characterized by a unique 4-substituted thiazol-2-ylthio moiety at the side chain. They exhibit potent anti-MRSA activity but they have insufficient activity against *E. faecium*. As far as Gram-negative bacteria are concerned, these three carbapenems are highly active against *H. influenzae* (including ampicillin-resistant strains), *M. catarrhalis*, and *B. fragilis*, and show antibacterial activity equivalent to that of imipenem for *E. coli*, *K. pneumoniae* and *Proteus* spp. [52]. Similar to other new

carbapenems, these agents may be indicated for nosocomial bacterial infections due to Gram-positive and Gram-negative bacteria, especially multiresistant Gram-positive cocci, including MRSA and vancomycin-resistant enterococci (VRE) [52].

2. Another new compound is CS-023 (RO 4908463). It is more stable to hydrolysis by human DHP-I than meropenem or imipenem and has a broad spectrum of activity against Gram-positive and Gram-negative organisms. CS-023 seems more effective than imipenem and meropenem against MRSA, with an MIC of 4 mg/l. CS-023 is characterized by a low protein binding ratio, a feature which can be useful because the plasma active fraction achieves rapid equilibrium with intracellular fluid [24].
3. ME 1036, previously named CP5609, is a novel parenteral carbapenem. In a recent study, the activity of ME1036 and comparators was evaluated against clinical blood culture isolates from patients with bacteremic community-acquired pneumonia (CAP) requiring hospitalization. The results showed that ME1036 had excellent activity against CAP isolates causing serious invasive infections, including MRSA [53].
4. Razupenem (SMP-601) is a novel compound in phase II of evaluation. In a recent *in vitro* study, razupenem was found to be active against ESBL-producers, but its activity was significantly reduced by AmpC enzymes and carbapenemases [54]. Razupenem's activity can be improved by combining it with other antimicrobial agents: *In vitro* studies have shown a synergistic activity with amikacin or ciprofloxacin against *B. cepacia* and *S. marcescens* [24].
5. Trinems, previously called tribactams, have a carbapenem-related structure with a cyclohexane ring attached across carbon 1 and 2. One of these, sanfetrinem, is administered orally as a hexatil ester. Activity of sanfetrinem against *P. vulgaris* and *K. oxytoca*, which produce a potent class A β-lactamase, was reported in a study from 1998, but no recent studies of trinems have been published [55].

Conclusion

XII

Infections due to MDR Gram-negative bacteria, such as ESBL or carbapenemase-producing Enterobacteriaceae and *A. baumannii* or *P. aeruginosa* remain a serious problem in the hospital setting. Although some promising novel molecules are in the late stages of development, few new antibiotics have been advanced for the treatment of most of the ESKAPE pathogens. Among agents potentially active against Gram-negatives are novel cephalosporins, carbapenems and β-lactamase inhibitors.

Fifth generation cephalosporins have acquired activity against MRSA, but they offer no advantage against Gram-negatives. They are inactive against MDR bacteria, and efficacy of ceftaroline was less than that of aztreonam against *P. aeruginosa*. Some of the novel carbapenems are active against resistant Gram-positives, but when difficult Gram-negatives are involved, their activity is similar to that of meropenem. Finally, β-lactamase inhibitors seem the most promising as they might restore the activity of already known β-lactams against β-lactamase-producing strains. However, their real clinical utility will be known only after results of large clinical trials are available.

Treating patients with infections due to resistant Gram-negative bacteria remains a serious challenge.

References

1. Rice LB (2008) Federal funding for the study of antimicrobial resistance in nosocomial pathogens: No ESKAPE. J Infect Dis 197: 1079 – 1081
2. Infectious Diseases Society of America (2004) Bad Bugs, No Drugs. As Antibiotic Discovery Stagnates... A Public Health Crisis Brews. IDSA, Alexandria
3. Spellberg B, Guidos R, Gilbert D, et al (2008) The epidemic of antibiotic-resistant infections: A call to action for the medical community from the Infectious Diseases Society of America. Clin Infect Dis 46: 155 – 164
4. The 10 x '20 initiative: Pursuing a global commitment to develop 10 new antibacterial drugs by 2020 (2010). Clin Infect Dis 50: 1081 – 1083
5. Bush K, Jacoby GA, Medeiros AA (1995) A functional classification scheme for beta-lactamases and its correlation with molecular structure. Antimicrob Agents Chemother 39: 1211 – 1233
6. Ambler RP (1980) The structure of beta-lactamases. Philosophical transactions of the Royal Society of London 289: 321 – 331
7. Kumarasamy KK, Toleman MA, Walsh TR, et al (2010) Emergence of a new antibiotic resistance mechanism in India, Pakistan, and the UK: A molecular, biological, and epidemiological study. Lancet Infect Dis 10: 597 – 602
8. Moore RA, Chan L, Hancock RE (1984) Evidence for two distinct mechanisms of resistance to polymyxin b in pseudomonas aeruginosa. Antimicrob Agents Chemother 26: 539 – 545
9. Poulakou G, Kontopidou FV, Paramythiotou E, et al (2009) Tigecycline in the treatment of infections from multi-drug resistant gram-negative pathogens. J Infect 58: 273 – 284
10. Keeney D, Ruzin A, Bradford PA (2007) Ram A, a transcriptional regulator, and acrab, an rnd-type efflux pump, are associated with decreased susceptibility to tigecycline in Enterobacter cloacae. Microb Drug Resist 13: 1 – 6
11. Gilbert D (2008) "The truth, if it exists, is in the details". Crit Care Med 36: 1368 – 1369
12. Deshpande LM, Jones RN, Fritsche TR, Sader HS (2006) Occurrence and characterization of carbapenemase-producing Enterobacteriaceae: Report from the sentry antimicrobial surveillance program (2000 – 2004). Microb Drug Resist 12: 223 – 230
13. Schwaber MJ, Carmeli Y (2007) Mortality and delay in effective therapy associated with extended-spectrum beta-lactamase production in Enterobacteriaceae bacteraemia: A systematic review and meta-analysis. J Antimicrob Chemother 60: 913 – 920
14. Lin YC, Chen TL, Ju HL, Chen HS, Wang FD, Yu KW, Liu CY (2006) Clinical characteristics and risk factors for attributable mortality in Enterobacter cloacae bacteremia. J Microbiol Immunol Infect 39: 67 – 72
15. Peleg AY, Franklin C, Bell JM, Spelman DW (2005) Dissemination of the metallo-beta-lactamase gene blaimp-4 among gram-negative pathogens in a clinical setting in Australia. Clin Infect Dis 41: 1549 – 1556
16. Bratu S, Landman D, Haag R, et al (2005) Rapid spread of carbapenem-resistant Klebsiella pneumoniae in New York city: A new threat to our antibiotic armamentarium. Arch Int Med 165: 1430 – 1435
17. Pintado V, San Miguel LG, Grill F, et al (2008) Intravenous colistin sulphomethate sodium for therapy of infections due to multidrug-resistant gram-negative bacteria. J Infect 56: 185 – 190
18. EARSS (2008) European Antimicrobial Resistance Surveillance System; Annual Report. Available at: http://www.ecdc.europa.eu/en/activities/surveillance/EARS-Net/Documents/2008_EARSS_Annual_Report.pdf Accessed Nov 2010
19. Munoz-Price LS, Weinstein RA (2008) Acinetobacter infection. N Engl J Med 358: 1271 – 1281
20. Yang Y, Janota K, Tabei K, et al (2000) Mechanism of inhibition of the class a beta -lactamases pc1 and tem-1 by tazobactam. Observation of reaction products by electrospray ionization mass spectrometry. J Biol Chem 275: 26674 – 26682
21. Bassetti M, Righi E, Viscoli C (2008) Novel beta-lactam antibiotics and inhibitor combinations. Expert Opin Investig Drugs 17: 285 – 296
22. Weiss WJ, Petersen PJ, Murphy TM, et al (2004) In vitro and in vivo activities of novel 6-

methylidene penems as beta-lactamase inhibitors. Antimicrob Agents Chemother 48: 4589 – 4596
23. Venkatesan AM, Agarwal A, Abe T, et al (2004) Novel imidazole substituted 6-methylidene-penems as broad-spectrum beta-lactamase inhibitors. Bioorg Med Chem 12: 5807 – 5817
24. Shahid M, Sobia F, Singh A, et al (2009) Beta-lactams and beta-lactamase-inhibitors in current- or potential-clinical practice: A comprehensive update. Crit Rev Microbiol 35: 81 – 108
25. Richter HG, Angehrn P, Hubschwerlen C, et al (1996) Design, synthesis, and evaluation of 2 beta-alkenyl penam sulfone acids as inhibitors of beta-lactamases. J Med Chem 39: 3712 – 3722
26. Tzouvelekis LS, Gazouli M, Prinarakis EE, Tzelepi E, Legakis NJ (1997) Comparative evaluation of the inhibitory activities of the novel penicillanic acid sulfone ro 48 – 1220 against beta-lactamases that belong to groups 1, 2b, and 2be. Antimicrob Agents Chemother 41: 475 – 477
27. Kaur K, Adediran SA, Lan MJ, Pratt RF (2003) Inhibition of beta-lactamases by monocyclic acyl phosph(on)ates. Biochemistry 42: 1529 – 1536
28. Buynak JD, Ghadachanda VR, Vogeti L, Zhang H, Chen H (2005) Synthesis and evaluation of 3-(carboxymethylidene)- and 3-(carboxymethyl)penicillinates as inhibitors of beta-lactamase. J Org Chem 70: 4510 – 4513
29. Page M, Desarbre E, Geier C, Hofer B. Activity of BAL30376 against gram-negative bacteria. 47th Interscience Conference on Antimicrobial Agents and Chemotherapy, American Society of Microbiology, Abstract F1 – 229
30. Cherry PC, Newall CE, Watson NS (1978) Preparation of the 7-oxo-4-oxa-1-azabicyclo(3.2.0)hept-2-ene system and the reversible cleavage of its oxazoline ring. J Chem Soc Chem Commun 11: 469 – 470
31. Jamieson CE, Lambert PA, Simpson IN (2003) In vitro activities of novel oxapenems, alone and in combination with ceftazidime, against gram-positive and gram-negative organisms. Antimicrob Agents Chemother 47: 2615 – 2618
32. Lee JH, Bae IK, Hee Lee S (2011) New definitions of extended-spectrum beta-lactamase conferring worldwide emerging antibiotic resistance. Med Res Rev (in press)
33. Queenan AM, Shang W, Kania M, Page MG, Bush K (2007) Interactions of ceftobiprole with beta-lactamases from molecular classes A to D. Antimicrob Agents Chemother 51: 3089 – 3095
34. Noel GJ, Bush K, Bagchi P, Ianus J, Strauss RS (2008) A randomized, double-blind trial comparing ceftobiprole medocaril with vancomycin plus ceftazidime for the treatment of patients with complicated skin and skin-structure infections. Clin Infect Dis 46: 647 – 655
35. Sader HS, Fritsche TR, Kaniga K, Ge Y, Jones RN (2005) Antimicrobial activity and spectrum of ppi-0903m (t-91825), a novel cephalosporin, tested against a worldwide collection of clinical strains. Antimicrob Agents Chemother 49: 3501 – 3512
36. Mushtaq S, Warner M, Ge Y, Kaniga K, Livermore DM (2007) In vitro activity of ceftaroline (ppi-0903m, t-91825) against bacteria with defined resistance mechanisms and phenotypes. J Antimicrob Chemother 60: 300 – 311
37. Vidaillac C, Leonard SN, Sader HS, Jones RN, Rybak MJ (2009) In vitro activity of ceftaroline alone and in combination against clinical isolates of resistant gram-negative pathogens, including beta-lactamase-producing enterobacteriaceae and pseudomonas aeruginosa. Antimicrob Agents Chemother 53: 2360 – 2366
38. Corey GR, Wilcox M, Talbot GH, et al (2010) Integrated analysis of CANVAS 1 and 2: phase 3, multicenter, randomized, double-blind studies to evaluate the safety and efficacy of ceftaroline versus vancomycin plus aztreonam in complicated skin and skin-structure infection. Clin Infect Dis 51: 641 – 650
39. Bassetti M, Nicolini L, Esposito S, Righi E, Viscoli C (2009) Current status of newer carbapenems. Curr Med Chem 16: 564 – 575
40. Keating GM, Perry CM (2005) Ertapenem: A review of its use in the treatment of bacterial infections. Drugs 65: 2151 – 2178
41. Bassetti M, Righi E, Fasce R et al (2007) Efficacy of ertapenem in the treatment of early ventilator-associated pneumonia caused by extended-spectrum beta-lactamase-producing organisms in an intensive care unit. J Antimicrob Chemother 60: 433 – 435

42. Anderson DL (2006) Doripenem. Drugs Today (Barc) 42: 399 – 404
43. Jones RN, Huynh HK, Biedenbach DJ (2004) Activities of doripenem (s-4661) against drug-resistant clinical pathogens. Antimicrob Agents Chemother 48: 3136 – 3140
44. Chen HY, Livermore DM (1994) Comparative in-vitro activity of biapenem against enterobacteria with beta-lactamase-mediated antibiotic resistance. J Antimicrob Chemother 33: 453 – 464
45. Perry CM, Ibbotson T (2002) Biapenem. Drugs 62: 2221 – 2234
46. Kumazawa J, Matsumoto T, Kumamoto Y (1992) Phase III comparative clinical trial of panipenem/betamipron (pam/bp) with imipenem/cilastatin sodium (ipm/cs) in complicated urinary tract infections. Nishinihon J Urol 54: 254 – 271
47. Hara K, Hiraga Y, Omichi M (1992) [A comparative study of panipenem/betamipron and imipenem/cilastatin in bacterial pneumonia]. Chemotherapy 40: 509 – 531
48. Hara K, Kouno SKH, Takebe K (1992) [A comparative study of panipenem/betamipron and imipenem/cilastatin in respiratory tract infections]. Chemotherapy 40: 613 – 673
49. Watanabe A, Tokue Y, Takahashi H, et al (2001) Comparative in-vitro activity of carbapenem antibiotics against respiratory pathogens isolated between 1999 and 2000. J Infect Chemother 7: 267 – 271
50. Sato N, Kijima K, Koresawa T, et al (2008) Population pharmacokinetics of tebipenem pivoxil (me1211), a novel oral carbapenem antibiotic, in pediatric patients with otolaryngological infection or pneumonia. Drug metabolism and pharmacokinetics 23: 434 – 446
51. Koga T, Masuda N, Kakuta M, Namba E, Sugihara C, Fukuoka T (2008) Potent in vitro activity of tomopenem (cs-023) against methicillin-resistant staphylococcus aureus and pseudomonas aeruginosa. Antimicrob Agents Chemother 52: 2849 – 2854
52. Ueda Y, Sunagawa M (2003) In vitro and in vivo activities of novel 2-(thiazol-2-ylthio)-1beta-methylcarbapenems with potent activities against multiresistant gram-positive bacteria. Antimicrob Agents Chemother 47: 2471 – 2480
53. Morrissey I, Biek D, Janes R (2009) Me1036, a novel carbapenem, with enhanced activity against clinical isolates causing bacteraemic community-acquired pneumonia. J Antimicrob Chemother 64: 209 – 210
54. Livermore DM, Mushtaq S, Warner M (2009) Activity of the anti-mrsa carbapenem razupenem (ptz601) against enterobacteriaceae with defined resistance mechanisms. J Antimicrob Chemother 64: 330 – 335
55. Babini GS, Yuan M, Livermore DM (1998) Interactions of beta-lactamases with sanfetrinem (gv 104326) compared to those with imipenem and with oral beta-lactams. Antimicrob Agents Chemother 42: 1168 – 1175

Antifungal Therapy in The ICU: The Bug, the Drug, and the Mug

J.M. Pereira and J.A. Paiva

Introduction

The incidence of invasive fungal infections has increased steadily, namely due to the increasing number of immunocompromised and critically ill patients. *Candida* spp. is by far the most frequent fungal pathogen isolated in critically ill patients, accounting for more than 85 % of fungal infections. Intensive care candidiasis represents 25 – 50 % of all invasive candidiasis. The incidence of candidemia, although rather variable from unit to unit, ranging from 2.8 to 22 per 10 000 patient days, is tenfold higher in the intensive care unit (ICU) than in the wards and *Candida* species are responsible for around 10 % of all ICU-acquired infections worldwide. In the recent Sepsis Occurrence in Acutely ill Patients (SOAP) study, *Candida* spp. accounted for 17 % of all cases of sepsis in the ICU and for 20 % of all ICU-acquired sepsis [1]. In the large, multicenter Extended Prevalence of Infection in the ICU (EPIC II) study, fungi were responsible for 20 % of all microbiologically documented infections and *Candida* spp. was the main fungal pathogen (17 %) [2]. However, previously uncommon or even new fungal pathogens are increasing in the ICU, namely *Aspergillus* spp. (mainly *Aspergillus fumigatus*), *Zygomycetes* (mainly *Mucor* and *Rhizopus*) and *Fusarium*. In recent years, several reports have described an increasing incidence of invasive pulmonary aspergillosis in critically ill patients admitted to the ICU, even in the absence of an apparent predisposing immunodeficiency, such as neutropenia or hematologic malignancy. Factors like the use of steroids, chronic obstructive pulmonary disease (COPD) and chronic liver failure seem to be associated with the development of invasive pulmonary aspergillosis in the ICU, whose incidence ranges from 0.3 % to as much as 5.8 % [3 – 5].

Despite antifungal therapy, mortality is high, ranging from 30 to 80 %. Invasive fungal infections are also associated with high morbidity, namely prolonged ICU length of stay, and considerable excess costs. Given its high mortality and high morbidity, early and adequate antifungal therapy is vital.

'Old' (fluconazole and polyenes) and 'new' (second generation azoles – voriconazole and posaconazole – and echinocandins – caspofungin, anidulafungin and micafungin) antifungals are now available for the management of severe fungal infections in the critically ill patient. The choice of antifungal therapy in the ICU should take into account the 'bug' (the fungus), the drug (pharmacokinetics/pharmacodynamics) and the 'mug' (patient).

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The 'Bug'

In order to ensure our antifungal therapy is adequate, it is fundamental to know the spectrum of activity of different classes of antifungals (**Table 1**).

Table 1. Antifungal spectrums of activity

Organism	Amphotericin B	Fluconazole	Voriconazole	Posaconazole	Anidulafungin	Caspofungin	Micafungin
Aspergillus species							
A. flavus	±	–	+	+	+	+	+
A. fumigatus	+	–	+	+	+	+	+
A. niger	+	–	+	+	+	+	+
A. terreus	–	–	+	+	+	+	+
Candida species							
C. albicans	+	+	+	+	+	+	+
C. glabrata	+	±	+	+	+	+	+
C. krusei	+	–	+	+	+	+	+
C. lusitaniae	–	+	+	+	+	+	+
C. parapsilosis	+	+	+	+	±	±	±
C. tropicalis	+	+	+	+	+	+	+
Cryptococcus neoformans	+	+	+	+	–	–	–
Coccidioides species	+	+	+	+	±	±	±
Blastomyces	+	+	+	+	±	±	±
Histoplasma species	+	+	+	+	±	±	±
Fusarium species	±	–	+	+	–	–	–
Scedosporium apiospermium	±	–	+	+	–	–	–
Scedosporium prolificans	–	–	±	±	–	–	–
Zygomycetes	±	–	–	+	–	–	–

+ signs indicate that the antifungal agent has activity against the organism specified. – signs indicate that the antifungal agent does not have activity against the organism specified. ± signs indicate that the antifungal agent has variably activity against the organism specified. Amphotericin B includes lipid formulations.

XII

Fluconazole is a fungistatic agent that is active against most *Candida* species, *Cryptococcus neoformans*, *Coccidioides immitis*, *Histoplasma capsulatum*, *Paracoccidioidis brasiliensis*, *Sporothrix shenckii* and *Blastomyces dermatiditis* [6, 7]. It is ineffective against *Aspergillus* and *Mucor* species. *Candida glabrata* is frequently resistant to fluconazole and fluconazole has virtually no activity against *Candida krusei*, which has intrinsic resistance to the drug [8–10]. The widespread use of fluconazole in repeated low-dose courses, as prophylaxis or therapy, has resulted in acquired fungal resistance. Fluconazole-resistant strains of *Candida albicans* have become more and more common among patients with acquired immunodeficiency syndrome (AIDS) [11, 12] and more recently in non-human immunodeficiency virus (HIV) patients [13–15]. The SCOPE program showed that the level of resistance of *C. albicans* to fluconazole was 9.6 %, varying between 2.9 % and 15.5 % with geographical location [9].

Itraconazole is a fungistatic agent active against *Aspergillus* species [16]; European studies report response rates of 63–70 % for aspergillosis and the response is better in pulmonary than in disseminated aspergillosis. Itraconazole is also

active against many *Candida* species, and isolates that are resistant to fluconazole are not necessarily cross-resistant to itraconazole [17], such as is the case of some *C. krusei* and *C. glabrata*. However, strains of *Candida* spp. which are highly resistant to fluconazole often have reduced susceptibility to itraconazole and even to the newer azoles, as the SCOPE program has shown [9, 18, 19].

Voriconazole has demonstrated broad-spectrum *in vitro* activity. It is fungistatic against *Candida* spp. including fluconazole-resistant *C. krusei*. Depending on the resistance phenotype, *C. albicans* and *C. glabrata* isolates show varying degrees of cross-resistance to voriconazole. Specifically, voriconazole is significantly less active against strains that are resistant to both fluconazole and itraconazole (RR phenotype) than against those that are resistant only to fluconazole (RS phenotype). *C. krusei* is susceptible to voriconazole regardless of resistance phenotype [20]. It is fungicidal against *Aspergillus* spp., including amphotericin B-resistant clinical isolates, as well as against *C. neoformans*, *Scedosporium* spp., and some *Fusarium* isolates. Voriconazole exhibits good activity against *Trichosporon* spp., *B. dermatitidis*, *C. immitis* and *H. capsulatum*. It is inactive against *Mucor* and *Rhizopus*. Ravuconazole has a broad spectrum of activity against pathogenic fungi including *Aspergillus* spp., *Candida* spp., *C. neoformans* and *Trichosporon* spp. [21–26]. The activity of ravuconazole against *Candida* spp. was comparable to that of voriconazole, with the exception of *C. glabrata* where ravuconazole is even less active [26]. *In vitro* studies demonstrate that posaconazole has a broad spectrum activity against *Aspergillus* spp., *Candida* spp., including strains resistant to fluconazole, *C. neoformans*, *Trichosporon* spp., *Zygomycetes* and dermatophytes [26–29]. It seems to be ten times more potent than itraconazole against *Aspergillus* spp.

Amphotericin B may be fungistatic or fungicidal, depending on the concentration obtained and the susceptibility of the fungus, but it has the widest spectrum of activity amongst all the antifungals, with fungicidal effect against *Candida* species, *Aspergillus* species, *B. dermatidis*, *C. immitis*, *C. neoformans*, *H. capsulatum*, *P. brasiliensis* and *S. schenckii*. It is effective in certain forms of mucormycosis, hyalophomycosis and phaeophyphomycosis, but often ineffective in pseudallescheriosis and trichosporonosis and some fusariosis. Treatment failure attributable to the development of amphotericin resistance is rare. *Candida lusitanae* is resistant to amphotericin B [30] and resistant strains of *Candida guillermondii*, *Candida tropicalis* and *C. krusei*, with alterations in the cell membrane, including reduced amounts of ergosterol, have been isolated during treatment. Susceptibility to amphotericin B varies among *Aspergillus* species, being less in *Aspergillus terreus* than in other *Aspergillus* species [31]. However, overall emergence of resistance during treatment is rare [32, 33]. Amphotericin B has been the drug of choice for severe invasive fungal infections in the last thirty years because of its broad fungicidal activity against *Candida* spp. and *Aspergillus* spp. [34, 35]. In clinical studies, response rates were 55 % for *Aspergillus* spp., 55–65 % for *Candida* spp. and 75 % for *Cryptococcus neoformans* [36, 37]. *Candida* with higher minimum inhibitory concentrations (MICs) to amphotericin B are difficult to treat and one should aim for serum levels of 1–2.5 mcg/ml [33].

The echinocandin antifungal spectrum is restricted to *Candida* spp. and *Aspergillus* spp., with few exceptions, and *Pneumocystis jiroveci*. These drugs are not active at clinically relevant concentrations against *Zygomycetes*, *C. neoformans*, *Fusarium* spp. or *Trichosporon* spp, and have only modest activity against *C. immitis*, *B. dermatididis*, *Scedosporium* spp., *Paecilomyces variotii* and *H. capsula-*

tum [38]. All three compounds are fungicidal *in vitro* and *in vivo* against most isolates of *Candida* spp., including *C. glabrata* and *C. krusei*, and fungistatic against *Aspergillus* spp. [38]. MICs of all three echinocandin antifungals are much lower than for amphotericin B and fluconazole against all common *Candida* spp. except *C. parapsilosis* and *C. guillermondii*, for which they are similar. The reduced *in vitro* activity of echinocandins against *C. parapsilosis* seems to be related to amino acid polymorphisms in the major subunit of glucan synthase (Fks1), the echinocandin target [39]. However, an association between MIC and treatment outcome is inconsistent since many isolates with raised MICs appear to respond to standard doses of echinocandins [40]. Very rarely, clinical failures have been associated with echinocandins and the mechanism of such failures appears to be related to amino acid substitutions in two 'hot spot' regions of Fks1 [39]. These mutations confer cross-resistance to all echinocandins agents. Interestingly, echinocandins have a postantifungal effect [36].

In invasive candidiasis, all current antifungals have been shown to be either equivalent or non-inferior to each other in several studies that included critically ill patients [40, 41]. In these clinical trials, success of therapy ranged from 60 % to 83 %. Only one recent randomized study suggested that an echinocandin may be superior to fluconazole as primary therapy for candidemia [42]. According to these results, several international recommendations considered fluconazole and echinocandins as first-line therapy for invasive candidiasis, leaving polyenes as a valid alternative due to their high potential for toxicity (see below). Candins should be preferred for the treatment of *C. glabrata* and *C. krusei* infections and fluconazole for *C. parapsilosis* infections [41, 43].

For invasive pulmonary aspergillosis, the best therapeutic option is voriconazole. This recommendation, supported by international society guidelines, is based on the results of the largest prospective, randomized trial for the treatment of invasive pulmonary aspergillosis [44]. In this study, voriconazole significantly improved not only survival but also overall response rate at 12 weeks and at the end of therapy. In addition, voriconazole was associated with fewer side effects than amphotericin B deoxycholate. A formulation of amphotericin B should be considered as an appropriate alternative for patients who are intolerant or refractory to the first line therapy. Polyenes, posaconazole, itraconazole and echinocandins (caspofungin and micafungin) can be used for salvage therapy [45].

The Drug

The selection of an appropriate antifungal agent depends on multiple factors in addition to the spectrum of activity, namely its pharmacokinetic and pharmacodynamic properties (**Table 2**).

Absorption

Until the early 1990s, intravenous therapy was the only option for the treatment of invasive fungal infections. Several antifungal agents, namely polyenes and echinocandins, do not have appreciable oral bioavailability, so they can only be administered parenterally. Currently, azoles can be administered orally with some differences between members of this class. Oral absorption of fluconazole is good, with more than 80 % of the ingested drug being found in the circulation

Table 2. Pharmacokinetics (PK) of the different antifungal agents

PK parameter	AMB deo	L-AMB	ABLC	ABCD	Fluconazole	Voriconazole	Posaconazole	Anidulafungin	Caspofungin	Micafungin
Oral bioavailability (%)	< 5	< 5	< 5	< 5	95	96		< 5	< 5	< 5
Food effect	NA	NA	NA	NA	No effect	↓	↑	NA	NA	NA
Protein binding (%)	> 95	> 95	> 95	> 95	12	58	99	85	97	99
CSF penetration (%)	0–4	< 5	< 5	< 5	> 60	60	NR	< 5	< 5	< 5
Vitreal penetration (%)	0–38	0–38	0–38	0–38	28–75	38	26	0	0	< 1
Urine penetration (%)	3–20	4.5	< 5	< 5	90	< 2	< 2	< 2	< 2	< 2
Metabolism	Hepatic	Unknown	Unknown	Unknown	Minor hepatic	Hepatic	Hepatic	None	Hepatic	Hepatic
Elimination	In situ	Unkown	Unkown	Unkown	Urine	Urine	Feces	None	Urine	Feces
Toxicity (%)	70–90	15–30	20–40		10–15	10–20		10–15	10–15	10–15
Hepatic	++	++	++	++	+	+	+	+	+	+
Renal	+++	++	+++	+++	–	–	–	–	–	-
Hematologic	+	+	+	+	NR	NR	NR	NR	+	+
Infusion-related	+++	++	+++	+++	–	–	NA	+	+	+
Electrolyte abnormalities	+++	++	++	++	NR	+	NR	+	+	NR

CSF: cerebrospinal fluid; NR: Not reported; NA: No data available; + signs indicate degree of toxicity from mild (+) to severe (+++); AMB deo: amphotericin B deoxycholate; L-AMB: liposomal amphotericin B; ABLC: amphotericin B lipid complex; ABCD: amphotericin B colloidal dispersion

and, unlike itraconazole, it is not affected by the presence of food, gastric pH or disease state. Therefore, identical serum concentrations are attained after enteral and parenteral administration [46]. Voriconazole is available in intravenous and oral formulations. The oral formulation has excellent bioavailability (approximately 96 %), which is reduced with high-fat meals. Like fluconazole, the absorption of voriconazole in not dependent upon gastric pH. Posaconazole is currently available only as an oral suspension with high oral bioavailability, especially when given with fatty foods [41].

Distribution and Penetration

The body distribution of antifungals is another important factor to take into account in the treatment of invasive fungal infections. As demonstrated by relatively large volumes of distribution, the available antifungal agents are widely distributed throughout the body with a few significant exceptions. The main factors affecting drug distribution are molecular size, charge, degree of protein binding and route of elimination.

Many antifungals have large molecular weight, so their ability to penetrate into the central nervous system (CNS) and achieve therapeutic concentrations is limited. Currently, flucytosine, fluconazole and voriconazole have the best cerebrospinal fluid (CSF) penetration, resulting in concentrations of at least 50 % of those seen in serum [47 – 49]. Interestingly, amphotericin B, which is undetectable in the CSF, has been the mainstay of treatment for cryptococcal meningitis. Hence, the relationship between antifungal CSF concentrations and clinical efficacy is a bit misleading. Echinocandins show negligible CSF and vitreal penetration. Thus, azoles and polyenes seem to be the best options for the treatment of severe ocular fungal infections.

Few antifungals are renally eliminated as unchanged drug or active metabolite. Currently, fluconazole and flucytosine are the only drugs that achieve reliable urine concentrations (> 50 % of serum exposure) when given systemically. Voriconazole is excreted in the urine (approximately 80 %), however almost completely (more than 98 %) as metabolites without clinically significant activity [50].

The degree of protein binding is another important issue that influences systemic exposure to the drug, since a protein bound-drug is not available for microbiologic activity. In fact, low serum proteins result in higher concentrations of available or active drug. The polyene agents and many azole antifungals, with the exception of voriconazole (estimated as 58 %) [51] and fluconazole (about 12 %), are highly protein bound (> 90 %) [52]. Protein binding with the echinocandin class varies from 85 % to 99 % for anidulafungin, caspofungin and micafungin [52].

Metabolism and Elimination

All azole antifungals undergo some degree of hepatic metabolism. For fluconazole, the role of metabolism in drug elimination is minimal, but this is not the case with itraconazole, voriconazole and posaconazole, which are highly dependent on metabolism for drug elimination [52].

The routes of metabolism and elimination of amphotericin B are complex [53]. Plasma initial half-life is 24 hours but elimination half-life reaches 15 days. After

12 hours, less than 10 % remains in the blood. Amphotericin B is slowly degraded and plasma levels remain detectable 7 to 8 weeks after treatment is stopped; the drug has been detected for longer than one year in liver, kidney and spleen.

Caspofungin is metabolized by both hepatic hydrolysis and N-acetylation and inactive metabolites are then eliminated in the urine. Micafungin is metabolized by non-oxidative metabolism within the liver. Unlike other echinocandins, anidulafungin is not hepatically metabolized and undergoes unique non-enzymatic degradation in the bloodstream [54].

Drug-drug Interactions

Azoles interfere with the elimination of drugs metabolized by the hepatic cytochrome, P450. The sedative effect of midazolam, the anticoagulant effect of warfarin, the hypoglycemic effect of sulfonylureas, the anticonvulsant effects of phenytoin and carbamazepine, and the effects of theophylline, cisapride and cyclosporine may be increased by fluconazole; on the other hand rifampicin accelerates clearance of fluconazole resulting in reduced serum levels [55 – 58].

As a cytochrome P450 inhibitor, voriconazole is subject to many drug interactions. Concomitant use of rifampin, carbamazepine, long acting barbiturates, cisapride, rifabutin, terfenadine and astemizole is contraindicated [59]. Voriconazole increases plasma concentrations of cyclosporine, tacrolimus, warfarin, statins, benzodiazepines, calcium channel blockers, sulfonylureas. Omeprazole and non-nucleotide reverse transcriptase inhibitors may inhibit voriconazole metabolism and consequently increase serum levels.

Since echinocandins are poor substrates for the cytochrome P450 enzymes and are not substrates for intestinal or tissue P-glycoprotein, fewer drug interactions are described. Slight increases in caspofungin clearance have been seen with powerful inducers of inhibitors of hepatic metabolism, such as efavirenz, phenytoin, nevirapine, nelfinavir, carbamazepine and dexamethasone, so a slight increase in the daily dose of caspofungin (70 mg/day) is appropriate [38]. A slightly reduced exposure to tacrolimus (20 %) was seen with co-administration of caspofungin and monitoring of tacrolimus concentrations is recommended [60]. Cyclosporine and caspofungin seem to interact, resulting in raised caspofungin concentrations, but no change in cyclosporine serum levels [38]. Micafungin may increase levels of sirolimus, nifedipine and cyclosporine. No significant drug-drug interactions have been described for anidulafungin. Results of a combination study of anidulafungin and cyclosporine in healthy volunteers showed a slight increase in exposure to anidulafungin [38].

No interactions were noted with other antifungals, such as itraconazole or amphotericin B [61].

Adverse Effects

Fluconazole is generally well tolerated. Nausea and vomiting are the most common adverse effects, but they seldom cause discontinuation of treatment [62, 63]. Elevation of hepatic enzymes occurs in a small percentage of individuals, but treatment should only be discontinued if there is symptomatic hepatitis or laboratory signs of persistent hepatic dysfunction, which are rare [6, 62, 64 – 66]. Stevens-Johnson syndrome has been described in AIDS and cancer patients, although a causal relationship has not been clearly established. The drug should be discontinued if bullous lesions or erythema multiforme develop [55, 56].

Visual disturbances, including blurring and photophobia, occurred in at least 20 % of subjects in clinical studies of voriconazole. These reactions were transient and typically resolved in spite of continued voriconazole. Patients should be cautioned to avoid driving at night and, as photosensitivity has occurred, advised to stay out of strong, direct sunlight while on voriconazole. The other most common adverse events in clinical trials were fever, nausea, vomiting, chills and abnormal liver function tests. Rare reactions included flushing, fever, diaphoresis, tachycardia, dyspnea, dizziness, nausea, pruritus and rash [50]. Serum levels should be below 5.5 mcg/ml at day 3 to avoid serious side effects [67].

Adverse effects of amphotericin B deoxycholate are significant and may be divided into infusion-related or acute and dose-related or late. The peak frequency of fever, rigors and other infusion-related reactions, caused by production of tumor necrosis factor (TNF) and prostaglandin E by macrophages [68], occurs on the first to third day of therapy and subsequently declines, generally subsiding after one week of therapy even without treatment [69, 70]. Longer infusion times were associated with a reduction in the incidence of infusion-related toxicities. Normochromic, normocytic anemia accompanies most 2 – 3 week courses of amphotericin B, with a decrease in hematocrit by as much as 35 %, occurring secondary to decreased production of erythropoietin rather than to diminished bone marrow production; this effect is reversible when the drug is discontinued [71]. Nephrotoxicity is the most significant toxic effect and about 80 % of patients receiving amphotericin B show some degree of renal impairment, especially those submitted to a cumulative dose higher than 0.5 – 1 g, with sodium depletion, older than 30 years old, with abnormal baseline renal function or receiving other nephrotoxic drugs [72]. Nephrotoxicity manifests as azotemia, decreased urinary concentration ability, renal tubular acidosis, symptomatic hypokalemia or renal magnesium wasting [73]. Signs of nephrotoxicity usually occur within the first four days of treatment. Preventive measures consist of avoiding salt depletion, use of concomitants antibiotics with sodium salts, loading with 0.9 % saline prior to infusion of amphotericin B [73] and use of pentoxifylline [74]. Daily monitoring for increased serum creatinine, hypokalemia and hypomagnesemia during the first weeks of therapy is advisable. Nephrotoxicity is usually reversible by increasing sodium loading, reducing dose, increasing dosing interval with total dose reduction or temporarily suspending the treatment when serum creatinine reaches approximately 3 mg/dl.

In addition to nephrotoxicity and infusion-related reactions, a unique pulmonary reaction can be seen, particularly with certain lipid preparations. With liposomal preparation of amphotericin B, a triad of infusional toxicity has been described consisting of a combination of pulmonary toxicity (chest pain, dyspnea and hypoxia); abdominal, flank or leg pain or flushing; and urticaria. Similarly, severe hypoxia has been described with amphotericin B colloidal dispersion and lipid-complex formulation use. Lipid formulations, namely liposomal amphotericin B, seem to be as effective as the conventional compound with less toxicity.

Adverse events and toxic effects of the echinocandins are few, making them safe agents to administer. The most frequent adverse effects are headache (3 % with micafungin and about 15 % with caspofungin), fever (around 35 % for caspofungin [75 – 77]), hepatotoxicity, phlebitis, histamine release and hemolysis (rare).

Dosage

For invasive candidiasis, a loading dose of fluconazole (12 mg/kg) followed by a daily dose ≥ 6 mg/kg should be administered, since higher doses seem to be associated with a better outcome [41].

In adults weighing more than 40 kg, the recommended oral dosing regimen for voriconazole includes a loading dose of 400 mg twice daily on day one followed by 200 mg twice daily. If it is administered intravenously, after a loading dose of 6 mg/kg twice daily, a maintenance dose of 3 – 4 mg/kg i.v. every 12 hours is recommended [41].

The dosage of posaconazole for salvage treatment in invasive aspergillosis is 800 mg administered in 2 or 4 divided doses. The dosage of the oral suspension for prophylaxis is 200 mg 3 times per day.

For most cases of invasive candidiasis, the usual dosage of Amb-d is 0.5 – 0.7 mg/kg/day, but dosages as high as 1 mg/kg/day should be considered for infections caused by less susceptible species, such as *C. glabrata* or *C. krusei*. The typical dosage for lipid formulations of amphotericin B is 3 – 5 mg/kg/day [41]. For invasive aspergillosis, amphotericin B lipid complex (ABLC) and amphotericin B coloidal dispersion (ABCD) are approved at dosages of 5 mg/kg/day and 3 – 4 mg/kg/day, respectively, and liposomal amphotericin B (L-AMB) is approved at a dosage of 3 – 5 mg/kg/day.

For the echinocandins, a loading dosage for caspofungin (70 mg/day) and anidulafungin (200 mg/day) is necessary. The maintenance dosage for caspofungin, micafungin and anidulafungin is 50 mg/day, 100 mg/day and 100 mg/day, respectively [41].

Taking into account their excellent pharmacokinetic properties, low toxicity and low drug-drug interactions, echinocandins are attractive antifungal compounds for the ICU physician.

The 'Mug'

XII

The host, namely the presence of organ dysfunction (**Table 3**), must be taken into account when selecting antifungal therapy.

Table 3. Dose adjustment and organ dysfunction

Organ dysfunction	AMB deo	L-AMB	ABLC	ABCD	Fluconazole	Voriconazole	Posaconazole	Anidulafungin	Caspofungin	Micafungin
Moderate to severe liver dysfunction	No	No	No	No	No	Yes	No	No	Yes	No
Renal dysfunction	No	No	No	No	Yes	No *	No	No	No	No

* i.v. voriconazole is contraindicated in patients with creatinine clearance < 50 ml/min; AMB deo: amphotericin B deoxycholate; L-AMB: liposomal amphotericin B; ABLC: amphotericin B lipid complex ; ABCD: amphotericin B colloidal dispersion

Renal Dysfunction

As 80 % of fluconazole is excreted by the kidney in its unchanged active form, dosages must be adjusted in renal failure and monitoring of serum levels is recommended, trying to maintain them at 6–20 mcg/ml [78]. The normal recommended dose should be given on day one, followed by a daily dose that should be reduced by 50 % if the creatinine clearance is between 11 and 50 ml/min. Dialysis removes 50 % of the drug and a dose must be administered after each dyalisis [79]. Empirical fluconazole should be administered at a daily dose of 800 mg for critically ill patients receiving continuous veno-venous hemodialysis (CVVHD) or continuous veno-venous hemodiafiltration (CVVHDF) with a combined ultrafiltration and dialysate flow rate of 2 l/h and at a daily dose of 400 mg for patients receiving continuous veno-venous hemofiltration (CVVHF). The dose may be decreased to 400 mg/day (CVVHD or CVVHDF) or to 200 mg/day (CVVHF) if the species is not *C. glabrata* and the fluconazole MIC is ≤ 8 mg/l [80]. In patients with a creatinine clearance lower than 50 ml/min, i.v. voriconazole should not be used as the risk of accumulation of cyclodextrine, to which the drug is complexed, exists. On the other hand, oral voriconazole does not require dosage adjustment for renal failure.

No dose adjustment is necessary for patients with decreased renal function, but amphotericin B compounds should be avoided in patients with impending renal failure or reversible renal dysfunction.

There is no need to adjust echinocandin dose in patients with renal dysfunction.

Hepatic Dysfunction

Hepatic disease can also affect the metabolism of several antifungals. Voriconazole is the only azole that needs dose reduction in patients with mild to moderate disease. In this group of patients, a single oral dose of voriconazole resulted in increases in the area under the curve (AUC) approximately 3.2 times higher than in normal subjects. Therefore, after the standard loading dose, only half of the recommended maintenance dose should be used in these patients. There are no data available in patients with severe hepatic impairment [51]. No dose adjustment is needed for polyenes and echinocandins other than caspofungin. Caspofungin maintenance dose should be reduced to 35 mg/day in patients with moderate to severe hepatic dysfunction.

Clinical/Hemodynamic State

The analysis of retrospective data in invasive candidiasis, suggests that hemodynamically stability should be taken into account for antifungal choices [41, 43]. As such, echinocandins, due to their safety profile, should be preferred as first line therapy for the treatment of invasive candidiasis in patients with severe sepsis or septic shock (hemodynamically unstable). Alternatively, lipid formulations of amphotericin B may be used in these patients. In hemodynamically stable patients without organ dysfunction, fluconazole is a reasonable choice for empiric therapy or microbiologically documented infection, based on its highly favorable safety profile. Alternative drugs to be considered are echinocandins, voriconazole or amphotericin B [41, 43].

Other Specific Populations

Patients with body weight less than 75 kg and albumin levels above 23.6 g/l usually have higher caspofungin serum levels than predicted. There is a higher clearance of caspofungin and of micafungin in children between 2 and 16 years and younger than 9 years old, respectively. There is no effect of age on anidulafungin clearance [81, 82].

Conclusion

Intensivists have access to several options for the treatment of invasive fungal infections. However, it is of paramount importance to know the properties of each antifungal in order to make the right choice. The epidemiology of fungal infections in the ICU is changing, so clinicians must always keep in mind the spectrum of activity of the different classes of antifungals. Antifungal spectra differ between the three major antifungal classes, and even between agents within the classes, and impact on the choice of antifungal drug. Pharmacokinetic/pharmacodynamic attributes, drug-drug interactions and toxicity profiles are also of paramount importance, as they allow antifungal choice to be adapted to the host's characteristics.

Therefore, to make the right choice do not forget "the bug, the drug, and the mug". Currently, echinocandins should be considered as first line therapy in patients with suspected invasive candidiasis, mainly in hemodynamically unstable patients or with prior use of azoles. For *C. glabrata* infections, an echinocandin is the preferred agent. In the management of infection due to *C. parapsilosis*, fluconazole is recommended. However, if the patient initially received an echinocandin, is clinically improving and follow-up cultures are negative, continuing the use of an echinocandin is a reasonable option. Voriconazole can be used as step-down therapy in infections due to *C. krusei* or voriconazole-susceptible *C. glabrata*, but close monitoring of side effects is needed. As long as the patient is not in severe sepsis or septic shock, invasive candidiasis by *C. albicans* or *C. tropicalis* may be treated with fluconazole [41, 43].

Weight, organ function, and concomitant medications are host characteristics that impact on antifungal selection. Namely i.v. voriconazole and amphotericin B should ideally be avoided when impending or potentially reversible renal dysfunction exists and the concomitant use of cytochrome P metabolized drugs may lead one to choose anidulafungin among the echinocandins.

The site of infection is also paramount. In deep organ candidiasis, namely endocarditis, meningitis, osteomyelitis and endophthalmitis, a polyene, mainly liposomal amphotericin B, with or without 5-flucytosine is the preferred treatment in unstable patients. Fluconazole may be used in stable patients or for step-down therapy in these situations [41, 83].

For primary treatment of invasive pulmonary aspergillosis, i.v. voriconazole is recommended as first line therapy for most critically ill patients. For patients who are intolerant or refractory to voriconazole, liposomal amphotericin B may be considered as an alternative primary therapy. For salvage therapy, several options are available including other lipid formulations of amphotericin B (ABCD or ABLC), posaconazole, itraconazole, caspofungin or micafungin or an association of voriconazole with an echinocandin [45].

For fusariosis, voriconazole, posaconazole and amphotericin B are the options and for zygomycosis, amphotericin B and posaconazole are the only available agents.

References

1. Vincent JL, Sakr Y, Sprung C, et al (2006) Sepsis in European Intensive Care Units: Results of the SOAP Study. Crit Care Med 34: 344 – 353
2. Vincent JL, Rello J, Marshall J, et al (2009) International Study of the Prevalence and Outcomes of Infection in Intensive Care Units. JAMA 302: 2323 – 2329
3. Garnacho-Montero J, Amaya-VillarR, Ortiz-Leyba C, et al (2005) Isolation of Aspergillus spp. from the respiratory tract in critically ill patients: risk factors, clinical presentation and outcome. Crit Care 9: R191 – 199
4. Meersseman W, Vandecasteele SJ, Wilmer A, Verbeken E, Peetermans WE, Van Wijngaerden E (2004) Invasive aspergillosis in critically ill patients without malignancy. Am J Respir Crit Care Med 170: 621 – 625
5. Vandewoude KH, Blot SI, Depuydt P, et al (2006) Clinical relevance of Aspergillus isolation from respiratory tract samples in critically ill patients. Crit Care 10: R31
6. Como JA, Dismukes WE (1994) Oral azoles as systemic antifungal therapy. N Engl J Med 330: 263 – 272
7. Saag MS, Dismukes WE (1988) Azole anti-fungal agents: emphasis on new triazoles. Antimicrob Agents Chemother 32: 1 – 8
8. Nguyen MH, Yu CY (1998) Voriconazole against fluconazole-susceptible and resistant Candida isolates: in vitro efficacy compared with that of itraconazole and ketoconazole. J Antimicrob Chemother 42: 253 – 256
9. Pfaller MA, Jones RN, Messer SAA, Edmond MB, Wenzel RP (1998) National surveillance of nosocomial bloodstream infections due to Candida albicans: frequency of occurrence and antifungal susceptibility in the SCOPE Program. Diagn Microbiol Infect Dis 31: 327 – 332
10. British Society for Antimicrobial Chemotherapy Working Party on Fungal Infections (1994) Management of deep Candida infection in surgical and intensive care units. Intensive Care Med 20: 522 – 528
11. Sanglard D, Ischer F, Monod M, Bille J (1996) Susceptibilities of Candida albicans multidrug transporter mutants to various antifungal agents and other metabolic inhibitors. Antimicrob Agents Chemother 40: 2300 – 2305
12. Hernaez ML, Gil C, Pla J, Nombela C (1998) Induced expression of the Candida albicans multidrug resistance gene CDR1 in response to fluconazole and other antifungals. Yeasts 14: 517 – 526
13. White MH, Bowden RA, Sandler ES, et al (1998) Randomized, double-blind clinical trial of amphotericin B colloidal dispersion versus amphotericin B in the empirical treatment of fever and neutropenia. Clin Infect Dis 27: 296 – 302
14. Marr KA, Lyons CN, Rustad T, Bowden RA, White TC (1998) Rapid, transient fluconazole resistance in Candida albicans is associated with increased mRNA levels of CDR. Antimicrob Agents Chemother 42: 2584 – 2589
15. Moran GP, Sanglard D, Donnelly SM, Shanley DB, Sullivan DJ, Coleman DC (1998) Identification and expression of multidrug transporters responsible for fluconazole resistance in Candida dubliniensis. Antimicrob Agents Chemother 42: 1819 – 1830
16. De Pauw BE, Meis JF (1998) Progress in fighting systemic fungal infection in hematological neoplasia. Support Cancer Center 6: 31 – 37
17. Johnson EM, Davey KG, Szekely A, Warnock DW (1995) Itraconazole susceptibilities of fluconazole susceptible and resistant isolates of five Candida species. J Antimicrob Chemother 36: 787 – 793
18. Pfaller MA, Jones RN, Doern GV, Sader HS, Hollis RJ, Messer SA (1998) International surveillance of bloodstream infections due to Candida species: frequency of occurence and antifungal susceptibilities of isolates collected in 1997 in the United States, Canada and South America for the SENTRY Program. J Clin Microbiol 36: 1886 – 1889

19. Pfaller MA, Jones RN, Messer SA, Edmond MB, Wenzel RP (1998) National surveillance of nosocomial bloodstream infections due to species of Candida other than Candida albicans: frequency of occurrence and antifungal susceptibility in the SCOPE program. Diagn Microbiol Infect Dis 30: 121 – 129
20. Pfaller MA, Messer SA, Hollis RJ, Jones RN, Diekema DJ (2002) In vitro activities of ravuconazole and voriconazole compared with those of four approved systemic antifungal agents against 6,970 clinical isolates of Candida spp. Antimicrob Agents Chemother 46: 1723 – 1727
21. Moore CB, Walls CM, Denning DW (2000) In vitro activity of the new triazole BMS-207147 against Aspergillus species in comparison with itraconazole and amphotericin B. Antimicrob Agents Chemother 44: 441 – 443
22. Diekema DJ, Pfaller MA, Messer SA, et al (1999) In vitro activities of BMS-207147 against over 600 contemporary clinical bloodstream isolates of Candida species from the SENTRY antimicrobial surveillance programme in North America and Latin America. Antimicrob Agents Chemother 43: 2236 – 2239
23. Fung-Tome JC, Huczko E, Minassian B, Bonner DP (1998) In vitro activity of a new oral triazole: BMS-207147. Antimicrob Agents Chemother 42: 313 – 318
24. Hata K, Kimura J, Miki H, Toyosawa t, Nakamura T, Katsu K (1996) In vitro and in vivo antifungal activities of ER-30346, a novel oral triazole with a broad antifungal spectrum. Antimicrob Agents Chemother 40: 2237 – 2242
25. Yamazumi T, Pfaller MA, Messer SA, Houston A, Hollis RJ, Jones RN (2000) In vitro activities of ravuconazole against 541 clinical isolates of Cryptococcus neoformans. Antimicrob Agents Chemother 44: 2883 – 2886
26. Pfaller MA, Messer SA, Hollis RJ, Jones RN (1998) In vitro susceptibilities of Candida bloodstream isolates to the new triazole antifungal agents BMS-207147, Sch 56592 and voriconazole. Antimicrob Agents Chemother 42: 3242 – 3244
27. Sheehan DJ, Hitchcock CA, Sibley CM (1999) Current and emerging azole antifungal agents. Clin Microbiol Rev 12: 40 – 79
28. Law D, Moore CB, Denning DW (1997) Activity of SCH 56592 compared with those of fluconazole and itraconazole against Candida spp. Antimicrob Agents Chemother 41: 2310 – 2311
29. Pfaller MA, Messer SA, Jones RN (1997) Activity of a new triazole, Sch 56592, compared with those of four other antifungal agents tested against clinical isolates of Candida spp. and Sacharomyces cerevisiae. Antimicrob Agents Chemother 41: 233 – 235
30. Bodey GP (1991) Antifungal agents. In: Bodey GP (ed) Candidiasis: Pathogenesis, Diagnosis and Treatment. Raven Press, New York, pp 371 – 384
31. Pfaller MA, Messer SA, Hollis RJ, Jones RN (2002) Antifungal activities of Posaconazole, Ravuconazole and Voriconazole compared to those of Itraconazole and Amphotericin B against 239 clinical isolates of Aspergillus spp. and other filamentous fungi: report from SENTRY antimicrobial surveillance program, 2000. Antimicrob Agents Chemother 46: 1032 – 1037
32. Richardson MD, Warnock DW (1997) Antifungal drugs. In: Richardson MD, Warnock DW (eds) Fungal Infections – Diagnosis and Management, 2nd edn. Blackwell Science, Oxford pp 21 – 28
33. Iwata K (1992) Drug resistance in human pathogenic fungi. Eur J Epidemiol 8: 407 – 421
34. Vincent JL, Anaissie E, Bruining H, et al (1998) Epidemiology, diagnosis and treatment of systemic Candida infection in surgical patients under intensive care. Intensive Care Med 24: 206 – 216
35. Flanagan PG, Barnes RA (1998) Fungal infections in the intensive care unit. J Hosp Infect 38: 163 – 177
36. Wey SB, Motomi M, Pfaller MA, Woolson RF, Wenzel RP (1988) Hospital acquired candidemia: the attributable mortality and excess length of stay. Arch Intern Med 148: 2642 – 2645
37. Warnock DW (1995) Fungal complications of transplantations: diagnosis, treatment and prevention. J Antimicrob Chemother 36: 73 – 84
38. Denning DW (2003) Echinocandin antifungal drugs. Lancet 362: 1142 – 1151
39. Perlin DS (2007) Resistance to echinocandin-class antifungal drugs. Drug Resist Updat 10: 121 – 130

40. Playford EG, Eggimann P, Calandra T (2008) Antifungals in the ICU. Curr Opin Infect Dis 21: 610 – 619
41. Pappas PG, Kauffman CA, Andes D, et al (2009) Clinical Practice Guidelines for the Management of Candidiasis: 2009 Update by the Infectious Diseases Society of America. Clin Infect Dis 48: 503 – 535
42. Reboli A, Rotstein C, Pappas PG, et al (2007) Anidulafungin versus Fluconazole for Invasive Candidiasis. N Eng J Med 356: 2477 – 2482
43. Guery BP, Arendrup MC, Auzinger G, et al (2009) Management of invasive candidiasis and candidemia in adult non-neutropenic intensive care unit patients: Part II. Treatment. Intensive Care Med 35: 206 – 214
44. Herbrecht R, Denning DW, Patterson TF, et al (2002) Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. N Engl J Med 347: 408 – 415
45. Walsh TJ, Anaissie EJ, Denning DW, et al (2008) Treatment of Aspergillosis: Clinical Practice Guidelines of the Infectious Diseases Society of America. Clin Infect Dis 46: 327 – 360
46. Blum RA, D'Andrea DT, Florentino BM, et al (1991) Increased gastric pH and the bioavailability of fluconazole and ketoconazole. Ann Intern Med 114: 755 – 757
47. Lutsar I, Roffey S, Troke P (2004) Voriconazole concentrations in the cerebrospinal fluid and brain tissue of guinea pigs and immunocompromised patients. Br J Clin Pharmacol 57: 218 – 222
48. Arndt CA, Walsh TJ, McCully CL, Balis FM, Pizzo PA, Poplack DG (1988) Fluconazole penetration into cerebrospinal fluid: implications for treating fungal infections of the central nervous system. J Infect Dis 157: 178 – 180
49. Foulds G, Brennan DR, Wajszczuk C, et al (1988) Fluconazole penetration into cerebrospinal fluid in humans. J Clin Pharmacol 28: 363 – 366
50. Donnelly JP, De Pauw BE (2004) Voriconazole- a new therapeutic agent with an extended spectrum of antifungal activity. Clin Microbiol Infect 10 (Suppl 1): 107 – 117
51. Bland SE (2002) Voriconazole. Pharmacotherapy Perspectives Nov/Dec: 32 – 39
52. Ashley E, Lewis R, Lewis JS, Martin C, Andes D (2006): Pharmacology of systemic antifungal agents. Clin Infect Dis 43 (Suppl 1): S28-S39
53. Groll AH, Piscitelli SC, Walsh TJ (1998) Clinical pharmacology of systemic antifungal agents: a comprehensive review of agents in clinical use, current investigational compounds and putative targets for antifungal drug development. Adv Pharmacol 44: 343 – 500
54. Raasch RH (2004) Anidulafungin: review of a new echinocandinantifungal agent. Expert Rev Anti Infect Ther 2: 499 – 508
55. Richardson MD, Kokki M (1988) Therapeutic Guidelines in Systemic Fungal Infections. Current Medical Literature, London
56. Silvestri L, Mur Laffon D, Gullo A (1998) Antifungal agents. In: van Saene HKF, Silvestri L, de la Cal MA (eds) Infection Control in the Intensive Care Unit. Springer, Milan, pp 50
57. Albengres E, Le Fouet H, Tillement JP (1998) Systemic antifungal agents. Drug Saf 18: 83 – 97
58. Michalets EL (1998) Update: clinically significant cytochrome P450 drug interactions. Pharmacotherapy 18: 84 – 112
59. Groll AH, Gea-Banacloche JC, Glasmacher A, Just-Nuebling G, Maschmeyer G, Walsh TJ (2003) Clinical pharmacology of antifungal compounds. Infect Dis Clin North Am 17: 159 – 191
60. Holland S, Stone J, Wickersham P, Deutsch P, Winchell G, Hesney M (2001) Drug interactions between caspofungin and tacrolimus. Program and Abstracts of the 41st Interscience Conference on Antimicrobial Agents and Chemotherapy. American Society for Microbiology, Chicago, A13 (abst)
61. Del Poeta M, Cruz MC, Cardenas ME, Perfect JR, Heitman J (2000) Synergistic antifungal activities of bafilomycin A(1), fluconazole and the pneumocandin MK-0991/caspofungin acetate with calcineurin inhibitors FK506 and L-685,818 against Cryptococcus neoformans. Antimicrob Agents Chemother 44: 739 – 746
62. Terrell CL HC (1992) Antifungal agents used for deep-seated mycotic infections. Mayo Clin Proc 67: 69 – 91
63. Saag MS, Dismukes WE (1988) Azole anti-fungal agents: emphasis on new triazoles. Antimicrob Agents Chemother 32: 1 – 8

64. Bronstein JA, Gros P, Hernandez E, Larroque P, Molinie C (1997) Fatal acute hepatitis necrosis due to dose-dependent fluconazole hepatotoxicity. Clin Infect Dis 25: 1266 – 1267
65. Munoz P, Moreno S, Berenguer J, Bernaldo de Quiros JL, Bouza E (1991) Fluconazole related hepatotoxicity in patients with acquired immunodeficiency syndrome. Arch Intern Med 151: 1020 – 1021
66. Hay RJ (1993) Risk/benefit of modern antifungal therapy: focus on hepatic reactions. J Am Acad Dermatol 29: S50-S54
67. Pascual A, Calandra T, Bolay S, Buclin T, Bille J, Marchetti O (2008) Voriconazole therapeutic drug monitoring in patients with invasive mycoses improves efficacy and safety outcomes. Clin Infect Dis 46: 201 – 211
68. Chia JKS, McManus EJ (1990) In vitro tumor necrosis factor induction assay for analysis of febrile toxicity associated with amphotericin B preparations. Antimicrob Agents Chemother 34: 906 – 908
69. Grasela TH Jr, Goodwin SD, Walawander MK, Cramer RL, Fuhs DW, Moriarty VP (1990) Prospective surveillance of intravenous amphotericin B use patterns. Pharmacotherapy 10: 341 – 348
70. Gelfand JA, Kimball K, Burke JF, Dinarello CA (1988) Amphotericin B treatment of human mononuclear cells in vitro results in secretion of tumour necrosis factor and interleukin-1. Clin Res 36: 456A
71. Lin AC, Goldwasser E, Bernard EM, Chapman SW (1990) Amphotericin B blunts erythropoietin response to anemia. J Infect Dis 161: 348 – 351
72. Gallis HA, Drew RH, Pickard WW (1990) Amphotericin B: 30 years of clinical experience. Rev Infect Dis 12: 308 – 329
73. Branch RA (1988) Prevention of amphotericin B induced renal impairment: a review on the use of sodium supplementation. Arch Intern Med 148: 2389 – 2394.
74. Khoo SH, Bond J, Denning DW (1994) Administering amphotericin B: a pratical approach. J Antimicrob Chemother 33: 203 – 213
75. Villanueva A, Arathoon EG, Noriega LM, Berman RS, DiNubile MJ, Sable CA (2001) A randomized double-blind study of caspofungin versus amphotericin for the treatment of candidal esophagitis. Clin Infect Dis 33: 1529 – 1535
76. Arathon EG, Gotuzzo E, Noriega LM, Berman RS, DiNubile M, Sable CA (2002) Randomized, double-blind, multicenter study of caspofungin versus amphotericin B for treatment of oropharyngeal and esophageal candidiasis. Antimicrob Agents Chemother 46: 451 – 457
77. Villanueva A, Gotuzzo E, Arathoon EG, et al (2002) A randomized double-blind study of caspofungin versus fluconazole for the treatment of esophageal candidiasis. Am J Med 113: 294 – 299
78. Graybill JR (1989) New antifungal agents. Eur J Clin Microbiol Infect Dis 8: 402 – 412
79. Toon S, Ross CE, Gokal R, Rowland M (1990) An assessment of the effects of impaired renal function and hemodyalisis on the pharmacokinetics of fluconazole. Br J Clin Pharmacol 29: 221 – 226
80. Trotman RL, Williamson JC, Shoemaker DM, Salzer WL (2005) Antibiotic dosing in critically ill adult patients receiving continuous renal replacement therapy. Clin Infect Dis 41: 1159 – 1166
81. Walsh TJ, Adamson PC, Seibel NL, et al (2005) Pharmacokinetics, safety, and tolerability of caspofungin in children and adolescents. Antimicrob Agents Chemother 49: 4536 – 4545
82. Nguyen TH, Hoppe-Tichy T, Geiss HK, et al (2007) Factors influencing caspofungin plasma concentrations in patients of a surgical intensive care unit. J Antimicrob Chemother 60: 100 – 106
83. Hollenbach E (2008) Invasive candidiasis in the ICU: evidence based and on the edge of evidence. Mycoses 51 (Suppl 2): 25 – 30

Mycobacterial Sepsis and Multiorgan Failure Syndrome

S. Jog, B. Pawar, and D. Patel

"Man is a creature composed of countless millions of cells: a microbe is composed of only one, yet throughout the ages the two have been in ceaseless conflict."
A.B. Christie

Introduction

Tuberculosis (TB) is a global disease with high prevalence in developing countries. According to the World Health Organization (WHO) fact sheet 2009, more than 2 billion (equal to one third of world's population) people are infected with TB bacilli. Of the cases detected, 5 % were cases of multi-drug resistant TB. Admission to a critical care unit is not required in the majority of cases. However, TB sepsis is a rapidly fatal disease that requires intensive care unit (ICU) admission and management and represents a big diagnostic and therapeutic challenge.

Mycobacterial sepsis was described first by Landouzy in the late 19th century and has been occasionally referred to as "sepsis tuberculosa gravissima" or "sepsis tuberculosa acutissima". As a disease, TB sepsis is not due to a virulent pathogen, but is due to host issues like depressed cell-mediated immunity resulting in lympho-hematogenous dissemination of tubercle bacilli. Only a few cases of TB sepsis have been described in the literature and it is generally considered a rare disease [1].

Pathogenesis

The outcome from sepsis due to serious infection has a number of determinants. The most important of these factors are host defense mechanisms, the environment, and the specific bacteria involved. TB sepsis has the same basic pathogenesis with a few additional factors.

Predisposing Conditions

Age is one of the most significant risk factors for development of TB sepsis. In the post-antibiotic era, the growing population of elderly adults, with a relative waning of cellular immunity, has become the most common group to develop TB sepsis [2, 3]. However, the increase in human immunodeficiency virus (HIV) and the increasing proportion of other adults with conditions associated with natural or iatrogenic impairment in cellular immunity has led to an additional peak of TB sepsis among young adults. The percentage of patients with TB sepsis and some other identifiable medical condition ranges from 38 to 70 % in large studies. Predisposing medical conditions include HIV, depressed immunity, alcohol abuse, malignancy, corticosteroids, connective tissue disease, renal failure, diabetes mellitus and pregnancy.

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Bacterial Factors

Catalase-peroxidase, which can resist oxidative stress, and lipoarabinomannan (LAM), which can induce cytokines and resist host oxidative stress, have been strongly implicated in the pathogenesis of TB sepsis [4]. Tumor necrosis factor (TNF)-α plays an important role in pathogenesis of tuberculosis. Increasing use of anti-TNF agents has led to an increase in reports of patient suffering from TB.

Immunology

Mycobacterium invasion triggers a cell-mediated immune response. Activated macrophages present the antigens to CD4+ T-helper cells and CD8+ T suppressor cells, which in turn release cytokines and lead ultimately to granuloma formation. Occasionally, dominance of Th-2 cytokines (interleukin [IL]-4, IL-5, IL-10) increases the risk of dissemination by inhibiting protective responses such as granuloma formation.

Clinical Features

TB sepsis occurs as a progressive primary infection, reactivation of latent infection and subsequent spread, or rarely as iatrogenic infection. The clinical manifestations are highly variable and non-specific. This can delay the diagnosis and account for the fact that diagnosis is missed, even in this era of rapid diagnostics. TB sepsis has been reported after extracorporeal shock wave lithotripsy [5], homograft valve replacement, and urethral catheterization [6]. In cases with various predisposing factors, the disease tends to have a more acute course and may lead to fulminant disease in the form of shock and potentially multiorgan system failure.

Pulmonary Involvement

Clinically significant pulmonary disease is noted in over 50 % of patients in most series. Patients report dyspnea or cough and have râles or rhonchi on physical examination. Hypoxemia, when looked for, is common.

Gastrointestinal Involvement

Signs or symptoms referable to the gastrointestinal tract included diffuse abdominal pain or pain localizing to the right upper quadrant, nausea, vomiting and diarrhea [7]. Hepatomegaly may be appreciated on physical examination more frequently than splenomegaly. Liver function test abnormalities are common. Cholestatic jaundice and ascites may be detected in occasional patients.

Central Nervous System (CNS) Involvement

Meningitis or tuberculoma is suggested clinically in 15 to 20 % of patients.

Other Systems

Seeding of every organ system has been documented including bone, joints and eyes. Involvement of the adrenals was found in as many as 42 % of autopsies of fatal cases. Overt adrenal insufficiency is rare, occurring in less than 1 % of reported cases of disseminated TB [8].

Diagnosis

The biggest challenge in the diagnosis of TB as a cause of sepsis is thinking about it as a possibility. Previous reports of diagnosis of TB sepsis have been based only on autopsy findings. With the advent of newer diagnostic modalities, it is possible to identify such patients faster and hence start effective treatment to decrease mortality.

Laboratory Evaluation

There is no specific hematological pattern found in TB [8]. Patients may have various degrees of normochromic normocytic anemia. Total white cell count may be normal or may show leukopenia. In some cases, thrombocytopenia may also be observed. Patients may present with pancytopenia, which may suggest bone marrow infiltration by granulomas or may suggest triggering of hemophagocytic reaction [10]. These findings are neither sensitive, nor specific for TB. However, in appropriate epidemiological and clinical conditions it should alert us to the possibility. The erythrocyte sedimentation rate (ESR) is elevated in the majority of patients with disseminated TB along with other acute phase reactants. Isolated hyponatremia is a frequent biochemical finding in patients with TB. No other biochemical marker is available for diagnosis of TB [8].

Testing for Latent TB

Newer *in vitro* assays are now available that can detect latent TB infection based on measurement of interferon gamma (IFN-γ), which is released by T cells in response to specific mycobacterial antigens. The QuantiFERON-TB Gold In-Tube (QFT-GIT) assay (Cellestis, Carnegie, Australia) and the T-SPOT.TB assay (Oxford Immunotec, Marlborough, USA) are the IFN-γ release assays that are approved by the US Food and Drug Administration (FDA). However, it is still not clear how these tests would perform in detecting latent infections in cases of TB sepsis [11].

Imaging

Imaging is useful for evaluating symptomatic patients with appropriate epidemiologic risk factors for TB. Presence of cavitation, upper lobe infiltrates or fibrosis, intra-thoracic lymphadenopathy, pleural effusion, pneumothorax may all suggest tuberculosis. The classic miliary pattern described with disseminated TB (as seen in **Fig. 1**) may not be apparent on presentation or until after a few weeks as the immune system is overwhelmingly suppressed. Computed tomography (CT) scan especially high resolution CT is more sensitive then chest radiography for detecting subtle parenchymal and nodular changes. However, its specificity for TB is

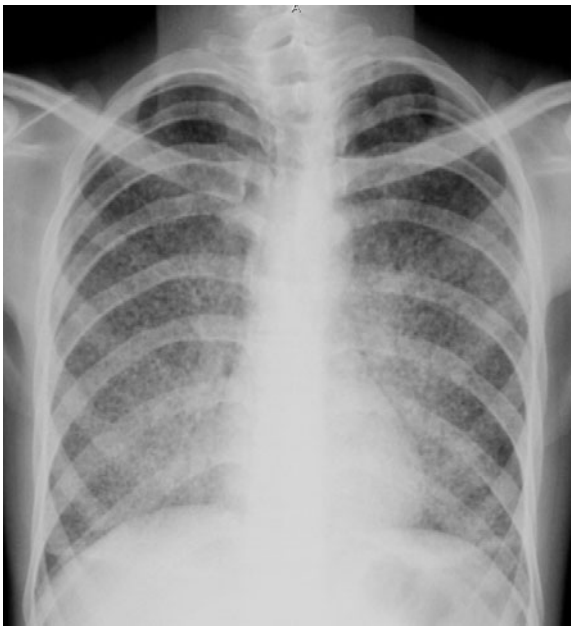

Fig. 1. Classic miliary shadows in lung fields in a case of tuberculosis with multiorgan dysfunction syndrome.

still not established. When any lesion amenable to CT-guided biopsy is present, it may help in establishing diagnosis. But there are no data on whether these can be helpful.

Microbiological Evaluation

Acid-fast bacillus smear

AFB smears of expectorated or induced sputum, bronchoalveolar lavage (BAL) fluid, gastric lavage, stool, pleural, pericardial and peritoneal fluid, cerebrospinal fluid (CSF), urine, blood, bone marrow aspirate, lymph node biopsy, liver biopsy and transbronchial biopsy have shown various degrees of sensitivity ranging from 30 % to 80 %. The probability of a positive smear increases with the number of sites sampled. CSF should only be examined in cases where neurological symptoms or signs are present. If the chest radiograph does not suggest pulmonary involvement, bronchoscopy may be less useful. Bronchoscopy with BAL did not add significantly to the diagnostic yield, if all the other sites were also sampled [12]. Further concentration of samples prior to processing for smear may help to increase sensitivity. Fluorochrome dye-based stains are more sensitive than the routine Ziehl-Neelsen stain [13]. However, neither of these staining methods helps differentiate between tuberculous and non-tuberculous mycobacteria; further testing with nucleic acid amplification is required to achieve this [14].

Cultures

Cultures are the gold standard for definitive diagnosis of TB. Mycobacterial blood cultures, preferably using lysis centrifugation techniques, are a rapid and non-invasive method of diagnosis. The conventional Lowenstein-Jensen medium used takes 4–6 weeks to detect growth. With evolution of diagnostic microbiology,

newer mediums are now available which can detect growth within 2 – 4 weeks. All specimens should be inoculated in a commercial automated radiometric detection system, which is more rapid and more sensitive than standard techniques.

Rapid Diagnostic Tests

Adenosine deaminase levels

Adenosine deaminase (ADA) levels represent a faster and cheaper way to establish diagnosis especially in resource-limited areas with a high prevalence of TB. Elevated concentrations of pleural fluid or peritoneal fluid ADA has been described in the setting of TB. Peritoneal and pleural fluid ADA values greater then 40 IU had a very high sensitivity and specificity for TB peritonitis and TB pleural effusions, respectively [15, 16]. The utility of ADA levels for diagnosis in areas of low prevalence and peritoneal fluid levels in cases of cirrhosis is still debatable. In pleural effusions, ADA was also found to be raised in empyema and rheumatoid disease. However, further studies have revealed that the increased ADA in TB effusion was mainly due to an increase in ADA2 levels, which was not the case with empyema and rheumatoid disease; measurement of ADA2 may thus improve sensitivity [17]. The sensitivity of ADA for TB is higher then a polymerase chain-reaction (PCR) based test, which has greater specificity in a high prevalence setting [18]. The role of ADA in the diagnosis of TB meningitis is still not well established [19].

Interferon gamma assay

Determination of IFN-γ levels in pleural fluid has good sensitivity (90 %) and specificity (97 %), and may be useful to differentiate tuberculous from non-tuberculous effusions [20].

Nucleic acid amplification test

Nucleic acid amplification testing is useful for rapid identification of *Mycobacterium tuberculosis* in respiratory samples; results can be available within two to seven hours. Currently two tests, enhanced MTD (enhanced *M. tuberculosis* direct test) and enhanced amplicor *M. tuberculosis* test 2 (AMTD2), are approved for nucleic acid amplification testing in smear-positive and smear-negative respiratory specimens. According to FDA data, the sensitivity of the tests for tuberculosis (compared with culture) is approximately 95 % in patients with a positive AFB smear, but only about 50 % in smear-negative cases. Specificity is greater than 95 % in smear-negative and smear-positive samples. Although the FDA has not yet approved the use of nucleic acid amplification testing on non-respiratory samples, research has shown that nucleic acid amplification testing can be very useful in these samples, especially gastric fluid, lymph node biopsies, and skin biopsies [21]. However, nucleic acid amplification tests do not perform well with pleural fluid samples because pleural fluid has many inhibitors which affect the test, resulting in poor sensitivity. When TB meningitis is suspected without extrameningeal disease, nucleic acid amplification tests give a better yield than any other test, but experience with these specimens is minimal and they require special handling [22]. Nucleic acid amplification tests have poor sensitivity in smear-negative cases. A negative result does not rule out a diagnosis of TB. Most published data regarding the performance of nucleic acid amplification tests are based upon laboratory trials. These studies do not completely address their clini-

cal applicability. It remains to be seen whether the routine use of nucleic acid amplification tests in non-research settings by less experienced and less trained technicians will result in a deterioration in performance.

Histopathology of tissue specimens

Histopathology continues to play an important role in the rapid diagnosis of TB. Liver biopsies have the highest yield. In case of disseminated disease? granulomas were demonstrable in nearly 100 % of liver biopsies (**Fig. 2**), 82 % of bone marrow biopsies and 72 % of transbronchial biopsies [8]. If biopsies are targeted based on involvement of specific organ systems, then the diagnostic yield is increased.

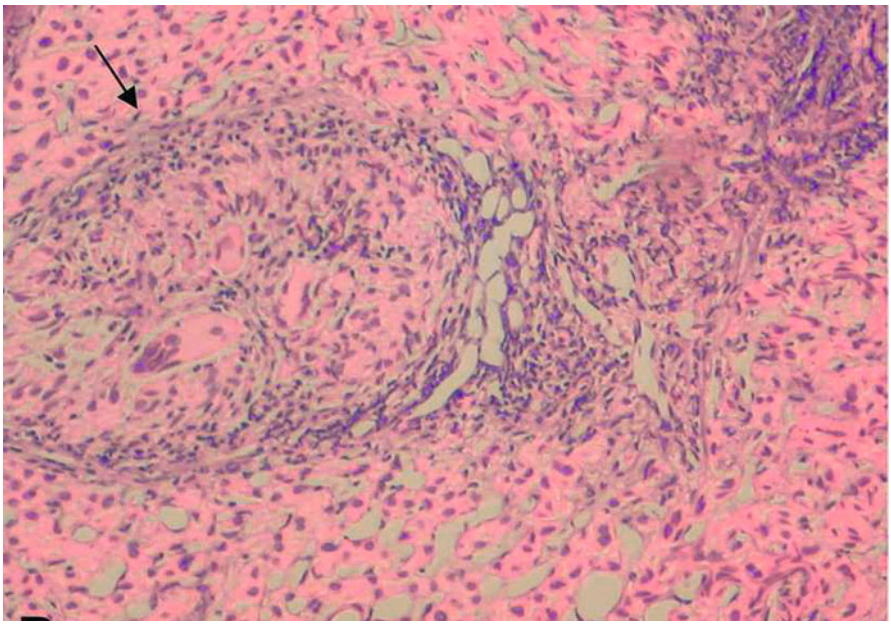

Fig. 2. Photomicrograph showing classic hepatic tubercular granuloma.

Drug susceptibility testing

Drug susceptibility testing for isoniazid, rifampin and ethambutol should be performed on initial isolates from each site of disease. The agar proportion and liquid radiometric methods are used mainly to detect mycobacterial drug resistance. The agar proportion method requires around 1 month for susceptibility testing after visible growth appears. This translates into presumptive treatment until susceptibility reports are available. Liquid radiometric methods reduce this time to 15–20 days. However, with the increasing number of cases of drug-resistant tuberculosis, it is imperative to reduce this time to as short as possible. Several rapid molecular or genotypic tests for tuberculosis drug susceptibility testing have emerged:

A) The microscopic-observation drug-susceptibility assay: This test combines organism detection and susceptibility testing using a single technique, by comparing mycobacterial growth in 24-well plates with liquid culture

medium in the presence and absence of antimycobacterial drugs [23]. The sensitivity of this assay compared to automated mycobacterial culture and Lowenstein-Jensen culture was 98 %. Median time to culture positivity was 7 days.

B) Phage-based assays: Despite good agreement of phage-based assays for detecting rifampin resistance compared to conventional testing, significant concerns have been raised regarding rates of contamination. Furthermore, with development of line probe assays, the exact scope and role of phage-based assays needs to be determined.

C) Line probe assays: These are automated molecular tests for diagnosis of *M. tuberculosis* and resistance to rifampin. They use real time PCR to amplify the specific *M. tuberculosis* sequence of the *rpoB* gene, which is then probed for mutations in the rifampin resistance determining region. Line probe assays provide sensitive detection of *M. tuberculosis* (97 %) and rifampin resistance (98 %) directly from untreated sputum in less then 2 hours [24].

D) Molecular beacons: These are labeled oligonucleotides that fluoresce when hybridized to a target sequence encoding genes for drug resistance. About 95 % of rifampin-resistant strains contain mutations within a single locus (*rpoB*), and rifampin resistance may be considered a surrogate marker for multidrug-resistant TB (MDR-TB); approximately 90 % of rifampin-resistant strains are also resistant to isoniazid [25].

Drug susceptibility testing is less reproducible when testing susceptibilities of second-line drugs, which are integral to the treatment of any patient with XDR-TB (extensively drug resistant TB). Furthermore, all marketed rapid technologies (i.e., PCR-based techniques) and the Microscopic Observation and Drug Susceptibility assay detect resistance only to first-line medications [23 – 25].

Treatment

Tuberculosis sepsis is uniformly fatal if not diagnosed and treated in time. Even with treatment, mortality is as high as 40 – 50 %. Delay in diagnosis and initiation of treatment is responsible for this high mortality. Currently there are no randomized trials that have evaluated the efficacy of different regimens in the treatment of TB sepsis and multi-organ dysfunction syndrome.

Anti-tuberculous Therapy

The American Thoracic Society (ATS), Centers for Disease Control and Prevention (CDC) and Infectious Diseases Society of America (IDSA) have issued joint guidelines for the treatment of TB [26]. The initial regimen is for two months followed by a continuation phase of either 4 or 7 months. The choice of treatment in the initial phase is empiric and is based on likely susceptibility. Four drugs are used in the initial phase: isoniazid, rifampin, pyrazinamide, and ethambutol. In drug susceptible cases, rifampin and isoniazid are used in the continuation phase for 4 or 7 months. Directly observed therapy is the best way to ensure completion [26]. The recommendations for disseminated disease are the same as for pulmonary disease. A longer duration of therapy is required for miliary TB, bone disease, and in the immunocompromised. In the presence of TB meningitis, the

duration needs to be extended to at least 12 month. Patients who show slow microbiologic or clinical response have high relapse rates and may benefit from extended therapy. The biggest challenge in patients with TB sepsis and multi-organ dysfunction is which drugs to give.

Isoniazid, rifampin, and pyrazinamide have significant hepato-toxicity. In patients with no pre-existing liver disease and normal liver function, standard four drug therapy may be started safely. Anti-tuberculous therapy should be discontinued if the patient's transaminase level increases three times above normal with symptoms or five times above normal without symptoms [26]. The optimal approach to resumption of anti-tuberculous therapy is uncertain. Three new drugs (e.g., an aminoglycoside and two oral agents, such as ethambutol and a fluoroquinolone) could be started until the transaminase concentration returns to less than twice the upper limit of normal (or to near baseline levels) [27]. For patients with severe unstable liver disease who require a regimen with no hepatotoxic agents, streptomycin, ethambutol, a fluoroquinolone and another second line oral drug may be used for a duration of 18 to 24 months. Alteration in dosing of antitubercular therapy, particularly of ethambutol and pyrazinamide, is necessary in patients with renal insufficiency. Lengthening the dosing interval is preferable to reducing the dose in order to optimize peak serum concentrations. Administration of all anti-TB drugs immediately after hemodialysis facilitates directly observed therapy (three times weekly) and minimizes premature removal of the drugs. In critical care, it is important to administer pyridoxine with isoniazid in order to avoid isoniazid-induced neuropathy. Isoniazid can also cause cytopenias, which may be synergistic with other toxicities or co-morbidities in the critically ill. Rifampin is a potential cytochrome P450 inducer. It is essential to review the entire drug chart in patients receiving rifampin to anticipate potential serious drug-drug interactions. Ethambutol may cause irreversible optic neuritis.

Drug-resistant TB

Certain demographic and historical features may raise suspicion of drug-resistant TB, including previous treatment for TB. The availability of rapid molecular drug sensitivity testing has made this diagnosis faster and easier. Modifications of conventional treatment are essential. Moxifloxacin may be a suitable alternative for patients who are intolerant of isoniazid or are infected with isoniazid-resistant *M. tuberculosis* [28]. Because rifampin is the cornerstone of all six-month regimens, resistance to this drug requires prolongation of treatment [26]. Treatment of MDR-TB (resistance to isoniazid and rifampin) should be guided by drug susceptibility testing whenever possible (**Table 1**). In many parts of the world, however, drug susceptibility testing is not available (at least initially), and empiric therapy must be used. The initial empiric therapy of TB in areas with a known high prevalence of MDR-TB or in patients who contract TB after contact with a patient with known MDR-TB, should include the standard recommendations plus whatever additional drugs are necessary to assure that at least four drugs effective against the most prevalent drug-resistant strains are included in the regimen [26].

XDR-TB is defined as resistance to both isoniazid and rifampin with additional resistance to at least one fluoroquinolone and one injectable agent (amikacin, kanamycin, or capreomycin). There are no randomized controlled trials on which to base strong recommendations for the pharmacotherapy of XDR-TB. In this scenario, the existing four-drug regimen should be strengthened, while waiting for results of drug susceptibility testing. An injectable agent (e.g., capreomycin),

Table 1. Suggested treatment regimens for the management of patients with drug-resistant pulmonary tuberculosis

Drug resistance	Suggested regimen	Duration (months)	Comments
INH	RIF, PZA, EMB (an FQN may strengthen regimen)	6	6-month regimens have yielded 95 % success rates despite resistance to INH [29]. Result was best if PZA was also used throughout the 6 months [30].
RIF	INH, PZA, EMB (a FQN may strengthen the regimen)	9 – 12	An injectable agent may be added in the initial 2 months of therapy.
INH and RIF (± SM)	FQN, PZA, EMB, IA, ± alternative agent	18 – 24	Resection surgery may be considered
INH, RIF (± SM), and EMB or PZA	FQN , IA, and two alternative agents	24	Resection surgery should be considered.

EMB: ethambutol; FQN: fluoroquinolone (most experience with ofloxacin, levofloxacin,or ciprofloxacin); INH: isoniazid; PZA: pyrazinamide; RIF: rifampin; SM: streptomycin; IA: injectable agent (streptomycin, amikacin, kanamycin or capreomycin). Alternative agents: ethionamide, cycloserine, p-aminosaliclyic acid, clarithromycin, amoxicillin/clavulanate, linezolid.

if the patient is not already on an injectable medication, one or two oral second-line medications (e.g., ethionamide and cycloserine or terizidone) and a third-line agent (e.g., amoxicillin-clavulanate, clarithromycin, linezolid or clofazamine) should be added. This may require that seven or more drugs be given until drug susceptibility results are obtained. Therapy should then be tailored according to drug susceptibility testing when available. The duration of therapy often extends for an average of 18 months after sputum conversion [31, 32].

Newer Anti-tubercular Therapy

Research has now accelerated for search of new therapies for TB. Moxifloxacin and gatifloxacin are currently being investigated in phase 3 trials to shorten the duration of treatment in drug-susceptible tuberculosis. The diarylquinoline, TMC207, offers a new mechanism of anti-TB action by inhibiting mycobacterial synthase. Preliminary phase 2 trial results for this agent in the setting of MDR-TB appear promising [33]. Nitroimidazoles (PA824 and OPD67683) have demonstrated good anti-mycobacterial activity in a mouse model and *in vitro* for drug sensitive and resistant strains of TB [34, 35].

Adjunctive Therapy

Corticosteroids

Current recommendations on steroids in the treatment of TB are based on limited evidence. The presence of associated adrenal insufficiency is an absolute indication for steroid therapy. Corticosteroid therapy may be beneficial in TB sepsis with TB meningitis, large pleural or pericardial effusion, acute respiratory distress syndrome (ARDS), immune complex nephritis and histiocytic phagocytosis.

Drotrecogin alfa

Only one report of the use of drotrecogin alfa (activated) in TB sepsis is available in the literature [36]. Further use in TB sepsis should be based on generally approved guidelines for the use of this product.

Immunotherapy

Uncontrolled trials and anecdotal reports suggest that adjunctive immunotherapy with IFN-γ may be useful in the management of MDR-TB [37].

Surgery

Surgical debulking of areas of pulmonary cavitation and localized disease has been advocated as an adjunct to medical therapy. In a carefully selected population of HIV-negative patients, resective surgery (lobectomy, wedge resection, or pneumonectomy) can help achieve relatively rapid sputum culture conversion and provide durable cure in patients with MDR- and XDR-TB [26, 38, 39]. Further research is needed regarding the selection of surgical candidates, timing of surgery, optimal medication regimens, and duration of therapy following surgery.

Micronutrient supplementation

The few trials available have demonstrated conflicting results regarding any potential benefits of this approach [40–42]. Further studies are needed before any recommendations can be made.

Conclusion

With the increasing populations of patients with HIV or diabetes and the widespread use of immunosuppressive medication, we may see increasing proportions of patients presenting with TB sepsis in the years to come. With the various diagnostic and therapeutic dilemmas surrounding TB, this may represent another menace in infectious disease management in the critical care setting. Many methods for fast diagnosis and newer drugs have emerged. But these methods have not gained widespread acceptance in health programs of countries with high disease prevalence. One of the biggest hurdles is the cost. With the greatest prevalence of TB in developing countries and among poorer populations, the focus should be on the development of cost-effective strategies and practical strategies of management. Ultimately, the major purpose of research is to develop solutions that can benefit the populations who need them most. The last decade has seen aggressive research in this field to address these larger issues also and it seems that we are just on the right track.

References

1. Bridges DA, Bedimo RG (2006) Severe tuberculosis sepsis in an immunocompetent patient Am J Med 119: e11–4
2. Alvarez S, Melale WR (1984) Extra pulmonary tuberculosis revisited: a review of experience at Boston and other hospitals. Medicine (Baltimore) 64: 25–55

3. Sime PJ, Chilvers ER, Leitch AG (1994) Miliary tuberculosis in Edinburgh – a comparison between 1984 -1992 and 1954 -1967. Respir Med 88: 609 – 611
4. Moreno C, Mehlert A, Lamb J (1988) The inhibitory effects of mycobacterial lipoarabinomannan and polysaccharides upon polyclonal and monoclonal human T cell proliferation. Clin. Exp Immunol 74: 206 – 210
5. Federmann M., Kley HK (1990). Miliary tuberculosis after extracorporeal shock-wave lithotripsy. N Engl J Med 323: 1212
6. Yekanath H, Gross PA, Vitenson JH (1980) Miliary tuberculosis following uretral catheterisation. Urology 16: 197 – 198
7. Ramesh J, Banait GS, Ormerod LP (2008) Abdominal tuberculosis in a district general hospital: a retrospective review of 86 cases. QJM 101: 189 – 195
8. Maartens G; Willcox PA; Benatar SR (1990) Miliary tuberculosis: rapid diagnosis, hematologic abnormalities, and outcome in 109 treated adults. Am J Med 89: 291 – 296
9. Hunt BJ, Andrews V, Pettingale KW (1987) The significance of pancytopenia in miliary tuberculosis. Postgrad Med J 63: 801 – 804
10. Pai M, Zwerling A, Menzies D (2008) Systematic review: T-cell-based assays for the diagnosis of latent tuberculosis infection: an update. Ann Intern Med 149: 177 – 184
11. Kobashi Y, Fukuda M, Yoshida K, Oka M (2007) An indeterminate QuantiFERON TB-2G response for miliary tuberculosis, due to severe pancytopenia. J Infect Chemother 13: 414 – 417
12. Conde MB, Soares SL, Mello FC, et al (2000) Comparison of sputum induction with fiberoptic bronchoscopy in the diagnosis of tuberculosis: experience at an acquired immune deficiency syndrome reference center in Rio de Janeiro, Brazil. Am J Respir Crit Care Med 162: 2238 – 2240
13. Steingart KR, Henry M, Ng V, et al (2006) Fluorescence versus conventional sputum smear microscopy for tuberculosis: a systematic review. Lancet Infect Dis 6: 570 – 581
14. Stender H, Mollerup TA, Lund K, et al (1999) Direct detection and identification of Mycobacterium tuberculosis in smear positive sputum samples by fluorescence in situ hybridization (FISH) using peptide nucleic acid (PNA) probes. Int J Tubercl Lung Dis 3: 830 – 837
15. Riquelme A, Calvo M, Salech F, et al (2006) Value of adenosine deaminase (ADA) in ascitic fluid for the diagnosis of tuberculous peritonitis: a meta-analysis. J Clin Gastroenterol 40: 705 – 710
16. Banales JL, Pineda PR, Fitzgerald JM, et al (1991) Adenosine deaminase in the diagnosis of tuberculous pleural effusions. A report of 218 patients and review of the literature. Chest 99: 355 – 357
17. Valdes L, Alvarez D, San Jose E, et al (1998) Tuberculous pleurisy: a study of 254 patients. Arch Intern Med 158: 2017 – 2021
18. Villegas MV, Labrada LA, Saravia NG (2000) Evaluation of polymerase chain reaction, adenosine deaminase, and interferon-gamma in pleural fluid for the differential diagnosis of pleural tuberculosis. Chest 118: 1355 – 1364
19. Tuon EF, Higashino HR, Banks MI, et al (2010) Adenosine deaminase and tuberculous meningitis- a systematic review with meta-analysis. Scand J Infect Disease 42: 198 – 207
20. Jiang J, Shi HZ, Liang QL, Qin SM, Qin XJ (2007) Diagnostic value of interferon-gamma in tuberculous pleurisy: a metaanalysis. Chest 131: 1133 – 1141
21. Shah S, Miller A, Mastellone A, et al (1998) Rapid diagnosis of tuberculosis in various biopsy and body fluid specimens by the AMPLICOR Mycobacterium tuberculosis polymerase chain reaction test. Chest 113: 1190 – 1194
22. Pfyffer GE, Kissling P, Jahn EM, Welscher HM, Salfinger M, Weber R (1996) Diagnostic performance of amplified Mycobacterium tuberculosis direct test with cerebrospinal fluid, other non respiratory, and respiratory specimens. J Clin Microbiol 34: 834 – 841
23. Arias M, Mello FC, Pavon A, et al (2007) Clinical evaluation of the microscopic-observation drug-susceptibility assay for detection of tuberculosis. Clin Infect Dis 44: 674 – 680
24. Boehme CC, Nabeta P, Hillemann D, et al (2010) Rapid molecular detection of tuberculosis and rifampin resistance. N Engl J Med 363: 1005 – 1015
25. Varma-Basil M, El-Hajj H, Colangeli R, et al (2004) Rapid detection of rifampin resistance in Mycobacterium tuberculosis isolates from India and Mexico by a molecular beacon assay. J Clin Microbiol 42: 5512 – 5516

26. Blumberg HM, Burman WJ, Chaisson RE, et al (2003) American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America: treatment of tuberculosis. Am J Respir Crit Care Med 167: 603
27. Ho CC, Chen YC, Hu FC, Yu CJ, Yang PC, Luh KT (2009) Safety of fluoroquinolone use in patients with hepatotoxicity induced by anti-tuberculosis regimens. Clin Infect Dis 48: 1526 – 1533
28. Dorman SE, Johnson JL, Goldberg S, et al (2009) Substitution of moxifloxacin for isoniazid during intensive phase treatment of pulmonary tuberculosis. Am J Respir Crit Care Med 180: 273 – 280
29. Mitchison DA, Nunn AJ (1986) Influence of initial drug resistance on the response to short-course chemotherapy of pulmonary tuberculosis. Am Rev Respir Dis 133: 423 – 430
30. Hong Kong Chest Service, British Medical Research Council (1987) Five-year follow-up of a controlled trial of five, 6 month regimens of chemotherapy for tuberculosis. Am Rev Respir Dis 136: 1339 – 1342
31. Keshavjee S, Gelmanova IY, Farmer PE, et al (2008) Treatment of extensively drug-resistant tuberculosis in Tomsk, Russia: a retrospective cohort study. Lancet 372: 1363
32. Mitnick CD, Shin SS, Seung KJ, et al (2008) Comprehensive treatment of extensively drug-resistant tuberculosis. N Engl J Med 359: 563 – 574
33. Diacon AH, Pym A, Grobusch M, et al (2009) The diarylquinoline TMC207 for multidrug-resistant tuberculosis. N Engl J Med 360: 2397 – 2405
34. Matsumoto M, Hashizume H, Tomishige T, et al (2006) OPC-67683, a Nitro-dihydro-imidazooxazole derivative with promising action against tuberculosis in vitro and in mice. PLoS Med 3: e466
35. Diacon AH, Dawson R, Hanekom M, et al (2010) Early bactericidal activity and pharmacokinetics of PA-824 in smear-positive tuberculosis patients. Antimicrob Agents Chemother 54: 3402 – 3407
36. Rubin ZA, Leonard MK, Martin GS (2006) Brief report: tuberculosis sepsis and activated protein C. Am J Med Sci 332: 48 – 50
37. Suarez-Mendez R, Garcia-Garcia I, Fernandez-Olivera N, et al (2004) Adjuvant interferon gamma in patients with drug – resistant pulmonary tuberculosis: a pilot study. BMC Infect Dis 4: 44
38. Sung SW, Kang CH, Kim YT, Han SK, Shim YS, Kim JH (1999) Surgery increased the chance of cure in multi-drug resistant pulmonary tuberculosis. Eur J Cardiothorac Surg 16: 187 – 193
39. Somocurcio JG, Sotomayor A, Shin S, et al (2007) Surgery for patients with drug-resistant tuberculosis: report of 121 cases receiving community-based treatment in Lima, Peru. Thorax 62: 416 – 421
40. Wejse C, Gomes VF, Rabna P, et al (2009) Vitamin D as supplementary treatment for tuberculosis: a double-blind, randomized, placebo-controlled trial. Am J Respir Crit Care Med 179: 843 – 850
41. Karyadi E, West CE, Schultink W, et al (2002) A double-blind, placebo-controlled study of vitamin A and zinc supplementation in persons with tuberculosis in Indonesia: effects on clinical response and nutritional status. Am J Clin Nutr 75: 720 – 727
42. Range N, Andersen AB, Magnussen P, et al (2005) The effect of micronutrient supplementation on treatment outcome in patients with pulmonary tuberculosis: a randomized controlled trial in Mwanza, Tanzania. Trop Med Int Health 10: 826 – 832

Pentraxin 3 (PTX3): Possible Role in Critical Care Medicine

T. Mauri, B. Bottazzi, and A. Pesenti

Introduction

Inflammation is a cornerstone of the pathophysiology of nearly all diseases treated in the intensive care unit (ICU) [1]. More than 90 % [2] of critically ill patients present clinical signs of systemic inflammatory response syndrome (SIRS): Fever, tachycardia, tachypnea and elevated white blood cell count. In particular, sepsis and acute lung injury/acute respiratory distress syndrome (ALI/ARDS), the two most important diseases, accounting for more than 50 % of deaths in ICU patients [3, 4], are characterized by a sudden activation of innate immunity and other inflammatory mechanisms [5]. Several pro- and anti-inflammatory mediators are involved, particularly in the early phase of these syndromes [6]. Studies conducted so far have shown that interleukin 1β (IL-1β) and tumor necrosis factor-α (TNF-α) [7, 8] play a key role, together with IL-6 and many others (e.g., procalcitonin, soluble triggering receptor expressed on myeloid cells [sTREM]-1, von-Willebrand factor, etc.). However, the pathophysiological role of most of the molecules suggested so far as markers of clinical severity and outcome in sepsis and ALI/ARDS is still largely obscure [9].

The long pentraxin PTX3, a distant relative of the acute phase C-reactive protein (CRP), was identified in the 1990s as an early induced gene in endothelial cells and macrophages. PTX3 is a key inflammatory mediator characterized by complex regulatory functions [10] and represents a novel candidate marker for inflammatory, infectious, and cardiovascular pathology [11]. In the present chapter, we will describe and discuss the role of PTX3 in critical care diseases.

PTX3: Role in Innate Immunity

Innate immunity is the first line of defense against pathogens and plays a key role in the initiation and activation of adaptive immunity. Innate immunity receptors, also called pattern-recognition molecules (PRMs), recognize a few highly conserved pathogen-associated molecular patterns (PAMPs) expressed by microorganisms [12]. Based on their localization, PRMs are divided into cell-associated receptors, either intracellular or cell surface bound, and soluble PRMs [13]. Soluble PRMs include collectins, ficolins, complement components and pentraxins, and represent the functional ancestor of antibodies [13].

Pentraxins are highly conserved proteins characterized by a cyclic multimeric structure [10]. CRP and serum amyloid P component (SAP) are the prototypical short pentraxins. CRP and SAP are produced in the liver in response to inflam-

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matory mediators, mostly IL-6 [14]. CRP levels in normal plasma are very low (≤ 0.3 mg/dl) but they can increase dramatically during the acute phase response. CRP's role as a marker of systemic inflammatory activation is widely recognized [15], even though its pathophysiological role is not entirely elucidated. Indeed, recent studies indicate that CRP gene polymorphisms associated with a marked increase in CRP levels are not associated with a higher risk of ischemic vascular disease [16, 17].

Long pentraxins are characterized by an N-terminal domain coupled to the C-terminal pentraxin domain [10]. At variance with CRP and SAP, the prototypic long pentraxin PTX3 is rapidly produced and released by various cell types, in particular macrophages, myeloid dendritic cells, endothelial and epithelial cells, in response to primary inflammatory signals like TNF-α and IL-1β [10]. In addition, PTX3 is stored in specific granules of neutrophils in a ready-to-use form which is promptly released upon microbial recognition [18],

PTX3 has antibody-like functions, binding pathogens, activating and regulating complement, and opsonizing particles [10, 13, 19, 20]. In addition, PTX3 performs complex peculiar regulatory functions in the inflammation process. Two scenarios can be depicted: On the one hand, *ptx3*-transgenic mice showed increased resistance to lipopolysaccharide (LPS) toxicity and to cecal ligation and puncture, whereas *ptx3*-deficient mice developed more myocardial damage in a model of cardiac ischemia and reperfusion injury [21, 22]. On the other hand, after intestinal ischemia and reperfusion injury, PTX3 overexpressing mice showed exacerbated inflammatory response and reduced survival rate, because of enhanced production of pro-inflammatory mediators (TNF-α in particular), thus suggesting a detrimental role of the protein [23, 24]. Recently, we observed that PTX3 binds P-selectin [19]. Using three *in vivo* models of P-selectin-dependent inflammation (pleurisy, acid-induced ALI and intra-vital microscopy analysis of mesenteric inflammation), we found that exogenously administered PTX3 and endogenous PTX3 released from hematopoietic cells acted as a negative feedback loop, preventing excessive P-selectin-dependent recruitment of neutrophils. It is likely that this pathway represents one of the molecular mechanisms involved in the regulatory role exerted by PTX3 on inflammation [19].

In conclusion, laboratory studies so far have shown that PTX3 plays a key role not only in innate immunity but also as a tuner of inflammation, and that its presence can be protective or deleterious for the host, depending on the type of injury and on PTX3 expression levels.

PTX3 in Human Pathology

Circulating PTX3 levels in humans are normally low (< 2 ng/ml) and they can increase dramatically under inflammatory conditions [11]. To date, many clinical studies have been conducted on a variety of human inflammatory/infectious diseases. The most preeminent results on PTX3 role have been disclosed in patients affected by the following disorders:

1. Autoimmune diseases*:* PTX3 is increased and correlates with severity in many autoimmune disorders, like inflammatory rheumatic disease, systemic sclerosis, systemic vasculitis and systemic lupus erythematosus (SLE) [25–28]. Interestingly, a recent study by Bassi and colleagues has shown that, in SLE

patients, anti-PTX3 antibodies are significantly prevalent and they might provide protection from renal involvement [29].
2. Pathologies of pregnancy: PTX3 plays a key role in human reproductive processes [30] and a recent clinical study observed a strong genetic association between PTX3 production and fertility [31]. Moreover, higher PTX3 levels are associated with preeclampsia development and severity [32, 33].
3. Cardiovascular disorders: Higher PTX3 levels are associated with unstable angina pectoris, coronary artery disease, hypertension and stiffness of large arteries [34–37]. Moreover, PTX3 seems to be an early marker of irreversible myocardial damage and the only independent predictor of mortality, among various mediators, within 24 hours from acute myocardial infarction (AMI) [38]. Thus PTX3 is a new candidate prognostic marker in ischemic heart disorders, including AMI [38, 39].
4. Febrile patients: A recent study by de Kruif et al. studied PTX3 plasma levels in 211 febrile patients admitted to the emergency department. PTX3 was associated with referral to ICUs, with development of congestive heart failure, and with longer hospital stay [40].
5. Localized infections: Increased levels of PTX3 have been observed in diverse infectious disorders including *Aspergillus fumigatus* infection, tuberculosis, leptospirosis, dengue and meningitis [41–43]. In all these conditions, PTX3 levels correlated with disease severity and had a prognostic value.

Interestingly, a very loose correlation has been observed between circulating levels of PTX3 and CRP in all the studies reported thus far, and plasma PTX3 seems to increase more rapidly than plasma CRP during inflammation and infection.

Given the abovementioned role of PTX3 in innate immunity and in various inflammatory/infectious diseases, researchers have started to explore the significance of PTX3 as a marker of severity and outcome predictor in ALI/ARDS and sepsis.

PTX3 in ALI/ARDS patients

We recently performed a prospective, controlled, observational study [44] in which we measured circulating PTX3 levels in 21 ALI/ARDS patients within 24 hours from intubation (day 1), 24 hours after the first sample, then every three days for the first month and then once a week, until discharge from the ICU. PTX3 was also measured in fluid obtained from bronchoalveolar lavage (BAL), which was performed when clinically indicated. In these ALI/ARDS patients, out of several day 1 parameters, PTX3 was the only one to be significantly different in survivors and non-survivors. Moreover, PTX3 plasma levels peaked on the first day, declining thereafter. Finally, PTX3 levels were positively correlated with lung injury score values (**Fig. 1 a**) and number of organ failures (**Fig. 1 b**). PTX3 was present in BAL fluid and BAL fluid samples that were positive on bacterial culture were associated with significantly higher PTX3 values [44].

Our results, supported by growing experimental evidence, seem to suggest a central role for PTX3 in ALI/ARDS [45]. PTX3, promptly released by neutrophils, may recognize the injurious noxae, promote phagocytosis of bacteria by migrated neutrophils, and enhance nitric oxide (NO) production and tissue factor expression [19]. Although results thus far seem very promising, PTX3's role in ALI/ARDS as an inflammatory mediator and as a marker of severity and outcome

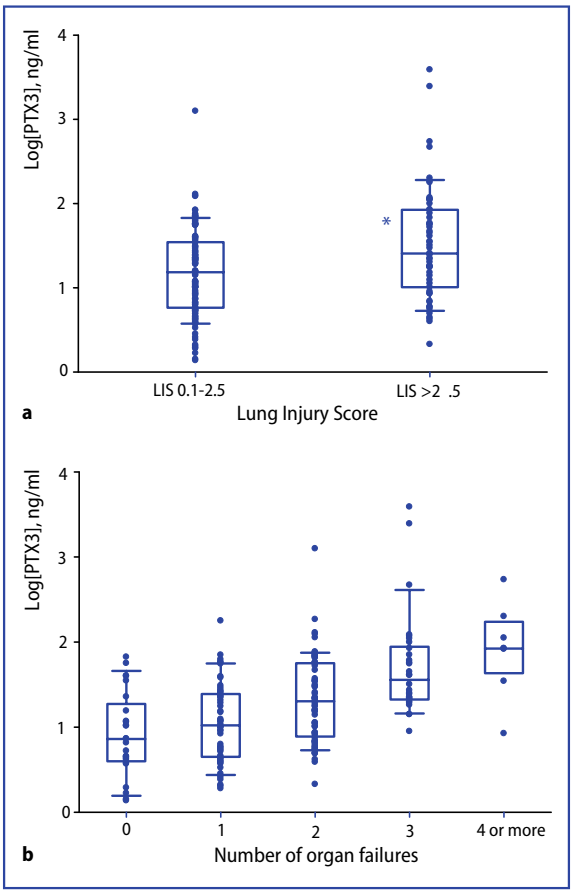

Fig. 1. Pentraxin 3 (PTX3) in acute lung injury/acute respiratory distress syndrome (ALI/ARDS) patients. In a study conducted on 21 patients with ALI/ARDS, plasma PTX3 was significantly associated with severity of lung injury (*$p < 0.001$, panel **a**) and number of organ failures ($p < 0.001$ by ANOVA, panel **b**). Boxes represent the median, 25th and 75th percentiles. The 10th and 90th percentiles are signified by whisker caps. From [44] with permission

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needs to be studied more both in animal models (e.g., *ptx3*-deficient mice) and in the clinical setting.

PTX3 in Septic Patients

To date, three clinical studies have investigated the significance of PTX3 during sepsis. In an explorative study by Muller and colleagues, baseline PTX3 plasma levels were measured in 101 patients admitted to a single ICU, with a diagnosis of SIRS, sepsis or septic shock. In this study, PTX3 was elevated in all patients in comparison to healthy controls, with a gradient from SIRS to septic shock [41]. A more recent study by Sprong et al., investigated PTX3 levels in 26 patients affected by severe meningococcal disease and admitted to a single ICU and found higher baseline levels in patients with hemodynamic shock in comparison with those without shock [42]. Finally, we recently performed an observational study on 90 patients with severe sepsis or septic shock admitted to three general ICUs. We measured plasma PTX3 levels every day for the first week, then every other

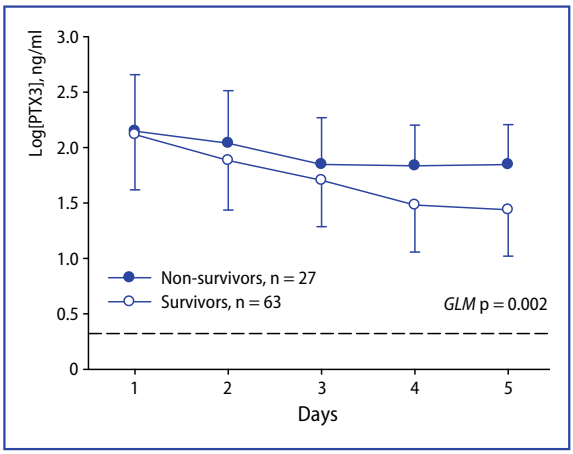

Fig. 2. Pentraxin 3 (PTX3) in septic patients. Persisting high levels of circulating PTX3 during the first five days after severe sepsis and septic shock onset were associated with 90-day mortality (n = 90 patients, p = 0.002 by general linear mixed model [GLM] for repeated measures). Values are shown as mean ± standard deviation, dashed line represents normal PTX3 values (< 2 ng/ml). From [46] with permission

day until day 13 and then every fifth day until the end of the study or until ICU discharge or death. We also recorded sepsis signs, disease severity and organ dysfunction. Mortality was assessed at day 90 from study entry. We found that PTX3 levels remained significantly higher in non-survivors in comparison to survivors over the first five days (**Fig. 2**). Moreover, on day 1, patients with septic shock had higher PTX3 levels than patients with severe sepsis. Finally, PTX3 was significantly correlated with signs of sepsis severity (i.e., heart rate, serum creatinine, platelet count), and with global clinical severity scores, like Simplified Acute Physiology Score (SAPS) II score and Sequential Organ Failure Assessment (SOFA) score, and number of organ failures [46].

Similarly to ALI/ARDS, clinical and laboratory studies seem to indicate a key role for PTX3 in sepsis. Interestingly, our study in septic patients also showed a correlation between circulating PTX3 increase and coagulation/fibrinolysis system dysfunction [46]. This observation corroborates experimental evidence connecting the coagulation/fibrinolysis system with inflammation activation and sepsis severity and deserves further scrutiny.

Conclusion

PTX3 is a recently discovered molecule involved in the acute phase of inflammation which exerts complex and delicate regulatory functions. Evidence is growing of a possible central role for PTX3 in a variety of human diseases. In particular, our research group has contributed to exploring the significance of PTX3 in the two most relevant diseases of critical care medicine: ALI/ARDS and sepsis. Early elevated PTX3 levels are associated with more severe forms of sepsis and ALI/ARDS and with outcome. However, it remains to be elucidated whether PTX3 plays a direct role or is just a marker of an established injury in these deadly syndromes. Hopefully, future studies aimed towards a clearer description of the role of PTX3 in critical care medicine will lead us to a deeper understanding of the pathophysiological mechanisms involved and, eventually, to the development of specific and effective therapies.

References

1. Koch A, Sanson E, Helm A, et al (2010) Regulation and prognostic relevance of serum ghrelin concentrations in critical illness and sepsis. Crit Care 14: R94
2. Sprung CL, Sakr Y, Vincent JL, et al (2006) An evaluation of systemic inflammatory response syndrome signs in the Sepsis Occurrence In Acutely Ill Patients (SOAP) study. Intensive Care Med 32: 421–427
3. Raurich JM, Vilar M, Colomar A, et al (2010) Prognostic value of the pulmonary dead-space fraction during the early and intermediate phases of acute respiratory distress syndrome. Respir Care 55: 282–287
4. Beale R, Janes JM, Brunkhorst FM, et al (2010) Global utilization of low-dose corticosteroids in severe sepsis and septic shock: a report from the PROGRESS registry. Crit Care 14: R102
5. Mauri T, Masson S, Pradella A, et al (2010) Elevated plasma and alveolar levels of soluble receptor for advanced glycation endproducts areassociated with severity of lung disfunction in ARDS patients. Tohoku J Exp Med 222: 105–112
6. Ware LB, Matthay MA (2000) The acute respiratory distress syndrome. N Engl J Med 342: 1334–1349
7. Park WY, Goodman RB, Steinberg KP, et al (2001) Cytokine balance in the lungs of patients with acute respiratory distress syndrome. Am J Respir Crit Care Med 164: 1896–1903
8. Hyers TM, Tricomi SM, Dettenmeier PA, Fowler AA (1991) Tumor necrosis factor levels in serum and bronchoalveolar lavage fluid of patients with the adult respiratory distress syndrome. Am Rev Respir Dis 144: 268–271
9. Luzzani A, Polati E, Dorizzi R, et al (2003) Comparison of procalcitonin and C-reactive protein as markers of sepsis. Crit Care Med 31: 1737–1741
10. Garlanda C, Bottazzi B, Bastone A, Mantovani A (2005) Pentraxins at the crossroads between innate immunity, inflammation, matrix deposition, and female fertility. Annu Rev Immunol 23: 337–366
11. Mantovani A, Garlanda C, Doni A, Bottazzi B (2008) Pentraxins in innate immunity: from C-reactive protein to the long pentraxin PTX3. J Clin Immunol 28: 1–13
12. Janeway CA Jr, Medzhitov R (2002) Innate immune recognition. Annu Rev Immunol 20: 197–216
13. Bottazzi B, Doni A, Garlanda C, Mantovani A (2010) An integrated view of humoral innate immunity: pentraxins as a paradigm. Annu Rev Immunol 28: 157–183
14. Pepys MB, Baltz ML (1983) Acute phase proteins with special reference to C-reactive protein and related proteins (pentaxins) and serum amyloid A protein. Adv Immunol 34: 141–212
15. Casas JP, Shah T, Hingorani AD, et al (2008) C-reactive protein and coronary heart disease: a critical review. J Intern Med 264: 295–314
16. Elliott P, Chambers JC, Zhang W, et al (2009) Genetic loci associated with C-reactive protein levels and risk of coronary heart disease. JAMA 302: 37–48
17. Zacho J, Tybjaerg-Hansen A, Jensen JS, et al (2008) Genetically elevated C-reactive protein and ischemic vascular disease. N Engl J Med 359: 1897–1908
18. Jaillon S, Peri G, Delneste Y, et al (2007) The humoral pattern recognition receptor PTX3 is stored in neutrophil granules and localizes in extracellular traps. J Exp Med 204: 793–804
19. Deban L, Castro Russo R, Sironi M, et al (2010) Regulation of leukocyte recruitment by the long pentraxin PTX3. Nat Immunol 11: 328–334
20. Moalli F, Doni A, Deban L, et al (2010) Role of complement and Fcγ receptors in the protective activity of the long pentraxin PTX3 against *Aspergillus fumigatus*. Blood 116: 5170–5180
21. Dias AA, Goodman AR, Dos Santos JL, et al (2001) TSG-14 transgenic mice have improved survival to endotoxemia and to CLP-induced sepsis. J Leukoc Biol 69: 928–936
22. Salio M, Chimenti S, De Angelis N, et al (2008) Cardioprotective function of the long pentraxin PTX3 in acute myocardial infarction. Circulation 117: 1055–1064
23. Soares AC, Souza DG, Pinho V, et al (2006) Dual function of the long pentraxin PTX3 in resistance against pulmonary infection with Klebsiella pneumoniae in transgenic mice. Microbes Infect 8: 1321–1329

24. Souza DG, Amaral FA, Fagundes CT, et al (2009) The long pentraxin PTX3 is crucial for tissue inflammation after intestinal ischemia and reperfusion in mice. Am J Pathol 174: 1309 – 1318
25. Hollan I, Bottazzi B, Cuccovillo I, et al (2010) Increased levels of serum pentraxin 3, a novel cardiovascular biomarker, in patients with inflammatory rheumatic disease. Arthritis Care Res (Hoboken) 62: 378 – 385
26. Iwata Y, Yoshizaki A, Ogawa F, et al (2009) Increased serum pentraxin 3 in patients with systemic sclerosis. J Rheumatol 36: 976 – 983
27. Fazzini F, Peri G, Doni A, et al (2001) PTX3 in small-vessel vasculitidis: an independent indicator of disease activity produced at sites of inflammation. Arthritis Rheum 44: 2841 – 2850
28. Kim J, Koh JK, Lee EY, et al (2009) Serum levels of soluble triggering receptor expressed on myeloid cells-1 (sTREM-1) and pentraxin 3 (PTX3) as markers of infection in febrile patients with systemic lupus erythematosus. Clin Exp Rheumatol 27: 773 – 778
29. Bassi N, Ghirardello A, Blank M, et al (2010) IgG anti-pentraxin 3 antibodies in systemic lupus erythematosus. Ann Rheum Dis 69: 1704 – 1710
30. Garlanda C, Maina V, Cotena A, Moalli F (2009) The soluble pattern recognition receptor pentraxin-3 in innate immunity, inflammation and fertility. J Reprod Immunol 83: 128 – 133
31. May L, Kuningas M, van Bodegom D, et al (2010) Genetic variation in pentraxin (PTX) 3 gene associates with PTX3 production and fertility in women. Biol Reprod 82: 299 – 304
32. Cetin I, Cozzi V, Papageorghiou AT, et al (2009) First trimester PTX3 levels in women who subsequently develop preeclampsia and fetal growth restriction. Acta Obstet Gynecol Scand 88: 846 – 849
33. Castiglioni MT, Scavini M, Cavallin R, et al (2009) Elevation of plasma levels of the long pentraxin 3 precedes preeclampsia in pregnant patients with type 1 diabetes. Autoimmunity 42: 296 – 298
34. Inoue K, Sugiyama A, Reid PC, et al (2007) Establishment of a high sensitivity plasma assay for human pentraxin 3 as a marker for unstable angina pectoris. Arterioscler Thromb Vasc Biol 27: 161 – 167
35. Matsui S, Ishii J, Kitagawa F, et al (2010) Pentraxin 3 in unstable angina and non-ST-segment elevation myocardial infarction. Atherosclerosis 210: 220 – 225
36. Yilmaz MI, Carrero JJ, Martin-Ventura JL, et al (2010) Combined therapy with renin-angiotensin system and calcium channel blockers in type 2 diabetic hypertensive patients with proteinuria: effects on soluble TWEAK, PTX3, and flow-mediated dilation. Clin J Am Soc Nephrol 5: 1174 – 1181
37. Miyaki A, Maeda S, Yoshizawa M, et al (2010) Is pentraxin 3 involved in obesity-induced decrease in arterial distensibility? J Atheroscler Thromb 17: 278 – 284
38. Latini R, Maggioni AP, Peri G, et al (2004) Prognostic significance of the long pentraxin PTX3 in acute myocardial infarction. Circulation 110: 2349 – 2354
39. Jenny NS, Arnold AM, Kuller LH, et al (2009) Associations of pentraxin 3 with cardiovascular disease and all-cause death: the Cardiovascular Health Study. Arterioscler Thromb Vasc Biol 29: 594 – 599
40. de Kruif MD, Limper M, Sierhuis K, et al (2010) PTX3 predicts severe disease in febrile patients at the emergency department. J Infect 60: 122 – 127
41. Muller B, Peri G, Doni A, et al (2001) Circulating levels of the long pentraxin PTX3 correlate with severity of infection in critically ill patients. Crit Care Med 29: 1404 – 1407
42. Sprong T, Peri G, Neeleman C, et al (2009) Ptx3 and C-Reactive Protein in Severe Meningococcal Disease. Shock 31: 28 – 32
43. Wagenaar JF, Goris MG, Gasem MH, et al (2009) Long pentraxin PTX3 is associated with mortality and disease severity in severe Leptospirosis. J Infect 58: 425 – 432
44. Mauri T, Coppadoro A, Bellani G, et al (2008) Pentraxin 3 in acute respiratory distress syndrome: an early marker of severity. Crit Care Med 36: 2302 – 2308
45. He X, Han B, Bai X, et al (2010) PTX3 as a potential biomarker of acute lung injury: supporting evidence from animal experimentation. Intensive Care Med 36: 356 – 364
46. Mauri T, Bellani G, Patroniti N, et al (2010) Persisting high levels of plasma pentraxin 3 over the first days after severe sepsis and septic shock onset are associated with mortality. Intensive Care Med 36: 621 – 629

The Role of IgM- and IgA-enriched Immunoglobulins in the Treatment of Sepsis and Septic Shock

G. Berlot, M.C. Vassallo, and F. Tartamella

Introduction

Intravenous immunoglobulins (IVIG) are currently used to treat several diseases including toxic shock syndrome, different vasculitis, toxic epidermolysis syndrome, Kawasaki syndrome, myasthenia gravis, etc. Primarily, IVIG are used with the aim of tampering with the immune system, taking advantage of their pleiotropic effects. The rationale behind the use of IVIGs includes their interaction with soluble molecules and surface membrane receptors ultimately influencing the global immune response and its inflammatory and anti-inflammatory paths. Moreover, IVIGs play a complex role, binding exogenous molecules, influencing the path of presentation of antigens, and interacting with mediators of the specific immune response, mostly depending on lymphocytes.

Several mechanisms have been described to explain the efficacy of IVIGs, including: (a) Amplification of the immune response through an increase in opsonization and phagocytosis and activation of the complement system; (b) decrease in the inflammatory response, by the reduced production of tumor necrosis factor (TNF)-α and other inflammatory mediators; and (c) increased release of soluble receptors for a number of cytokines [1, 2]. Interestingly, IVIGs play their role by interacting with the active phase of sepsis and with the counter-regulatory mechanisms or compensatory anti-inflammatory response syndrome [3, 4]. Although the pathophysiological basis for their use is well established, the results of several randomized controlled trials (RCTs) aimed at investigating the clinical effects of IVIGs have been controversial [5], probably due to the relatively small numbers of patients included and the heterogeneity of their underlying conditions [6].

Structure and Function of Immunoglobulins

It is well known that non-self antigens are initially recognized by innate immunity, which consists of antigen presenting cells. These monocyte cell lines are entrusted with the task of processing antigens and presenting the resulting epitopes to the cells of specific immunity, mostly belonging to lymphocyte cell lines. Surface membrane receptors of the antigen presenting cells recognize common non-specific antigenic determinants and cannot match the wide variability of microbial antigenic epitopes.

Specific immunity, also known as adaptive immunity because of its ability to cope with continuously changing antigens, involves antibodies encoded by genes

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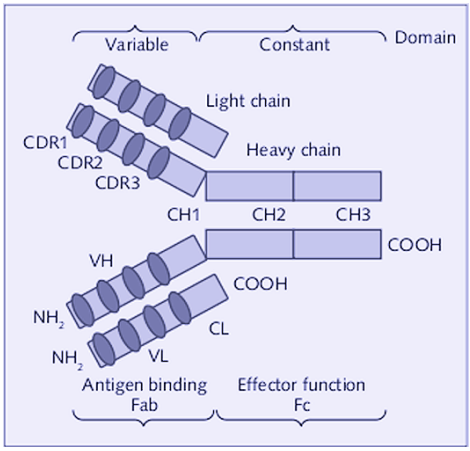

Fig. 1. Schematic two-dimensional structure of an immunoglobulin G (IgG) molecule. VH and VL indicate the variable regions of the heavy and light chains, respectively. CDR: complementary determining region; COOH: carboxyl; Fab: fragment antigen binding; Fc: fragment crystallizable region; NH_2: amino

that undergo somatic recombinations and hypermutations. The distinction between innate and specific immunity appears rather simplistic, as the two systems converge at multiple points [7, 8]. For example, opsonization by antibodies promotes internalization and presentation of epitopes by cells of the innate immunity, which in turn boost the activation of T helper lymphocytes, thus promoting the activation of specific immunity and production of antibodies.

Antibodies are secreted by plasma cells, which are derived from activated B lymphocytes. Antibodies belong to five different classes of immunoglobulins (IgG, IgA, IgM, IgE, and IgD). The IgG class has a prototypical structure and consists of a Y-shaped molecule made of two identical heavy (H) and light (L) peptide chains (**Fig. 1**). H and L chains are both divided into a variable (V) domain that binds antigens, and a constant (C) region that activates the various components of the immune system, triggering specific responses (for example, phagocytosis, antibody- and cell-mediated cytotoxicity, and complement-mediated lysis). The region connecting the two functional parts can undergo conformational changes in order to re-shape the molecule according to the antigen variability.

In conclusion, immunoglobulins can be considered as biochemical transducers that are able to:

- neutralize bacterial toxins;
- opsonize bacteria, promoting their destruction and amplifying the mechanism of antigen presentation by innate immunity;
- regulate inflammatory and anti-inflammatory activity as soluble receptors binding circulating cytokines;
- modulate the complement cascade [1, 8].

Rationale for the use of Intravenous Immunoglobulins in Sepsis

On the basis of their specificity, IVIG preparations can be grouped into monoclonal – containing a single class of immunoglobulin directed against a single epitope (e.g., TNF-α soluble receptors, etc) – or polycloclonal – containing antibodies directed against multiple epitopes. The additional immunomodulatory effects

attributed to the latter class are due to naturally occurring autoantibodies and some non-immune proteins present in the preparations [1].

Both types of immunoglobulin have been used in septic patients, with different results [2, 9, 10]. Monoclonal antibodies are currently used to treat some diseases which, unlike sepsis, are characterized by local instead of diffuse inflammatory activity. For example, monoclonal antibodies are used for the treatment of Crohn's disease and rheumatoid arthritis [11]. However, monoclonal antibodies are not free of adverse effects. Administration of an anti-TNF-α antibody (infliximab), for example, was associated with pulmonary and skin infections caused by intracellular species and with the reactivation of tuberculosis [12].

In recent years, several RCTs have been conducted in order to test the efficacy of monoclonal antibodies against endotoxin, sepsis mediators and surface receptors. However, results are conflicting and some trials seem to show an advantage in the control arm [13]. Moreover, only *post hoc* analyses could identify small subsets of patients who received benefit from this approach [5]. Different biases have been suggested to explain these results, including the different endpoints considered by the investigators (e.g., 28-day vs 56-day survival), the appropriateness of other treatments of sepsis, and the presence of other concomitant diseases [13].

Polyclonal preparations contain variable amounts of IVIG directed against a variety of Gram-negative and Gram-positive epitopes and bacteria-derived substances, including endotoxin. Several preparations contain predominantly IgG with only traces of other immunoglobulins (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 the immunoglobulin concentrations, the various preparations also differ with regard to the stabilizers used [1]. Unlike monoclonal IVIGs, polyclonal IVIGs are widely used in septic patients despite the lack of very large, positive RCTs fully satisfying the evidence-based medicine (EBM) criteria.

With regard to the type of preparation of IVIG, different meta-analyses have shown an increased survival in patients treated with eIg compared with preparations containing only IgG [17, 18]. As the endotoxin molecule represents a target for IgM [14], this effect is particularly evident in patients affected by Gram-negative infections [19].

Clinical Indications for IVIG in Sepsis

As recommended by the Surviving Sepsis Campaign Executive Committee, the administration of IVIG should be limited to pediatric sepsis [20]. However, this position does not take in account a meta-analysis showing that the risk of death was lower in septic patients who received polyclonal IVIGs than in controls (RR= 0.64, 95 % CI = 0.51 – 0.80) [21], with this beneficial effect being significant in adults (RR = 0.62 95 % CI: 0.49 – 0.79) but not in pediatric patients (RR = 0.70; 95 % CI: 0.42 – 1.18). These results have been confirmed by a more recent meta-analysis including a larger number of subjects, in which a better survival was shown in adult septic patients given polyclonal IVIG compared with controls (n = 2621; RR 0.74, 95 % CI 0.62 – 0.89) [22]. The difficulties encountered in defining the exact role of IVIGs can be imagined if one considers that only 20 studies out of > 4000 were considered eligible by Turgeon et al. for their systematic review [22].

IVIGs have been used both as a prophylactic measure in patients with a high risk of infection and as a biological therapy of sepsis. They have been used for reducing the risk of early neonatal sepsis or postoperative infections in open heart surgery. However, any clinical advantage in newborns with low weight at birth should still be considered speculative as it has not been definitely proved [23, 24]

Patients undergoing heart surgery are at a high risk of sepsis for different reasosn, including the underlying conditions, the presence of multiple invasive devices and prolonged ICU length of stay. Moreover, the use of 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 [25]. There is evidence that IVIGs may reduce morbidity in postoperative heart surgery patients with an Acute Physiology and Chronic Health Evaluation (APACHE) score ≥ 24 on the first postoperative day after CPB [26–28]. These results have been confirmed in a more recent trial where the beneficial effect of IVIG, however, appeared to be confined to more severely ill patients [29].

A beneficial effect of polyclonal IVIG has also been shown in critically ill patients affected by toxic shock syndrome secondary to severe streptococcal group A infections [30, 31]. Obviously, IVIG cannot replace conventional surgical drainage and antibiotic therapy. Yet promptness in surgical drainage of septic foci might account for the conflicting results existing in recent literature. A number of RCTs have showed a more favorable outcome in surgical patients at risk of or with established sepsis who were given IVIG when compared with controls [25–27, 32–35]. Conversely, in medical patients, including those with malignancies and neutropenia, the role of IVIG appears to be less definite [36, 37].

Along with the encouraging results in surgical patients, more recent reviews have confirmed a significant effect of IVIG on overall mortality in mixed populations of septic patients. Notably, updated results from the Cochrane Collaboration corroborate previous evidence, although the sensitivity analysis of trials with a low risk of bias persistently fails to show a reduction in mortality both in adult and newborn septic patients [21]. These ambiguous results may be ascribed to a number of factors, such as the different time intervals elapsing between diagnosis and treatment, the exclusion of elderly patients, the overall effect of other underlying diseases, and others. Indeed, the timing of administration appears to play a pivotal role, as suggested by Berlot and Dimastromatteo, 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 [38].

Conclusion

The treatment of sepsis is multifaced and requires different competencies. Administration of IVIG cannot replace conventional surgical drainage and antibiotic therapy, and represents only an adjunctive therapy of sepsis. 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 conflicting results whereas the administration of the less specific IVIG was associated with better outcomes.

On the basis of the published literature, it is possible to conclude that:

a) Some patients, e.g., those undergoing heart surgery and premature newborns with low birth weight may benefit from IVIGs when they are administered as a prophylactic measure.
b) Surgical patients treated with IVIG seem to have better outcomes than do controls.
c) The effects of IVIG on medical patients are less clear, probably as other concomitant disorders can influence the outcome independently of sepsis.
d) IgM-enriched IVIG preparations (eIg) exhibited a larger effect in reducing the risk of death in severe sepsis and septic shock than those containing only IgG.
e) The efficacy of IVIGs is probably time-dependent, being maximal in the early phases of severe sepsis and/or septic shock.

However, administration of IVIG is still not recommended in the Surviving Sepsis Campaign guidelines and further studies are needed to dismiss any remaining doubt on their efficacy.

References

1. Späth PJ (1999) Structure and function of immunoglobulins. Sepsis 3: 197–218
2. Werdan K (1999) Supplemental immune globulins in sepsis Clin Chem Lab Med 37: 341–349
3. Bone RC (1996) Sir Isaac Newton, Sepsis, SIRS and CARS. Crit Care Med 24: 1125–1138
4. Hotchkiss RS, Karl IE (2003) The pathophysiology and treatment of sepsis. N Engl J Med 348: 138–150
5. Deans KJ, Haley M, Natanson C, Eichacker PQ, Minneci PC (2005) Novel therapies for sepsis: a review. J Trauma 58: 867–874
6. Pildal J, Gøtzsche PC (2004) Polyclonal immunoglobulins for the treatment of bacterial sepsis: a systematic review. Clin Infect Dis 39: 38–46
7. Cohen J (2002) The immunopathogenesis of sepsis. Nature 420: 885–891
8. Medzhitov R, Janeway C Jr (2000) Innate immunity. N Engl J Med 343: 337–344
9. Werdan K (2001) Intravenous immunoglobulin for prophylaxis and therapy of sepsis. Curr Opin Crit Care 7: 354–361
10. Werdan K (1999) Immunoglobulins in sepsis: therapeutic use of immunoglobulins. Sepsis 3: 239–346
11. Breedveld F (2000) Therapeutic monoclonal antibodies. Lancet 355: 735–740
12. Scott DL, Kingsley GH (2006) Tumor necrosis factor inhibitors for rheumatoid arthritis. N Engl J Med 355: 704–712
13. Abraham E (1992) Why immunomodulatory therapies have not worked in sepsis. Intensive Care Med 25: 556–566
14. Little D, Regan M, Keane RM, Bouchier-Hayes D (1993) Perioperative immune modulation. Surgery 114: 87–91
15. Safdar A, Armstromg D (2001) Infectious morbidity in critically ill patients with cancer. Crit Care Clin 17: 531–550
16. Kalb TH, Lorin S (2002) Infection in the chronic critically ill: unique risk profile in a newly defined population. Crit Care Clin 18: 529–552
17. Neilson AR, Burchardi H, Schneider H (2005) Cost-effectiveness of immunoglobulin M-enriched immunoglobulin (Pentaglobin) in the treatment of severe sepsis and septic shock. J Crit Care 20: 239–249
18. Norby-Teglund A, Haque KN, Hammarström L (2006) Intravenous polyclonal IgM-enriched immunoglobulin therapy in sepsis: a review of clinical efficacy in relation to microbiological aetiology and severity of sepsis. J Intern Med 260: 509–516
19. Maury E, Blanchard HS, Chauvin P et al (2003) Circulating endotoxin and antiendotoxin antibodies during severe sepsis and septic shock. J Crit Care 18: 115–120

20. Dellinger RP, Levy MM, Carlet JM, et al (2008) Surviving Sepsis Campaign: International guidelines for management of severe sepsis and septic shock. Intensive Care Med 34: 17–60
21. Alejandra MM, Lansang MA, Dans LF Mantaring JB (2002) Intravenous immunoglobulin for treating sepsis an septic shock. Cochrane Database Syst Rev CD001090
22. Turgeon AF, Hutton B, Fergusson DA et al (2007) Meta-analysis: intravenous immunoglobulin in critically ill adult patients with sepsis. Ann Intern Med 146: 193–203
23. Jenson HB, Pollock BH (1998) The role of intravenous immunoglobulin for the prevention and treatment of neonatal sepsis. Semin Perinatol 22: 50–63
24. Shenoi A, Nagesh NK, Maiya PP, Bhat SR, Subba Rao SD (1999) Multicenter randomized placebo controlled trial of therapy with intravenous immunoglobulin in decreasing mortality due to neonatal sepsis. Indian Pediatr 36: 1113–1138
25. Sablotzki A, Friedrich I, Holzheimer RG, Kress HG, Werdan K, Silber RE (1999) Prophylactic use of immunoglobulins in cardiac surgery. Sepsis 3: 247–253
26. Pilz G, Kreuzer E, Kääb S, Appel R, Werdan K (1994) Early sepsis treatment with immunoglobulins after cardiac surgery in score-identified high risk patients. Chest 105: 76–82
27. Pilz G, Appel R, Kreuzer E, Werdan K (1997) Comparison of early IgM-enriched immunoglobulin vs polyvalent IgG administration in score-identified post cardiac surgical patients at high risk for sepsis. Chest 111: 419–426
28. Rankin JS, Glower DD, Teichmann TL, Muhlbaier LH, Stratton CW (2006) Immunotherapy for refractory pulmonary infection after adult cardiac surgery: immune dysregulation syndrome. J Heart Valve Dis 14: 783–791
29. Buda S, Riefolo A, Biscione et al (2005) Clinical experience with polyclonal IgM-enriched immunoglobulins in a group of patients affected by sepsis after cardiac surgery. J Cardiovas Vasc Anesth 19: 440–445
30. Norrby-Teglund A, Ihendyane N, Daremberg J (2003) Intravenous immunoglobulin adjunctive therapy in sepsis, with special emphasis on severe invasive group A streptococcal infections. Scand J Infect Dis 35: 683–689
31. Daremberg J, Ihendyane N, Sjölin Jet al (2003) Intravenous immunoglobulins G therapy in streptococcal toxic shock syndrome: a European randomized, double-blind, placebo-controlled trial. Clin Infect Dis 37: 333–340
32. Rodriguez A, Rello J, Neira J et al (2005) Effects of intravenous immunoglobulin and antibiotics on survival for severe sepsis undergoing surgery. Shock 23: 298–304
33. Dominioni L, Dionigi R, Zanello M et al (1991) Effects of high-dose IgG on survival of surgical patients with sepsis score of 20 or greater. Arch Surg 126: 236–240
34. Cafiero F, Gipponi M, Bonalumi U, Piccardo A, Sguotti C, Corbetta G (1992) Prophylaxis of infection with intravenous immunoglobulins plus antibiotics for patients at risk for sepsis undergoing surgery for colorectal cancer: results of a randomized, multicentre clinical trial. Surgery 112: 24–31
35. Schedel I, Dreikhausen U, Newtig B, et al (1991). Treatment of gram negative septic shock with immunoglobulin preparation: a prospective, randomized clinical trial. Crit Care Med 19: 1104–1113
36. Hentrich M, Fehnle K, Ostermann H, et al (2006) IgMA-enriched immunoglobulin in neutropenic patients with sepsis syndrome and septic shock: a randomized, controlled multiple-center trial. Crit Care Med 34: 1319–1325
37. Tugrul S, Ozcan PE, Akinci O, et al (2002) The effects of IgM-enriched immunoglobulin preparations in patients with severe sepsis (ISRCTN28863830). Crit Care 6: 357–362
38. Berlot G, Dimastromatteo G (2004) Use of IgM and IgA-enriched immunoglobulins in the treatment of severe sepsis and septic shock. Clinical experience. Minerva Anestesiol 70: 739–745

XIII Liver Failure

Spontaneous Bacterial Peritonitis in Patients with Cirrhosis and Ascites

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Introduction: Definition and Epidemiology

Spontaneous bacterial peritonitis (SBP) is a bacterial infection of ascitic fluid developed in patient without any intra-abdominal, surgically treatable source of infection [1]. In our experience, SBP is the second most common bacterial infection in patients with cirrhosis and ascites, coming after urinary tract infection [1–4]. In unselected patients with ascites, the prevalence of SBP is 1.5–3.5 % in outpatients [5, 6] and 10 % in inpatients [6]. Approximately half of the episodes of SBP are present at the time of hospital admission and the rest are acquired during hospitalization [1].

Pathogenesis of Spontaneous Bacterial Peritonitis

Bacterial translocation is the *conditio sine qua non* for the development of SBP [6]. Bacterial translocation is defined as the migration of bacteria or bacterial products from the intestinal lumen to the mesenteric lymph nodes [6]. In recent years, studies have shown increased bacterial translocation in cirrhotic rats [6]. This 'pathological bacterial translocation' in cirrhosis is related to several factors, including bacterial overgrowth, increased intestinal permeability and systemic and local defects in host immunity [6].

Bacterial Overgrowth

Intestinal bacterial overgrowth plays a key role in bacterial translocation in cirrhosis and is the result, at least partly, of a decrease in small-bowel motility and the delayed intestinal transit present in these patients [7]. It seems that autonomic dysfunction, increased nitric oxide (NO) synthesis and the oxidative stress of the mucosa are the main causes for decreased intestinal motility [7].

Intestinal Permeability

The intestinal mucosal barrier represents a physical and biological hurdle to bacterial translocation. Mucins, secretory mucosal immunoglobulin A antibodies, alfa-defensins, lysozymes and the tight junctions protect the epithelium against local and systemic bacterial invasion [8]. Cirrhotic patients were found to have increased intestinal permeability compared to healthy controls [9]. Furthermore, there was a significant correlation between the increased intestinal permeability,

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the severity of the liver disease and history of SBP [9]. Several factors increase intestinal permeability in cirrhosis, including ultrastructural changes in the intestinal mucosa, such as widening of intracellular spaces, vascular congestion, edema of the lamina propria, fibromuscular proliferation, a decreased villous/crypt ratio, wall thickening and tight junctions disruption [10]. Oxidative stress of the intestinal mucosa increases lipid peroxidation and glycosylation of the brush border membranes and mucins [11]. These changes are accompanied by changes in bacterial flora in the gut, which have increased hydrophobicity and adherence to the mucosa that may facilitate translocation across the mucosa. The inflammatory pathway also appears to affect intestinal permeability. In experimental cirrhosis, overproduction of tumor necrosis factor (TNF)-α and NO have been described [6], altering the structure of the intestinal mucosa, decreasing expression of tight junctions (zona occludens 1; ZO-1) and increasing intestinal permeability [12].

Host Immunity in Cirrhosis

The intestinal tract is also an active immune organ. Gut-associated lymphoid tissue (GALT) comprises four compartments: Peyer's patches, lamina propria lymphocytes (including dendritic cells), intraepithelial lymphocytes, and mesenteric lymph nodes. The interaction between intestinal bacteria and gut epithelium stimulates GALT, triggering innate and acquired immune responses. Physiologic bacterial translocation to mesenteric lymph nodes is part of the immune response, allowing local immune stimulation without inducing systemic and local inflammation [6]. In cirrhosis, because of local and systemic immune deficiencies, mesenteric lymph nodes are unable to contain bacterial infection. This 'pathological' bacterial translocation process is followed by bacteremia, ascitic fluid inoculation and inflammatory response [6]. In recent years, several lines of evidence have confirmed that a pathological bacterial translocation can occur as a 'continuum event' in up to 32–42 % of patients with cirrhosis and ascites [13].

Innate Immunity in cirrhosis

Peripheral mononuclear cells are increased markedly in number and present an over expression of Toll-like receptors (TLRs) [14] and an overproduction of TNF-α [15]. Neutrophils showed reduced phagocytic activity, probably due to low serum and ascitic complement levels as well as defects in Fc gamma-receptor expression or tuftsin deficiency [16, 17].

Acquired immunity in cirrhosis

The absolute number of circulating T lymphocytes is reduced in cirrhotic patients [18]. On the other hand, percentages of T lymphocytes, senescent CD8+ or pre-apoptotic CD4+ and CD8+ T cells are increased in cirrhotic patients compared with healthy controls [18]. This is probably because prolonged antigenic stimulation of T lymphocytes, with a significant number of effector cells implicated in the antigenic response, leads to a higher probability of activation-induced death (activation induced cell death describes the induction of cell death in already activated T cells by restimulation of their T cell receptors) [18]. It is possible to speculate that immunosuppression, associated classically with liver cirrhosis, may be in part secondary to an exhausted state of the acquired immunity. Recently, in experimental cirrhosis, it has been established that hyperactivity

of the splanchnic sympathetic nervous system impairs host defense, playing a role in the translocation of Gram-negative bacteria [19].

Risk Factors

We will consider below three classes of predisposing factors for SBP: Genetic factors, disease-related factors, and environmental factors.

Genetic Factors

Some genes that predispose to development of SBP have been identified recently. Presence of the nucleotide-binding oligomerization domain containing 2 (NOD2) variants, p.R702W, p.G908R, and c.3020insC, has been shown to increase the development of SBP 3-fold, probably by increasing intestinal permeability [20]. Monocyte chemotactic protein-1 (MCP-1) polymorphism 2518 genotype AA has been reported to be a risk factor for development of SBP in alcoholic cirrhosis [21]. Further studies are needed to identify additional genetic factors predisposing to the development of SBP.

Severity of Liver Disease

The Model of End-stage Liver Disease (MELD) score and Child-Pugh score correlate directly with the onset of SBP [22]. Serum bilirubin level > 2.5 mg/dl, low level of serum albumin, creatinine level > 1.2 mg/dl, serum sodium level ≤ 130 mmol/L, hepatic venous pressure gradient > 12 mmHg reflect the severity of liver disease and represent a risk factor for the development of SBP [23, 24]. Protein ascitic levels < 1.5 g/dl and low concentrations of C3 correlate with SBP; they probably reduce opsonization of bacteria [16, 24]. Gastrointestinal bleeding increase the risk of SBP 4-fold [1]; a possible explanation for this finding is that the hemorrhagic shock increases bacterial translocation and intestinal permeability. In patients who survive an episode of SBP, the 1-year cumulative recurrence rate is 70 % [1].

Environmental Factors

Proton pump inhibitor therapy increases bacterial colonization of the upper gastrointestinal tract, predisposes to bacterial overgrowth and translocation and has been recently associated with SBP [25].

Clinical Presentations and Complications of SBP

In up to 3 % of outpatients, SBP was diagnosed by a paracentesis which was performed to control ascites [5]. In hospitalized cirrhotic patients with ascites, SBP can also be asymptomatic [5]. More frequently, patients with SBP may have one or more of the signs or symptoms reported in **Box 1** [1].

In the general population, high serum levels of C-reactive protein (CRP) suggest the presence of a bacterial infection [26]. Since CRP is an 'acute-phase response protein' produced by hepatocytes, the diagnostic value of CRP measure-

Signs and/or symptoms of systemic inflammation:
- hyper- hypothermia
- chills
- altered white blood cell count
- tachycardia
- tachypnea

Septic shock

Symptoms and/or signs of peritonitis:
- abdominal pain
- abdominal tenderness
- vomiting
- diarrhea
- ileus

Worsening of liver function (e.g., development of hepatic encephalopathy):

Renal failure:
- hepatorenal syndrome
- acute tubular necrosis
- pre-renal failure

Gastrointestinal bleeding

Box 1. Clinical presentation of spontaneous bacterial peritonitis

ment may be limited in 'infected' patients with cirrhosis and liver failure. However, studies performed in patients with cirrhosis found significantly higher serum CRP levels in patients with bacterial infection (including SBP) than in those without [26]. Interestingly, increased serum procalcitonin concentrations, another biomarker of infection, were found in patients with cirrhosis and bacterial infection [26].

SBP leads frequently to a broad spectrum of complications, such as hepatorenal syndrome (HRS), hepatic encephalopathy, gastrointestinal bleeding and septic shock [4]. In addition, these patients may have sepsis-induced hyperglycemia, defective arginine-vasopressin secretion, adrenal insufficiency, or compartmental syndrome. Development of complications contributes to the high rate mortality of SBP [1, 4]. The most frequent complication is renal failure, which occurs in 33 % of these patients [27]. The development of renal dysfunction and type 1 HRS suggests a poor prognosis with an in-hospital mortality rate ranging from 40 %-78 % and a median survival rate from the moment of onset of 2 weeks [4, 28]. Septic shock also affects the prognosis, with a mortality rate exceeding 70 % [4].

Diagnosis

Neutrophil Count in Ascitic Fluid

Peritoneal infection causes an inflammatory reaction resulting in an increased number of neutrophils in ascitic fluid. The greatest sensitivity for the diagnosis of SBP is reached with a cut-off neutrophil count of 250/mm^3, although the greatest specificity is reached with a cut-off of 500 neutrophils/mm^3 [1, 3]. In patients with hemorrhagic ascites with a fluid red blood cell (RBC) count > 10 000/mm^3 (due to

concomitant malignancy or traumatic tap), a correction factor of 1 neutrophil per 250 RBCs has been proposed, since this is the maximum expected ratio of neutrophils to RBCs normally present in peripheral blood [1]. Manual counts are recommended, because they are more than the automated counts [1]. Nevertheless, one recent study found excellent correlation between these two techniques, even at low counts, suggesting that automated counting may replace manual counts [29]. In contrast, the use of reagent strips cannot be recommended for the rapid diagnosis of SBP because of their inadequate diagnostic accuracy [29].

Ascitic Fluid Culture

Ascitic fluid should be inoculated at the bedside using blood culture bottles that include aerobic and anaerobic media [1]. The minimum amount of ascitic fluid inoculated in each bottle is 10 ml [1]. Despite the use of sensitive methods, ascites culture is negative in 60 % of patients with clinical manifestations suggestive of SBP and increased ascites neutrophils [1, 2]. Gram-negative bacteria used to be responsible for nearly 80 % of SBP cases, with *Escherichia coli* and *Klebsiella pneumonia* accounting for most. Aerobic Gram-positive bacteria, mostly *Streptococcus viridians*, *Staphylococcus aureus* and *Enterococcus spp*, were isolated in approximately 20 % of cases [1, 2]. Recent epidemiological data, however, suggest a similar proportion between Gram-negative and Gram-positive bacteria, probably because of use of norfloxacin prophylaxis and more invasive procedures [2].

A recent study has shown that 30 % of isolated Gram-negative bacteria are resistant to quinolones and 30 % are resistant to trimethoprim-sulfamethoxazole. Furthermore, seventy percent of quinolone-resistant Gram-negative bacteria are also resistant to trimethoprim-sulfamethoxazole [2]. The incidence of SBP due to quinolone-resistant Gram-negative bacteria is higher in patients on norfloxacin therapy than in patients 'naïve' for this treatment. In contrast, the rate of cephalosporin-resistant Gram-negative bacteria was low in patients with SBP whether or not they were receiving norfloxacin prophylaxis [2]. Finally, the epidemiology of SBP in patients with cirrhosis is changing quickly in nosocomial SBP. Currently there is already a strong difference between community-acquired SBP, in which Gram-negative bacteria are still predominant, and nosocomial SBP, in which Gram-positives are now predominant [2]. Likewise, the rate of cephalosporin-resistant Gram-negative bacteria as well as cephalosporin-resistant Gram-positive bacteria, is higher in nosocomial SBP when compared to community-acquired SBP [30, 31].

Types of Diagnosis

Patients with an ascitic fluid neutrophil count ≥ 250 cells/mm^3 and positive cultures are defined as patients with culture positive SBP. Patients with an ascitic fluid neutrophil count ≥ 250 cells/mm^3 and negative culture have 'culture negative neutrocytic ascites' [1], but their clinical presentation is similar to that of patients with culture positive SBP [1]. Moreover, as both groups of patients have significant morbidity and mortality, they should be treated in a similar way.

Some patients have 'bacterascites' in which cultures are positive but there is a normal ascitic neutrophil count (< 250/mm^3) [1]. In some of these patients, bacterascites is the result of secondary bacterial colonization of ascites from a concomitant extraperitoneal infection (e.g., pneumonia or urinary tract infection).

Table 1. Management of bacterascites

PMN count	Treatment
< 250/mm^3 and a second ascitic fluid culture positive	Antibiotic treatment appears to be the most judicious option (further investigation necessary for this recommendation)
< 250/mm^3 and symptoms/signs of an extraperitoneal infection (pulmonary, urinary tract infection)	Antibiotic treatment according to the *in vitro* susceptibility of bacteria isolated in ascites (it is likely that this bacterium is also responsible for the extraperitoneal infection)
< 250/mm^3 and second ascitic fluid culture negative	No further action is required

These patients usually have general and extra-peritoneal symptoms and signs of infection. In other patients, 'bacterascites' is due to the spontaneous colonization of ascites, and they can either be clinically asymptomatic or have abdominal pain and/or fever. Whereas in some patients, particularly in those who are asymptomatic, bacterascites represents a transient and spontaneously reversible colonization of ascites, in other patients, especially if symptomatic, bacterascites is the first step in the development of SBP [1]. In patients with bacterascites who have symptoms or signs of infection, antibiotic therapy should be administered immediately according to the antibiogram [1]. In other cases, a repeat paracentesis for neutrophil count and culture is recommended first. The subsequent management of bacterascites is reported in **Table 1**.

Differential Diagnosis

The vast majority of cirrhotic patients with ascites and peritoneal infection have SBP. However, a small group of patients have bacterial peritonitis secondary to perforation or acute inflammation of intra-abdominal organs, abdominal wall infections or previous abdominal surgical procedures [32]. With the exception of peritonitis secondary to the two latter conditions, in which the precise nature of peritoneal infection is obvious, the differential diagnosis between spontaneous (primary) and secondary peritonitis can be difficult [32]. The differentiation is important because secondary peritonitis usually does not resolve unless patients are treated surgically. Conversely, surgical therapy may be accompanied by significant deterioration in the clinical status of cirrhotic patients with SBP [32].

Secondary peritonitis should be suspected when at least one of the following features is present [33]:

- reduction in ascitic fluid neutrophil count of less than 25 % (or even an increase) of the pretreatment value after two days of antibiotic treatment in follow-up paracenteses performed during therapy.
- More than one organism isolated from ascites, strongly suggestive of perforated bowel (particularly when the growth of anaerobic bacteria or fungi is observed).
- Runyon's criteria, represented by neutrocytic ascites with at least two of three criteria: ascitic fluid total protein > 1 g/dl (in contrast to SBP which selectively occurs in low-protein ascites), glucose < 50 mg/dl (due to bacterial glucose utilization), or lactate dehydrogenase (LDH) > 225 mU/ml (most likely due to more rapid metabolic rate and disintegration of ascitic neutophils) [33].

These criteria seem to be very sensitive in the detection of secondary peritonitis but their specificity is low [33].

In clinical practice, to distinguish 'secondary peritonitis' from SBP, patients should undergo appropriate radiological investigation like chest x-ray and abdominal computed tomography (CT) scan [32]. As reported in the recent study by Soriano et al., Runyon's criteria and/or polymicrobial ascitic fluid culture were present in 95.6 % of the cases of secondary bacterial peritonitis, and abdominal CT was diagnostic in 85 % of patients in whom diagnosis was confirmed by surgery or autopsy [32]. It seems advisable that the diagnosis of secondary bacterial peritonitis should be based on Runyon's criteria and microbiological data, together with an aggressive approach that includes prompt abdominal CT and an early surgical evaluation.

Treatment and Prognosis

Empirical Antibiotic Treatment (Box 2)

Empirical antibiotic therapy must be initiated immediately after the diagnosis of SBP. Several antibiotics can be used for the initial therapy of SBP: Cefotaxime or other third-generation cephalosporins, or amoxicillin-clavulanic acid or quinolones (**Table 2**) [1, 28, 34–39].

- Third generation cephalosporins: In the 1980s, cefotaxime and other third generation cephalosporins were investigated extensively for the treatment of SBP because Gram-negative aerobic bacteria from the enterobacteriaceae and non-enterococcal streptococcous species were the most common causative microorganisms, and for the favorable pharmacokinetic properties of these antibiotics (i.e., antibiotic concentration in the ascitic fluid > MIC90 of causative microrganisms) [1].
  The optimal cost-effective dosage has only been investigated for cefotaxime. In the first randomized, comparative study cefotaxime was more effective in achieving resolution of SBP and other infections than ampicillin plus tobramycin [34]. Furthermore, 10 % of patients treated with ampicillin plus tobramycin developed nephrotoxicity and superinfections, whereas no patients treated with cefotaxime showed this complication. Two other randomized, controlled trials showed that 5-day therapy was as effective as 10-day treatment and a dose of 4 g/day was comparable to a dose of 8 g/day in terms of rate of resolution of the infection, recurrence of SBP during hospitalization,

Box 2. Empirical antibiotic treatment of spontaneous bacterial peritonitis (SBP): General rules

- Start antibiotic therapy as soon as possible
- Third generation cephalosporins or penicillin plus penicillinase inhibitor still represent the antibiotics of choice in community-acquired SBP.
- Consider a broader spectrum therapy in nosocomial SBP (carbapenems plus lipopeptides or glycylcycline)
- Quinolones can be used in patients with community-acquired SBP if they were not receiving prophylaxis with oral quinolones and only in countries without a high incidence of quinolone-resistant bacterial infections
- Avoid aminoglycosides and/or other known nephrotoxic drugs
- Repeat paracentesis after 48 h to assess response to therapy

Table 2. Main studies on antibiotic therapy for spontaneous bacterial peritonitis in cirrhosis

First Author, year [ref]	Treatments	N° of patients	Infection resolution (%)	In-hospital survival (%)
Félisart, 1985 [34]	Tobramycin (1.75 mg/kg/8 h i.v.) plus ampicillin (2 g/4 h i.v.)	36	56	61
	vs cefotaxime (2 g/4 h i.v.)	37	85§	73
Runyon, 1991 [40]	Cefotaxime 5 days (2 g/8 h i.v.)	43	93	77
	vs cefotaxime 10 days (2 g/8 h i.v.)	47	91	67
Gomez-Jimenez, 1993 [41]	Cefonicid (2 g/12 h i.v.)	30	94	67
	vs ceftriaxone (2 g/24 h i.v.)	30	100	70
Rimola, 1995 [35]	Cefotaxime (2 g/6 h i.v.)	71	77	69
	vs cefotaxime (2 g/12 h i.v.)	72	79	79
Navasa, 1996 [36]	Ofloxacin (400 mg/12 h PO)	64	84	81
	vs cefotaxime (2 g/6 h i.v.)	59	85	81
Sort, 1999 [37]	Cefotaxime (2 g/6 h i.v.)	63	94	71
	vs cefotaxime (2 g/6 h i.v.) plus i.v. albumin	63	98	90**
Ricart, 2000 [38]	Amoxycillin/clavulanic acid (1/0.2 g/8 h)	24	87	87
	i.v. followed by 0.5/0.125 g/8 h PO	24	83	79
	vs cefotaxime 1 g/6 h i.v.)			
Terg, 2000 [39]	Ciprofloxacin (200 mg/12 h i.v. for 7 days)	40	76	77
	vs ciprofloxacin (200 mg/12 h i.v. for 2 days, followed by 500 mg/12 h PO for 5 days)	40	78	77
Tuncer, 2003 [62]	Ciprofloxacin (500 mg/12 h)	15	80	NA
	vs cefotaxime (2 g/8 h)	17	76	
	or ceftriaxone (2 g/24 h)	17	83	
Chen, 2005 [63]	Cefotaxime (1 g/6 h)	19	79	79
	vs amikacin (500 g/24 h)	18	61	72
Angeli, 2006 [28]	Ceftazidime (2 g b.d./24 h i.v.),	61	84	77
	vs "switch therapy" with ciprofloxacin (200 mg b.d./24 h i.v., for 8 days followed by 500 mg PO/24 h, for 8 days)	55	80	86

* Studies appear in chronological order; § $p < 0.02$ *vs* tobramycin plus ampicillin; ** $p < 0.01$ *vs* Cefotaxime alone; NA=not available

and hospital mortality [35, 40]. These results suggest that the high efficacy of cefotaxime in SBP can be maintained with short-course therapy and with doses lower than those formerly used, with a significant cost reduction (a minimum dose of 2 g/12 h i.v. should be administered in patients with normal renal function, with a recommended minimum duration of therapy of 5 days). There were no significant differences in rates of SBP resolution or in hospital survival using

other cephalosporins, including cefonicid, ceftriaxone and ceftazidime, compared to cefotaxime [28, 41].

- Penicillin plus penicillinase-inhibitors: In one clinical randomized controlled trial, amoxicillin-clavulanic acid was reported to be as effective as cefotaxime in the treatment of SBP, and was not associated with relevant adverse effects [38]. Considering also the low cost of this therapy, amoxicillin plus clavulanic acid can be consider a valid alternative to cephalosporins.
- Quinolones: Ciprofloxacin, moxifloxacin and ofloxacin administered intravenously and/or per os have been compared to cephalosporins and amoxycillin plus clavulanic acid in clinical randomized controlled trials: the effectiveness was comparable in terms of mortality and SBP resolution [28, 36, 39, 42]. In one randomized controlled study, switching therapy to ciprofloxacin (intravenous ciprofloxacin followed by oral ciprofloxacin) was more cost-effective than intravenous ceftazidime in cirrhotic patients who were not on prophylaxis with quinolones [28]. Quinolones are a valid alternative to third generation cephalosporins or penicillin plus penicillinase inhibitor in the treatment of SBP in patients who are not receiving prophylaxis with quinolones.
- Aminoglycosides: Aminoglycosides have only moderate efficacy, and are associated with nephrotoxicity [34]. Because cirrhotic patients present an increased risk of developing nephrotoxicity, potential nephrotoxic antibiotic therapy (such as aminoglycosides) should be avoided as empirical therapy for SBP.

Unfortunately, recent changes in the epidemiology of bacterial infections and particularly of SBP in cirrhosis have decreased the efficacy of the third generation cephalosporins as well as that of alternative therapies such as amoxycillin-clavulanic acid or quinolones [30, 31]. Hospitalization before the development of SBP seems to be associated with a high probability that the infection is sustained by multiresistant bacteria [31]. Nosocomial SBP due to extended-spectrum beta-lactamase-producing enterobacteriaceae (*E. coli* and *Klebsiella* species) or to multiresistant Gram-positive bacteria (*Enterococcus faecium*, methicillin-resistant *Staphylococcus aureus* [MRSA]) is often associated with a failure of the first-line empirical antibiotic treatment [30, 31, 43]. In fact it has been observed recently that the resolution of SBP in patients treated with third generation cephalosporins or amoxycillin/clavulanic acid was significantly reduced to 30–40 % in patients with cirrhosis and nosocomial SBP [43]. Hospital mortality and 30-day mortality have been shown to be higher in SBP due to multiresistant bacteria than in SBP due to common bacteria (66.7 % vs 30 %, $p < 0.0025$) [31]. Most patients with SBP due to multiresistant bacteria die within the first 5 days after the diagnosis of SBP [31]. In addition, the change in antibiotic therapy after the failure of the first-line treatment was associated with a poor survival [31]. These observations suggest that a more effective first-line empirical antibiotic therapy should be planned in patients with cirrhosis and nosocomial SBP including antibiotics with a broader spectrum, such as carbapenems and glycopeptides or glycylcyclines. In order to establish the best empirical antibiotic treatment of nosocomial SBP in patients with cirrhosis further large controlled clinical studies are needed.

As far as community acquired-SBP is concerned, multiresistant bacteria were isolated only in 3 % of patients. Thus, cefotaxime or other third-generation cephalosporins, or amoxycillin-clavulanic acid can still be used for initial therapy of

SBP in these patients. Quinolones should be used only in patients with community-acquired SBP who are not on prophylaxis with norfloxacin at the time of diagnosis of SBP and only in countries without a high rate of *E. coli* resistant to quinolones.

Resolution of infection in SBP is associated with an improvement in symptoms and signs [1]. For those patients who do not improve, treatment failure should be recognized early by performing a paracentesis after 48 h of antibiotic treatment; a reduction in ascitic fluid neutrophil count of less than 25 % of the pretreatment value suggests failure to respond to therapy [1, 35]. This should indicate further evaluation or modification of antibiotic treatment according to *in vitro* sensitivity or on an empiric basis as previously discusses.

Intravenous Albumin in Patients with SBP

SBP and other bacterial infections may precipitate a further deterioration in circulatory function, hepatic dysfunction, and can induce an impairment in renal function [3, 4, 27, 28]. The impairment in renal function in patients with cirrhosis and ascites as a result of SBP, biliary tract infections or urinary tract infections often meets the diagnostic criteria for type 1 HRS. Development of type 1 HRS is one of the strongest predictors of mortality in SBP and is associated with 30 % hospital mortality despite infection resolution if this complication is not prevented or treated [27, 37]. In the only study assessing the effect of albumin infusion on renal function and survival in SBP, 126 patients without shock were randomized to receive either cefotaxime or cefotaxime with intravenous albumin [37]. Albumin was given at a dose of 1.5 g/kg body weight within six hours of SBP diagnosis, followed by 1 g/kg on day 3. Albumin infusion significantly decreased the incidence of type 1 HRS (from 33 % to 10 %), and improved in-hospital mortality (10 % vs 29 %) and three month mortality (22 % vs 41 %) compared with cefotaxime alone. Patients who did not receive albumin did not receive any other fluid support. The rationale for use of albumin is to improve the blood effective circulating volume, which is usually reduced in SBP. Because of the reduction in effective circulating volume, these patients developed frequently renal failure, that represents a principal cause of death in SBP. Albumin can also bind endotoxins, reducing pro-inflammatory cytokines and NO [44]. It is unclear whether fluid support with crystalloids or other colloids would have produced the same results. There is only one hemodynamic study performed in patients with SBP showing that treatment with albumin is associated with significant improvement in circulatory function compared with equivalent doses of hydroxyethyl starch [45]. However, recently a pilot study reporting rates of renal impairment and mortality in high risk patients with SBP suggested that gelanfundin 4 % given with ceftriaxone may be a less expensive therapeutic alternative to albumin [46]. Interestingly, albumin significantly decreased the incidence of type 1 HRS in patients with baseline serum bilirubin ≥ 4 mg/dl and in those with baseline serum creatinine ≥ 1 mg/dl [37]. More recently, Terg et al. in a retrospective review of patients with SBP confirmed that serum bilirubin levels > 4 mg/dl and serum creatinine levels > 1 mg/dl at the time of diagnosis represented significant risk factors for the clinical outcomes of patients with SBP [47]. Finally it has been observed that treatment of SBP-induced type 1 HRS with terlipressin and albumin reduced the mortality rate due to the infection by almost 20 % [28].

Prognosis

When SBP was initially described in medical literature, in the 1960s, prognosis was really poor, with an in-hospital mortality of 100 % [48]. Outcome has been considerably improved because of early diagnosis and use of effective antibiotic therapy; however, SBP still has a high rate of mortality. Recently, a meta-analysis of 101 studies (7062 patients) reported a median mortality of 43.7 %: 31.5 % at 1 month and 66.2 % at 12 months [49]. The median overall mortality was 49 % for 1978 – 1999 and 31.5 % for 2000 – 2009, solely due to reduced mortality at 30 days, because no significant differences were documented at 3 months or at 1 year after the episode of SBP [49].

Prophylaxis of SBP

Since SBP is thought to result from the translocation of enteric Gram-negative bacteria, the ideal therapeutic agent should be safe, affordable and effective at eliminating Gram-negative bacteria from the gut while preserving the protective anaerobic flora (selective intestinal decontamination). Given the high cost and inevitable risk of developing resistant organisms, the use of prophylactic antibiotics must be strictly restricted to those at highest risk of SBP. In addition, alternative approaches to prophylaxis of SBP should be developed in patients who are at risk of developing SBP. Three types of patient with cirrhosis should be considered at high risk of developing SPB and, therefore, as candidates for a prophylactic strategy: 1) patients with or even without ascites admitted with acute gastrointestinal hemorrhage; 2) patients with ascites and low total protein content in ascitic fluid and no prior history of SBP (primary prophylaxis); and 3) patients with ascites and a prior history of SBP (secondary prophylaxis).

Patients Admitted with Acute Gastrointestinal Hemorrhage

The incidence of infections is particularly high (ranging from 25 % to 65 % in patients with advanced cirrhosis and/or severe hemorrhage [5]. In addition, bacterial infection in patients with variceal bleeding is associated with increased rates of failure to control bleeding, rebleeding, and hospital mortality [50, 51]. In this context, antibiotic prophylaxis was not only shown to prevent infection in the setting of gastrointestinal bleeding, but was also shown to help prevent rebleeding and to improve survival [3]. A meta-analysis of five studies performed in patients with gastrointestinal bleeding has shown that antibiotic prophylaxis significantly decreased both the incidence of severe infections (SBP and/or septicemia) and mortality [51, 52]. Moreover, in a study that reported a reduction in mortality in variceal hemorrhage from 43 % to 15 % over a 20-year period, antibiotic prophylaxis was independently associated with improved survival [53]. The most common approach in the prophylaxis of bacterial infections in cirrhotic patients with gastrointestinal hemorrhage is selective intestinal decontamination with oral norfloxacin (400 mg/12 h for 7 days) [3, 52]. Nevertheless, this approach has led to a rapid emergence of quinolone resistance in cirrhotic patients treated with norfloxacin to prevent SBP [54]. In 2006, Fernandez et al. showed that ceftriaxone (1 g/day) for 7 days was more effective than oral norfloxacin (400 mg twice daily) in the prevention of bacterial infections in patients with advanced cirrhosis and

at least 2 of the following inclusion criteria: Ascites, severe malnutrition, encephalopathy, bilirubin > 3 mg/dl, and gastrointestinal hemorrhage [55]. In particular, the probability of developing proved or possible infections, proved infections, and spontaneous bacteremia or spontaneous bacterial peritonitis was significantly lower in patients receiving ceftriaxone (11 % versus 33 %, p = 0.003; 11 % versus 26 %, p = 0.03; and 2 % versus 12 %, p = 0.03, respectively) [55].

Patients with Low Total Protein Content in Ascitic Fluid and no Prior History of SBP

Cirrhotic patients with low ascitic fluid protein concentration (< 10 g/l) and/or high serum bilirubin levels are at risk of developing a first episode of SBP [24, 56]. In a prospective study, patients with total ascitic protein < 10 g/l developed SBP at a rate of 20 % over a one-year follow up period, while patients with total ascites protein > 10 g/l did not develop SBP in a two-year period [24]. One open-label randomized trial was performed comparing primary continuous prophylaxis with norfloxacin to inpatient-only prophylaxis in patients with cirrhosis and ascitic fluid total protein level ≤ 1.5 g/dl or serum bilirubin level > 2.5 mg/dl [57]. The study demonstrated a reduction in SBP in the continuous treatment group, at the expense of development of a gut flora more resistant to norfloxacin in the same group [57] (**Table 3**). In a second trial which was a randomized, placebo-controlled study of norfloxacin (400 mg/day) for primary prophylaxis of SBP in patients with low ascitic fluid protein levels (< 15 g/l), norfloxacin significantly decreased the incidence of infections due to Gram-negative bacteria but had no

Table 3. Main studies on antibiotic prophylaxis of spontaneous bacterial peritonitis (SBP) in cirrhosis*

First author, year [ref]	Type of patients	Treatments	N° of patients	Incidence of SBP n (%)	p value
Ginès, 1990 [59]	Patients with prior SBP	Norfloxacin *vs* placebo	40 40	5 (12) 14 (35)	0.02
Soriano, 1991 [56]	Patients with and without prior SBP	Norfloxacin *vs* no treatment	32 31	0 (0) 7 (22.5)	< 0.02
Singh, 1995 [61]	Patients with and without prior SBP	Trimethoprim-sulfamethoxazone *vs* no treatment	30 30	1 (3) 7 (23)	–
Rolachon, 1995 [60]	Patients with and without prior SBP	Ciprofloxacin *vs* placebo	28 32	1 (4) 7 (22)	< 0.05
Novella, 1997 [57]	Patients without prior SBP	Continuous norfloxacin *vs* norfloxacin only during hospitalization	56 53	1 (1.8)	< 0.01
Grangé, 1998 [42]	Patients with prior SBP	Norfloxacin *vs* placebo	53 54	0 (0) 5 (9)	NA
Fernandez, 2007 [23]	Patients with prior SBP	Norfloxacin *vs* placebo	35 33	2 10	0.02
Terg, 2008 [58]	Patients with prior SBP	Ciprofloxacin *vs* placebo	50 50	2 (4) 7 (14)	0.076

* Studies appear in chronological order; NA: not available

significant effect on the probability of developing SBP or survival [29, 42]. More recently, two trials provided evidence of beneficial effects of long-term quinolone therapy in patients at risk of SBP [23, 58]. In the first, Fernandez et al. performed a randomized double-blind, placebo-controlled trial of norfloxacin (400 mg/day) in patients with cirrhosis and low protein ascitic levels (< 15 g/l) with advanced liver failure, classified as a Child-Pugh score ≥ 9 points with serum bilirubin level ≥ 3 mg/dl or impaired renal function (serum creatinine level ≥ 1.2 mg/dl, blood urea nitrogen level ≥ 25 mg/dl), or serum sodium level ≤ 130 mEq/l [23]. Norfloxacin administration significantly reduced the 1-year probability of developing SBP (7 % versus 61 %) and HRS (28 % versus 41 %). Norfloxacin also significantly improved the 3-month probability of survival (94 % versus 62 %; $p = 0.03$ at 3 months and 60 % versus 48 %; $p = 0.05$ at one year). In the second, Terg et al. performed a randomized, double-blind, placebo-controlled trial of ciprofloxacin (500 mg/day) in patients with < 15 g/l of ascitic fluid proteins [58]. In the ciprofloxacin group, SBP occurred almost four times less frequently than in the placebo group but the difference was not statistically significant. Nevertheless, the probability of remaining free of bacterial infections was higher in patients receiving ciprofloxacin (80 % versus 55 %; $p = 0.05$), and the probability of survival at 1 year was higher in patients receiving ciprofloxacin (86 % versus 66 %; $p< 0.04$).

Patients with Prior SBP

In patients who survive an episode of SBP, the cumulative recurrence rate at one year is approximately 70 % [59]. Probability of survival at one year after an episode of SBP is 30 – 50 % and falls to 25 – 30 % at two years. There is only one randomized, double-blind, placebo-controlled trial of oral norfloxacin (400 mg/day) in patients who had had one episode of SBP [59]. Norfloxacin was found to reduce the probability of recurrence of SBP from 68 % to 20 % and the probability of SBP due to Gram-negative bacteria from 60 % to 3 % [59]. Survival benefits could not be determined by the study as prophylactic therapy was discontinued at 6 months. Three other randomized prophylactic studies are available but they included heterogeneous groups of patients with and without previous episodes of SBP [56, 60, 61]. Patients with low ascites fluid protein concentrations (< 15 g/l) were included in two of these studies, one evaluating norfloxacin and the other ciprofloxacin [56, 60]. In the third trial, trimethoprim-sulfamethoxazole was used [61]. The three studies showed a significant decrease in the incidence of SBP with antibiotic prophylaxis.

Conclusion

SBP is a frequent and severe complication in patients with cirrhosis and ascites admitted to hospital. A diagnostic paracentesis, with a polymorphonuclear leukocyte count in ascites, must be performed in all patients with cirrhosis admitted to hospital as well as in cirrhotic patients with any systemic or abdmominal evidence of infection and/or a worsening of their general condition, hepatic function or renal function. Empirical antibiotic treatment should be immediately started at diagnosis of SBP. Third generation cephalosporins, penicillin plus penicillinase inhibitors and quinolones are indicated in empirical therapy, taking into account that nosocomial SBP can be frequently sustained by bacteria resistant to first line

therapy. Administration of albumin (at a dose of 1.5 g/kg at diagnosis of SBP, and 1 g/kg on the third day) could prevent renal damage due to severe hypovolemia in high risk patients.

Antibiotic prophylaxis is indicated in three groups of patients with a high risk of developing SBP. Long-term administration of norfloxacin 400 mg once a day is recommended in patients with previous SBP and in high risk patients presenting an ascitic fluid total protein level ≤ 1.5 g/dl associated with advanced liver failure (Child-Pugh score ≥ 9 points with serum bilirubin level ≥ 3 mg/dl and/or serum creatinine level ≥ 1.2 mg/dl, blood urea nitrogen level ≥ 25 mg/dl, and/or serum sodium level ≤ 130 mEq/l). In patients with cirrhosis who are bleeding from the upper gastrointestinal tract, i.v. ceftriaxone (1 g/day) for 7 days should be preferred. As a result of the optimization of their management of SBP, the short term prognosis for patients with SBP has significantly improved. New prevention strategies, focusing on intestinal permeability and bacterial overgrowth should be performed. In future, the identification of new genes associated with the onset of SBP could allow early identification of high risk patients. In nosocomial SBP, randomized controlled trials using more broad spectrum antibiotics (such as carbapenems, lypopeptides or glycylcyclines) should be performed. Unfortunately, patients who survive a SBP episode have a poor long term prognosis because of the associated severe impairment of liver function. In these patients, the selection program for liver transplantation must be as fast as possible.

References

1. Rimola A, Garcia-Tsao G, Navasa M, et al (2000) Diagnosis, treatment and prophylaxis of spontaneous bacterial peritonitis: a consensus document. International Ascites Club. J Hepatol 32: 142–153
2. Fernandez J, Navasa M, Gomez J, et al (2002) Bacterial infections in cirrhosis: epidemiological changes with invasive procedures and norfloxacin prophylaxis. Hepatology 35: 140–148
3. Wong F, Bernardi M, Balk R. et al (2005) Sepsis in cirrhosis: report on the 7th meeting of the International Ascites Club. Gut 54: 718–725
4. Fasolato S, Angeli P, Dallagnese L, et al (2007) Renal failure and bacterial infections in patients with cirrhosis: epidemiology and clinical features. Hepatology 45: 223–229
5. Evans LT, Kim WR, Poterucha JJ, et al (2003) Spontaneous bacterial peritonitis in asymptomatic outpatients with cirrhotic ascites. Hepatology 37: 897–901
6. Wiest R, Garcia-Tsao G. (2005) Bacterial translocation (BT) in cirrhosis. Hepatology 41: 422–433
7. Chang CS, Chen GH, Lien HC, et al (1998) Small intestine dysmotility and bacterial overgrowth in cirrhotic patients with spontaneous bacterial peritonitis. Hepatology 28: 1187–1190
8. Spaeth G, Gottwald T, Specian RD, et al (1994) Secretory immunoglobulin A, intestinal mucin, and mucosal permeability in nutritionally induced bacterial translocation in rats. Ann Surg 220: 798–808
9. Scarpellini E, Valenza V, Gabrielli M, et al (2010) Intestinal permeability in cirrhotic patients with and without spontaneous bacterial peritonitis: Is the ring closed? Am J Gastroenterol 105: 323–327
10. Misra V, Misra S, Dwivedi M, et al (1997) Histomorphometric study of portal hypertensive enteropathy. Am J Clin Pathol 108: 652–657
11. Ramachandran A, Prabhu R, Thomas S, et al (2002) Intestinal mucosal alterations in experimental cirrhosis in the rat: role of oxygen free radicals. Hepatology 35: 622–629
12. Song HL, Lv S, Liu P (2009) The roles of tumor necrosis factor-alpha in colon tight junction protein expression and intestinal mucosa structure in a mouse model of acute liver failure. BMC Gastroenterol 22: 70

13. Such J, Francés R, Muñoz C, et al (2002) Detection and identification of bacterial DNA in patients with cirrhosis and culture-negative, nonneutrocytic ascites. Hepatology 36: 135 – 141
14. Riordan SM, Skinner N, Nagree A, et al (2003) Peripheral blood mononuclear cell expression of toll-like receptors and relation to cytokine levels in cirrhosis. Hepatology 37: 1154 – 1164
15. Genesca J, Marti R, Rojo F, et al (2003) Increased tumour necrosis factor alpha production in mesenteric lymph nodes of cirrhotic patients with ascites. Gut 52: 1054 – 1059
16. Such J, Guarner C, Enriquez J, et al (1988) Low C3 in cirrhotic ascites predisposes to spontaneous bacterial peritonitis. J Hepatol 6: 80 – 84
17. Gomez F, Ruiz P, Schreiber AD (1994) Impaired function of macrophage Fc gamma receptors and bacterial infection in alcoholic cirrhosis. N Engl J Med 331: 1122 – 1128
18. Márquez M, Fernández-Gutiérrez C, Montes-de-Oca M, et al (2009) Chronic antigenic stimuli as a possible explanation for the immunodepression caused by liver cirrhosis. Clin Exp Immunol 158: 219 – 229
19. Worlicek M, Knebel K, Linde HJ, et al (2010) Splanchnic sympathectomy prevents translocation and spreading of E coli but not S aureus in liver cirrhosis. Gut 59: 1127 – 1134
20. Appenrodt B, Grünhage F, Gentemann MG, et al (2010) Nucleotide-binding oligomerization domain containing 2 (NOD2) variants are genetic risk factors for death and spontaneous bacterial peritonitis in liver cirrhosis. Hepatology 51: 1327 – 1333.
21. Gäbele E, Mühlbauer M, Paulo H, et al (2009) Analysis of monocyte chemotactic protein-1 gene polymorphism in patients with spontaneous bacterial peritonitis. World J Gastroenterol 15: 5558 – 5562
22. Obstein KL, Campbell MS, Reddy KR, et al (2007) Association between model for end-stage liver disease and spontaneous bacterial peritonitis. Am J Gastroenterol 102: 2732 – 2736
23. Fernández J, Navasa M, Planas R, et al (2007) Primary prophylaxis of spontaneous bacterial peritonitis delays hepatorenal syndrome and improves survival in cirrhosis. Gastroenterology 133: 818 – 824
24. Andreu M, Solá R, Sitges-Serra A, et al (1993) Risk factors for spontaneous bacterial peritonitis. Gastroenterology 104: 1133 – 1138
25. Bajaj JS, Zadvornova Y, Heuman DM, et al (2009) Association of proton pump inhibitor therapy with spontaneous bacterial peritonitis in cirrhotic patients with ascites. Am J Gastroenterol 104: 1130 – 1134
26. Bota DP, Van Nuffelen M, Zakariah AN, et al (2005) Serum levels of C-reactive protein and procalcitonin in critically ill patients with cirrhosis of the liver. J Lab Clin Med 146: 347 – 351
27. Follo A, Llovet JM, Navasa M, et al (1994) Renal impairment after spontaneous bacterial peritonitis in cirrhosis: incidence, clinical course, predictive factors and prognosis. Hepatology 20: 1495 – 1501
28. Angeli P, Guarda S, Fasolato S, et al (2006) Switch therapy with ciprofloxacin vs. intravenous ceftazidime in the treatment of spontaneous bacterial peritonitis in patients with cirrhosis: similar efficacy at lower cost. Aliment Pharmacol Ther 23: 75 – 84
29. Nguyen Khac E, Cadranel JF, et al (2008) Review article: the utility of reagent strips in diagnosis of infected ascites in cirrhotic patients. Aliment Pharmacol Ther 28: 282 – 288
30. Song KH, Jeon JH, Park WB, et al (2009) Clinical outcomes of spontaneous bacterial peritonitis due to extended-spectrum beta-lactamase-producing Escherichia Coli and Klebsiella species: a retrospective matched case-control study. BMC Infect Dis 9: 41
31. Umgelter A, Reindl W, Miedaner M, et al (1984) Failure of current antibiotic first-line regimens and mortality in hospitalized patients with spontaneous bacterial peritonitis. Infection 37: 2 – 8
32. Soriano G, Castellote J, Alvarez C, et al (2010) Secondary bacterial peritonitis in cirrhosis: a retrospective study of clinical and analytical characteristics, diagnosis and management. J Hepatol 52: 39 – 44
33. Akriviadis EA, Runyon BA (1990) Utility of an algorithm in differentiating spontaneous from secondary bacterial peritonitis. Gastroenterology 98: 127 – 133
34. Felisart J, Rimola A, Arroyo V, et al (1985) Cefotaxime is more effective than is ampicillin-tobramycin in cirrhotics with severe infections. Hepatology 5: 457 – 462

35. Rimola A, Salmerón JM, Clemente G, et al (1995) Two different dosages of cefotaxime in the treatment of spontaneous bacterial peritonitis in cirrhosis: results of a prospective, randomized, multicenter study. Hepatology 21: 674–679
36. Navasa M, Follo A, Llovet JM, et al (1996) Randomized, comparative study of oral ofloxacin versus intravenous cefotaxime in spontaneous bacterial peritonitis. Gastroenterology 111: 1011–1017
37. Sort P, Navasa M, Arroyo V, et al (1999) Effect of intravenous albumin on renal impairment and mortality in patients with cirrhosis and spontaneous bacterial peritonitis. N Engl J Med 341: 403–409
38. Ricart E, Soriano G, Novella MT, et al (2000) Amoxicillin-clavulanic acid versus cefotaxime in the therapy of bacterial infections in cirrhotic patients. J Hepatol 32: 596–602
39. Terg R, Cobas S, Fassio E, et al (2000) Oral ciprofloxacin after a short course of intravenous ciprofloxacin in the treatment of spontaneous bacterial peritonitis: results of a multicenter, randomized study. J Hepatol 33: 564–569
40. Runyon BA, McHutchison JG, Antillon MR, et al (1991) Short-course versus long-course antibiotic treatment of spontaneous bacterial peritonitis. A randomized controlled study of 100 patients. Gastroenterology. 100: 1737–1742
41. Gómez-Jiménez J, Ribera E, Gasser I, et al (1993) Randomized trial comparing ceftriaxone with cefonicid for treatment of spontaneous bacterial peritonitis in cirrhotic patients. Antimicrob Agents Chemother 37: 1587–1592
42. Grange JD, Roulot D, Pelletier G., et al (1998) Norfloxacin primary prophylaxis of bacterial infections in cirrhotic patients with ascites: a double-blind randomized trial. J Hepatol 29: 430–436
43. Acevedo JC (2009) Current efficacy of recommended empirical antibiotic therapy in patients with cirrhosis and bacterial infection. J Hepatol 50 (Suppl 1): S5 (abst)
44. Chen TA, Tsao YC, Chen A, et al (2009) Effect of intravenous albumin on endotoxin removal, cytokines, and nitric oxide production in patients with cirrhosis and spontaneous bacterial peritonitis. Scand J Gastroenterol 4: 1–7
45. Fernández J, Monteagudo J, Bargallo X, et al (2005) A randomized unblinded pilot study comparing albumin versus hydroxyethyl starch in spontaneous bacterial peritonitis. Hepatology 42: 627–634
46. Cartier M, Terg R, Lucero R, et al (2010) Pilot study: polygeline 4 % plus antibiotics in the treatment of high-risk cirrhotic patients with spontaneous bacterial peritonitis. Aliment Phrmacol Ther 32: 43–48
47. Terg R, Gadano A, Cartier M, et al (2009) Serum creatinine and bilirubin predict renal failure and mortality in patients with spontaneous bacterial peritonitis: a retrospective study. Liver Int 29: 415–419
48. Conn MD, Harold O (1964) Spontaneous peritonitis and bacteremia in laennec's cirrhosis caused by enteric organisms. Ann Intern Med 60: 568–580
49. Arvaniti V, D'Amico G, Fede G, et al (2010) Infections in patients with cirrhosis increase mortality 4-fold and should be used in determining prognosis. Gastroenterology 139: 1246–1256
50. Goulis J, Armonis A, Patch D, et al (1998) Bacterial infection is independently associated with failure to control bleeding in cirrhotic patients with gastrointestinal hemorrhage. Hepatology 27: 1207–1212
51. Bernard B, Grange JD, Khac EN, et al (1999) Antibiotic prophylaxis for the prevention of bacterial infections in cirrhotic patients with gastrointestinal bleeding: a meta-analysis. Hepatology 29: 1655–1661
52. Soriano G, Guarner C, Tomas A. et al (1992) Norfloxacin prevents bacterial infection in cirrhotics with gastrointestinal hemorrhage. Gastroenterology 103: 1267–1272
53. Carbonell N, Pauwels A, Serfaty L, et al (2004) Improved survival after variceal bleeding in patients with cirrhosis over the past two decades. Hepatology 40: 652–659
54. Aparicio JR, Such J, Pascual S, et al (1999) Development of quinolone-resistant strains of Escherichia coli in stools of patients with cirrhosis undergoing norfloxacin prophylaxis: clinical consequences. J Hepatol 31: 277–283
55. Fernández J, Ruiz del Arbol L, Gómez C, et al (2006) Norfloxacin vs ceftriaxone in the

prophylaxis of infections in patients with advanced cirrhosis and hemorrhage. Gastroenterology 131: 1049 – 1056
56. Soriano G, Guarner C, Teixidó M, et al (1991) Selective intestinal decontamination prevents spontaneous bacterial peritonitis. Gastroenterology 100: 477 – 481
57. Novella M, Solà R, Soriano G, et al (1997) Continuous versus inpatient prophylaxis of the first episode of spontaneous bacterial peritonitis with norfloxacin. Hepatology 25: 532 – 536
58. Terg R, Fassio E, Guevara M, et al (2008) Ciprofloxacin in primary prophylaxis of spontaneous bacterial peritonitis: A randomized, placebo-controlled study. J Hepatol 48: 774 – 779
59. Gines P, Rimola A, Planas R, et al (1990) Norfloxacin prevents spontaneous bacterial peritonitis recurrence in cirrhosis: results of a double-blind, placebo-controlled trial. Hepatology 12: 716 – 724
60. Rolachon A, Cordier L, Bacq Y, et al (1995) Ciprofloxacin and long-term prevention of spontaneous bacterial peritonitis: results of a prospective controlled trial. Hepatology 22: 1171 – 1174
61. Singh N, Gayowski T, Yu VL, et al (1995) Trimethoprim-sulfamethoxazole for the prevention of spontaneous bacterial peritonitis in cirrhosis: a randomized trial. Ann Intern Med 122: 595 – 598
62. Tuncer I, Topcu N, Durmus A, Turkdogan MK (2003) Oral ciprofloxacin versus intravenous cefotaxime and ceftriaxone in the treatment of spontaneous bacterial peritonitis. Hepatogastroenterology 50: 1426 – 1430
63. Chen TA, Lo GH, Lai KH, et al (2005) Single daily amikacin versus cefotaxime in the short-course treatment of spontaneous bacterial peritonitis in cirrhotics. World J Gastroenterol 11: 6823 – 6827

Acute-on-chronic Liver Failure: An Entity Still in Search of Itself?

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Liver Failure Associated With Cirrhosis: Magnitude of the Problem

The development of liver failure in a patient with cirrhosis represents a decisive time point in terms of medical management and of prognosis since this condition is frequently associated with rapidly evolving multi-organ dysfunction [1, 2]. The lack of liver detoxification, metabolic and regulatory functions, and an altered immune response leads to life-threatening complications, such as renal failure, increased susceptibility to infection, hepatic coma, and systemic hemodynamic dysfunction [1, 2]. Not surprisingly, the combined impact of these complications leads to mortality rates as high as 50 to 90 %. In addition to the impressive (and disappointing) mortality rates, this situation is unlikely be altered in the next decade since recent World Health Organization projections predict that cirrhosis will become the ninth most common cause of death in the Western world by 2015 [3]. Currently in the USA, liver disease is the tenth most common cause of death and accounts for an associated economic burden of approximately 1 % of the total national health care expenditure ($1.2 trillion) [4]. The problem is, therefore, of relevance to the general public and warrants further efforts in terms of awareness, prevention, fine-tuning, and renewal of the therapeutic armamentarium targeting the earliest stages of viral hepatitis, non-alcoholic fatty liver disease, and alcohol-related liver disease, which represent the most prevalent liver disorders.

XIII

(Re-)Defining Liver Failure Associated with Cirrhosis: Towards the Construct of a Treatment-directed Classification?

Cirrhosis is a critical last phase in a relentless evolution of progressive parenchymal cell damage and death, nodular parenchymal regeneration and progressive fibrosis [5]. However, only upon appearance of complete fibrous vascularized septa, which serve as intrahepatic shunt-vessels, is the 'true cirrhotic state' achieved [5]. Liver insufficiency in this context is considered when the threshold of a critical functional liver cell mass ("the critical mass hypothesis" of Tygstrup) is surpassed (**Fig. 1**) [1, 6].

In recent years, the recognition of clinically different patterns of liver failure associated with cirrhosis, has led to the demarcation of two different entities: 'end-stage' and 'acute-on-chronic' liver failure [1, 2]. Although substantial overlap exists between these two entities in clinical presentation (jaundice, hepatic encephalopathy, hyperdynamic circulatory state and/or hepatorenal

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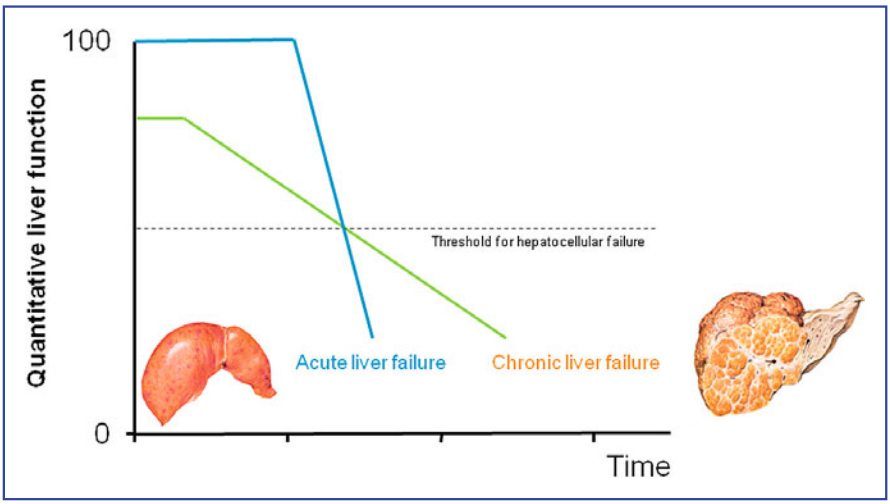

Fig. 1. The 'critical mass' concept

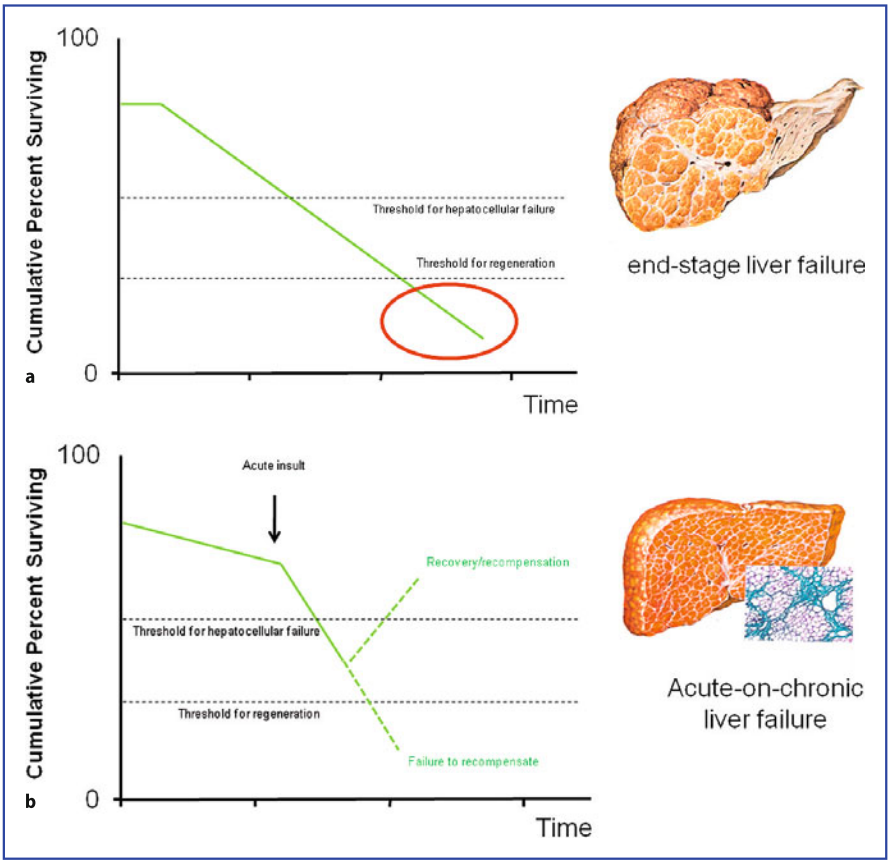

Fig. 2a. End-stage liver failure. **b** Acute-on-chronic liver failure

syndrome), the main difference between them is the potential to regenerate/recompensate and the presence/absence of a precipitating event (**Fig. 2**). More specifically, while acute-on-chronic liver failure refers to an acute deterioration of liver function and other end-organs over a period of weeks following a precipitating event (such as variceal hemorrhage, sepsis or an hepatotoxic factor) in a patient with previously well or fairly well compensated chronic liver disease, 'end-stage liver disease' refers to a chronically decompensated patient due to relentless progressive deterioration of the underlying chronic liver disorder (**Figs. 2a** and **b**).

The reason for the emergence of this conceptual dissection lies in striving for an improved armamentarium for liver failure. From a therapeutic perspective, it is clear that in the case of end-stage liver disease only liver transplantation will rescue the patient, whereas for acute-on-chronic liver failure, any attempt to move the decompensation back to above the critical threshold of functional liver mass is of interest. These attempts are strongly motivated by the growing disparity between the increasing number of patients qualifying for liver transplantation and the relatively static number of available donor organs. Moreover, even if a transplant is 'reasonably' to be expected based on the Model for End-stage Liver Disease (MELD)-allocation system, this 'reasonable' time frame varies considerably among cases and therapeutic strategies are needed to 'bridge' patients since multi-organ dysfunction continues to evolve and imperils the per-operative and post-transplantation outcome.

Potential Mechanisms Involved in Acute-on-chronic Liver Failure: SIRS, Bacterial Infections and Organ Failure

At present, the exact mechanisms that lead from a compensated cirrhotic state to acute-on-chronic liver failure remain poorly understood although major determining factors are considered to be a dynamic and reciprocal interplay between enhanced intestinal permeability (leading to translocaton of bacteria and their products), an imbalanced immune reaction, and an aggravated intrahepatic microcirculatory dysfunction and subsequent worsened hyperdynamic state [1, 2, 7–14].

Bacterial translocation is a frequent phenomenon in cirrhotic patients. Infection is the cause in 30–50 % of cirrhosis cases admitted to the hospital [9]. The increased bacterial translocation and increased levels of circulating lipopolysaccharide (LPS) or bacterial products is presumed a prerequisite for the development of acute-on-chronic liver failure but is insufficient to explain the whole picture. More specifically, it needs to be accompanied by an inadequate immune response and subsequent aggravated vascular hypo/hyperreactivitity (depending on the vascular territory).

The former component, immune dysfunction, is a complex, highly-interactive and multifactorial matter in cirrhotic patients [9]. On the one hand, there is decreased opsonization capacity (related to the decreased synthetic capacity of the cirrhotic liver), which is crucial in bacterial phagocytosis, and bactericidal activity of these same phagocytic cells. Additionally, the function of Kupffer cells, which represent major effectors of the reticuloendothelial system, is seriously impaired because of portosystemic shunting that leads to the evasion of portal and systemic bacteria from the action of the reticuloendothelial sys-

tem. Moreover, this latter effect also explains why other bacterial products such as endotoxins and cytokines fail to clear. Although the persistence of microbes, their toxins or injury are important triggers to an inflammatory reaction, the constellation of sepsis, or a syndrome resembling it, is primarily caused by the host's imbalanced reaction to these initiating injuring factors [11–13, 15–17]. More specifically, on presence of microbes or any form of tissue damage (hypoxia, ischemia, toxic agent, ...), local pro-inflammatory and anti-inflammatory reactions are simultaneously initiated in an attempt to confine and control invading microbes locally, destroy damaged tissue and repair damage. If the initiating infectious or non-infectious factors overwhelm the local response or the local response becomes exaggerated, spilling of pro-inflammatory mediators into the systemic circulation results in recruitment of a systemic response which we recognize clinically as the systemic inflammatory response syndrome (SIRS) [15–17]. The severity of the disease syndrome resulting from this cascade of systemic mediators depends on the balance of SIRS and the compensatory anti-inflammatory syndrome (CARS) [15–17]. In the context of acute-on-chronic liver failure, SIRS and CARS have been shown to be present in a disproportional manner: Exaggerated SIRS by means of increased levels of pro-inflammatory cytokines (interleukin [IL]-1, IL-6 and tumor necrosis factor [TNF]-α) that activate white blood cells [11, 18], and defective CARS, as demonstrated by decreased HLA-DR expression on monocytes, leading to overwhelming infections [12, 13]. This latter aspect is also called 'immune paralysis'. When the equilibrium between pro-inflammatory and anti-inflammatory forces is seriously compromised, by overwhelming SIRS, defective CARS or an oscillation between severe inflammation and immunosuppression, a condition called 'immunologic dissonance' arises as a result of these two forces ultimately reinforcing each other instead of maintaining balance. This ultimately leads to a multiorgan dysfunction syndrome, septic shock or anergy.

In parallel, and partially because of the unbalanced immune dysfunction, the hyperdynamic state typical of advanced cirrhosis, is further aggravated, ultimately leading to inability to maintain adequate perfusion pressure. This constellation leads to progressive ischemia and dysfunction of several end-organs such as the kidney (hepatorenal syndrome), the brain (hepatic encephalopathy), ... finally leading to multiorgan failure and death.

Precise Diagnostic and Prognostic Criteria for Acute-on-chronic Liver Failure: An Ongoing Search towards the Truth

Although in concept, the currently used working definition of acute-on-chronic liver failure, as mentioned above, seems straight forward to use, medical practice is hampered by an often complex clinical picture, the lack of identification of a clear precipitant, differentiation from a patient with end-stage liver disease and problems in determining the ideal moment and/or necessity or usefulness of certain therapeutic intervention [1, 2]. The additional lack of elucidation of the pathophysiological pathways also adds weight in this matter as does the fact that the natural history of patients with acute-on-chronic liver failure remains poorly documented since there are only a handful of prospective studies available [19, 20]. Not surprisingly, there is a growing demand from the hepatological community for improvement in the definition, diagnostic criteria and characterization of the

acute-on-chronic liver failure syndrome. Moreover, this should be done in a multidisciplinary fashion together with intensivists, histopathologists, infectiologists, etc.

With regard to prognosis or assessment of severity, it is clear that our current liver orientated scores (like Child-Pugh and MELD) have limited value [1, 2, 20]. This follows from the observation that once extra-hepatic organ failure is initiated, mortality is determined by the degree of this end-organ dysfunction and not the severity of the liver disease (short-term mortality range 46–89 %) [20–23]. Organ failure scores, such as Acute Physiology and Chronic Health Evaluation (APACHE) II and Sequential Organ Failure Assessment (SOFA) scores, might therefore be more relevant [20–23]. Additionally, the quest for other risk factors, markers of early diagnosis (at a time when therapeutic intervention might still be effective), or assessment of severity of disease is ongoing.

In a recently published own cohort of patients with acute-on-chronic liver failure compared to chronic decompensated end-stage patients with underlying alcoholic cirrhosis (n = 250 in total), we confirmed, in a prospective comparative manner, the clinical usefulness of positive SIRS-criteria [20]. Moreover, we documented infection as the major precipitating factor for SIRS. Although the high incidence of SIRS at admission (69 %) did not initially reflect the number of overtly documented bacterial infections (28 %), later on during admission the number of patients with documented infections (58 %) paralleled the number of SIRS positive patients (67 %). This finding favors the premise that a number of patients had an occult infection at admission and developed overt infection very soon after admission. This finding was further substantiated by the histopathological finding of ductular bilirubinostasis, which is the descriptive term for the presence of bile plugs in dilated ductules at the interface between the portal tract and parenchyma and is highly sensitive for sepsis.

In an attempt to solve and validate the aforementioned issues, a European, multicenter, observational prospective case-only study is currently recruiting: the CANONIC-core study (CLIF Acute-oN-ChrONic LIver Failure in Cirrhosis) which is conducted under the aegis of the CLIF (Chronic LIver Failure) Consortium. This study aims to better define the natural history of acute-on-chronic liver failure and to evaluate its prevalence, precipitating mechanisms, risk factors for development, short-term and mid-term survival, and risk factors for mortality. For this purpose, this study aims to study a cohort of about 1200 consecutive patients admitted to the hospital for more than 24 hours for a complication of cirrhosis.

Therapeutic Options for Acute-on-chronic Liver Failure

In acute-on-chronic liver failure, as in other forms of liver failure, the lack of liver detoxification, metabolic and regulatory functions of the liver leads to life-threatening complications, such as renal failure, hepatic coma and systemic hemodynamic dysfunction, and culminates rapidly into multiorgan failure. Current medical therapy involves management of the precipitating event and treatment of complications until the liver eventually recovers, leaving us with no other treatment options than transplantation if these attempts fail. However, the shortage of cadaveric organs and other transplant-related problems have prompted the need for alternative methods to provide liver support. Since liver failure in acute-on-

chronic liver failure – by definition – is potentially reversible, considerable effort has been invested in the development of liver support systems. Currently, most of the experience is available for non-biological support systems. For more exhaustive reading, we refer the readers to available in-depth reviews [1, 2, 7, 24]. In the following paragraphs, we aim to give a brief summary of the principle, types and current available data.

Rational Basis for Non-biological Liver Support

The rational basis for the development of liver support in liver failure was the observation that, although severity and rapidity of development varied between the different entities of liver failure, clinical manifestations were always similar with the presence of encephalopathy, worsening jaundice, aggravating hyperdynamic circulation, hepatorenal syndrome and increased susceptibility to infections, eventually culminating in multiorgan failure [1, 2, 7, 24]. This led several groups to the assumption that these manifestations originated in an accumulation of toxins as a lack of detoxification by the failing liver [25–27]. The 'toxin-hypothesis' was further supported by the observation that the serum level of bilirubin, a surrogate marker for toxins, was correlated with mortality in both acute-on-chronic liver failure and acute liver failure [27]. At present, in acute-on-chronic liver failure most of the data available are for non-biologic liver support systems.

Currently Available Devices

The Molecular Adsorbent Recirculating System: MARS (Gambro)
The device was developed by Stange and Mitzner in 1993 and applied for the first time in humans in 1996 [28, 29]. The MARS system is currently the most extensively used non-biological liver support system. The system is based on the principles of dialysis, filtration, and adsorption (**Fig. 3**). It requires no plasma separation step or direct plasma perfusion over sorbents since it combines the efficacy of sorbents to remove albumin-bound molecules with the biocompatibility of the modern dialysis membrane. In practice, blood from the patient passes through a hollow-fiber dialysis module where it is dialyzed across an albumin impregnated polysulfone membrane (MARS Flux dialyzer, membrane thickness 100 nm, pore size 50 kDa, surface area 2.1 m^2), which enables the exchange of water-soluble and protein bound toxins by an albumin-coated membrane against a dialysate containing 'recycled' protein. The membrane transiently absorbs and holds the toxins. The toxins are released upon contact with the membrane according to the concentration gradient and are carried to the other side of the membrane where dialysis against the albumin-rich dialysate (600 mL of 20 % human albumin) removes the toxins from the membrane. The toxin-enriched albumin solution is then first passed through another dialyzer countercurrent to a standard buffered dialysis solution where clearance of water-soluble substances occurs by diffusion. The solution is then further purified on-line from albumin bound toxins by incorporation of non-specific adsorbents (an anion exchanger column and an uncoated charcoal column), resulting in regeneration ('recycling') of the dialysate allowing re-uptake of new toxins from the blood.

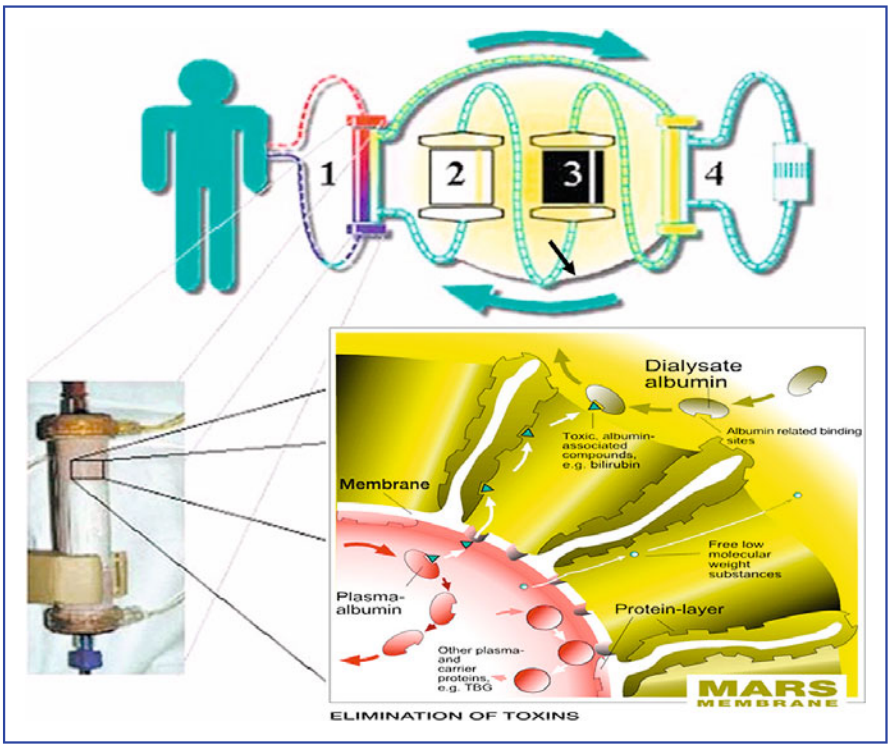

Fig. 3. Representative scheme of the MARS device. TBG: thyroid-binding globulin

Prometheus or FPSA (fractionated plasma separation and adsorption) (Fresenius)

The Prometheus system combines FPSA with high-flux hemodialysis for the removal of both albumin-bound and water-soluble toxins (**Fig. 4**) [30]. The clearance of toxins is achieved in several steps. First, albumin is separated from blood by a novel capillary albumin dialyzer (AlbuFlow, Fresenius Medical Care AG, Bad Homburg, Germany). The AlbuFlow is made of polysulfone hollow fibers and is permeable to albumin (sieving coefficient 0.6), and hence to albumin-bound substances. Blood flow rate is 150 – 200 ml/min. Subsequently, the albumin filtrate in the FPSA circuit is perfused through a column with neutral resin (prometh01) and a second column with an anion exchanger resin adsorber (prometh02), whereby the bound toxins are captured by direct contact with the high-affinity adsorbing material. The 'native' albumin is then returned to the patient. The FPSA recirculation circuit is driven by a roller pump at 300 ml/min. Finally, after passage through the AlbuFlow, the patient's blood is dialyzed through a high-flux dialyzer (FX50), whereby water-soluble toxins are eliminated. Maintenance and monitoring of the extracorporeal circuit is performed by a modified 4008 hemodialysis unit.

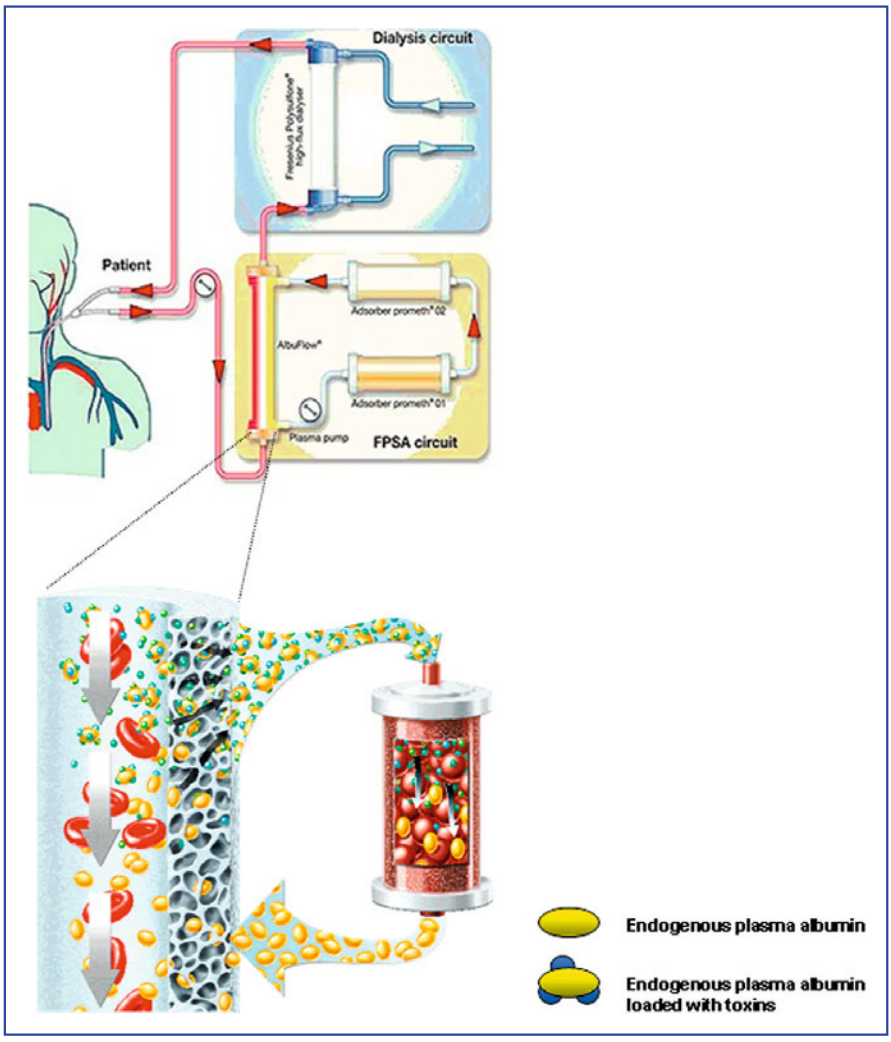

Fig. 4. Representative scheme of the Prometheus device

HepaWash®

The HepaWash system is somewhat comparable to the MARS-device but differs from this latter by the fact that it regenerates ('cleans') the exogenous albumin in the secondary circuit to at much larger extent based on additional specific pH and temperature changes at the level of the filters (**Fig. 5**). Due to the technical approach described above and additional inventions, the treatment is expected to be several times more effective than currently available therapies. The proof of concept has been recently demonstrated in a preclinical study in animals with acute liver failure. Human studies are currently on the way.

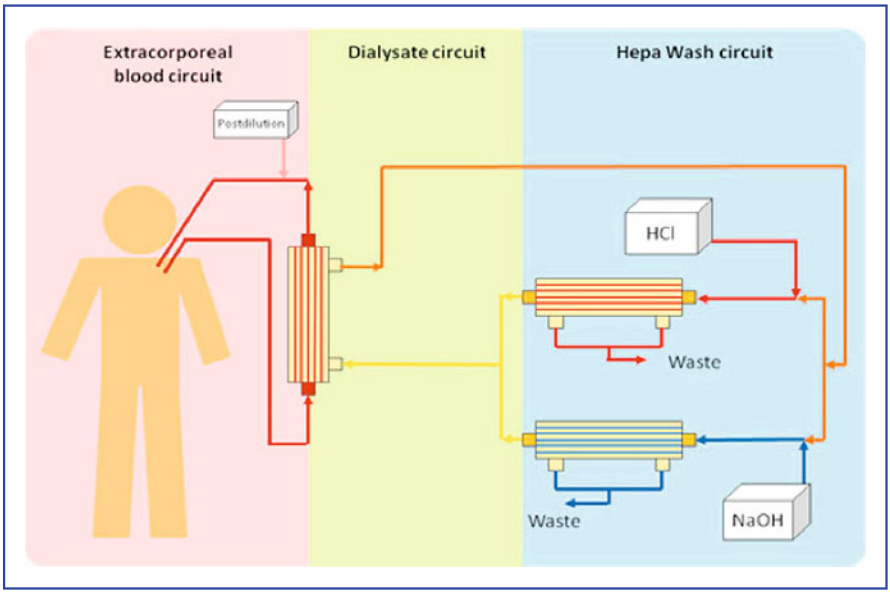

Fig. 5. Representative scheme of the HepaWash device

Clinical Impact of Liver Support on Survival

Human data are available only for MARS and Prometheus. The available studies, albeit often small and uncontrolled, clearly suggest biochemical and neurological improvement after MARS and Prometheus therapy with an additional positive hemodynamic effect only with MARS (**Table 1**) [30–40]. The survival benefit that is supposed to come forth out of these beneficial effects is however less obvious.

Table 1. MARS and Prometheus in acute on chronic liver failure

Study	Number	Controlled	Improvement in Biochemical	CVS	CNS	Survival
MARS						
Stange et al [31]	13	No	Yes	N/A	Yes	69 %
Schmidt et al [32]	8	No	Yes	Yes	No	50 %
Jalan et al [33]	8	No	Yes	Yes	Yes	50 %
Di Campli et al [34]	13	No	Yes	N/A	Yes	38 %
Mitzner et al [35]	13	Yes	Yes	Yes	No	38 %
Heemann et al [36]	23	Yes	Yes	Yes	Yes	37.5 % vs 0 %
Sen et al [37]	18	Yes	Yes	No	Yes	90 % vs 55 %
Hassanein et al [38]	70	Yes	N/A	N/A	Yes	N/A
Laleman et al [39]	18	Yes	Yes	No	N/A	66 vs 33 vs 33 %
PROMETHEUS						
Rifai et al [30]	11	No	Yes	No	No	28 %
Skwarek et [40]	13	No	Yes	N/A	N/A	23 % at 6 months
Laleman et al [39]	18	Yes	Yes	No	N/A	66 vs 33 vs 33 %

Survival benefit with MARS in patients with acute-on-chronic liver failure was observed in a small study [36]. In the absence of supportive large-sample randomized controlled data, the scientific community turned towards meta-analysis of the available data. Unfortunately, contrasting results were obtained in the two available meta-analyses regarding the effect on survival of non-biological liver support in acute-on-chronic liver failure. The first meta-analysis [41] of four randomized and two selected non-randomized trials in patients with acute-on-chronic liver failure by Khuroo and Farahat showed no effect on mortality. On the other hand, explorative analysis (14 studies, 588 patients) by the Cochrane database-group revealed a significant reduction of mortality in the MARS group as compared with the standard medical treatment group [42]. However, it is questionable whether a meta-analysis really helps answer the question of whether liver support improves survival at the present time, since the total number of patients enrolled in the individual studies was too small and with too many differences in primary indication, primary end-point, and treatment protocols for intervention and standard treatment. The attempt to use a meta-analysis before there are sufficient data can, therefore, lead to wrong conclusions in a negative or in a positive sense.

Due to the aforementioned controversies, hope was placed in two multicenter randomized controlled trials with MARS (MARS-RELIEF: MARS-therapy up to 10 sessions of 6 – 8 hours versus standard medical therapy, n = 189 patients, average MELD 28) [43] or Prometheus (HELIOS: Prometheus-therapy up to 8 – 11 treatments of minimal 4 hours versus standard medical therapy, n = 145, average MELD 27) [44]. Both studies have now ended and a primary analysis of both trials was presented in abstract form at the last European Association for the Study of the Liver (EASL)-meeting in Vienna 2010. In the MARS-RELIEF trial, there was no effect on 28-day survival compared to standard medical therapy (59.2 vs 60 %). No data were available with regard to later time-points or subgroup-analyses. In the HELIOS-trial, 28 day-survival was comparable to that in MARS-RELIEF and also non-significant (66 vs 63 %). Reported predefined subgroup analyses here showed a benefit of Prometheus in patients with hepatorenal syndrome type 1 ($p = 0.004$) and MELD > 30 ($p = 0.02$). The full papers are awaited.

Conclusion

The appearance of liver failure in a patient with cirrhosis represents a decisive time point in terms of both medical management and prognosis since this condition is frequently associated with rapidly evolving multi-organ dysfunction. In recent years, the recognition of clinically different patterns of liver failure associated with cirrhosis, has led to the demarcation of two different entities: 'end-stage' and 'acute-on-chronic' liver failure.

This latter condition refers to an acute deterioration of liver function and other end-organs over a period of weeks following a precipitating event such as variceal hemorrhage, sepsis or an hepatotoxic factor, in a patient with previously well or fairly well compensated chronic liver disease. The syndrome is accompanied by a 30-day mortality varying on average from 40 – 60 %, supporting the overall demand for increased knowledge in regard to characterization, pathophysiology, prognostic determinants and early markers of the disease to allow intervention at a time when it may still be effective. In an attempt to meet these

requests a European, multicenter, observational prospective study, the CANONIC-core study, is currently being conducted.

In terms of treatment, advanced and high-quality medical intensive care remains of utmost importance to either tide these patients over the acute decompensation or to bridge them to transplantation. The concept of liver support systems remains appealing and, in experimental ways, challenging. However, with a lack of clear survival benefit at present, these devices are not (yet) ready for implementation for general use and should be further examined in large-sample randomized controlled trials.

References

1. Laleman W, Wilmer A, Evenepoel P, Verslype C, Fevery J, Nevens F (2006) Review article: non-biological liver support in liver failure. Aliment Pharmacol Ther 23: 351 – 363
2. Jalan R, Williams R (2002) Acute-on-chronic liver failure: pathophysiological basis of therapeutic options. Blood Purif 20: 252 – 261
3. World Health Organization. Projections of mortality and burden of disease to 2030, Available at: http://www.who.int/healthinfo/global_burden_disease/projections2002/en/index.html Accessed Nov 2010
4. Martin JA, Smith BL, Mathews TJ, Ventura SJ (1998) Births and deaths: preliminary data for 1998. In: National Center for Health Statistics. National Vital Statistics Report. Vol. 47, No. 25. MD: National Center for Health Statistics, Hyattsville
5. Desmet VJ, Roskams T (2004) Cirrhosis reversal: a duel between dogma and myth. J Hepatol 40: 860 – 867
6. Vilstrup H, Iversen J, Tygstrup N (1986) Glucoregulation in acute liver failure. Eur J Clin Invest 16: 193 – 197
7. Sen S, Williams R, Jalan R (2002) The pathophysiological basis of acute-on-chronic liver failure. Liver 22: 5 – 13
8. Thalheimer U, Triantos CK, Samonakis DN (2005) Infection, coagulation, and variceal bleeding in cirrhosis. Gut 54: 556 – 563
9. Tandon P, Garcia-Tsao G (2008) Bacterial infections, sepsis, and multiorgan failure in cirrhosis. Semin Liver Dis 28: 26 – 42
10. Antoniades CG, Berry P, Wendon J (2008) The importance of immune dysfunction in determining outcome in acute liver failure. J Hepatol 49: 845 – 861
11. Rosenbloom AJ, Pinsky MR, Bryant JL (1995) Leukocyte activation in the peripheral blood of patients with cirrhosis of the liver and SIRS. Correlation with serum interleukin-6 levels and organ dysfunction. JAMA 274: 58 – 65
12. Lin CH, Tsai IF, Ho YP (2007) Endotoxemia contributes to the immune paralysis in patients with cirrhosis. J Hepatol 46: 816 – 826
13. Wasmuth HE, Kunz D, Yagmur E (2005) Patients with acute on chronic liver failure display 'sepsis-like' immune paralysis. J Hepatol 42: 195 – 201
14. Navasa M, Fernandez J, Rodes J (1999) Bacterial infections in liver cirrhosis. Ital J Gasteroenterol Hepatol 31: 616 – 625
15. Bone RC, Grodzin CJ, Balk RA (1997) Sepsis: a new hypothesis for pathogenesis of the disease process. Chest 112: 235 – 243
16. Cazzaniga M, Dionigi E, Gobbo G (2009) The systemic inflammatory response syndrome in cirrhotic patients: relationship with their in-hospital outcome. J Hepatol 51: 475 – 482
17. Bone R (1996) Sir Isaac Newton, sepsis, SIRS, and CARS. Crit Care Med 24: 1125 – 1128
18. Albillos A, Hera Ad Ade L, Reyes E, Monserrat J (2004) Tumour necrosis factor-alpha expression by activated monocytes and altered T-cell homeostasis in ascitic alcoholic cirrhosis: amelioration with norfloxacin. J Hepatol 40: 624 – 631
19. Sarin SK, Kumar A, Almeida JA (2009) Acute-on-chronic liver failure: consensus recommendations of the Asian Pacific Association for the study of the liver (APASL). Hepatol Int 3: 269 – 282
20. Katoonizadeh A, Laleman W, Verslype C, et al (2010) Early features of acute-on-chronic alcoholic liver failure: a prospective cohort study. Gut 59: 1561 – 1569

21. Aggarwal A, Ong JP, Younossi ZM, Nelson DR, Hoffman-Hogg L, Arroliga AC (2001) Predictors of mortality and resource utilization in cirrhotic patients admitted to the medical ICU. Chest 119: 1489 – 1497
22. Zimmerman JE, Wagner DP, Seneff MG, Becker RB, Sun X, Knaus WA (1996) Intensive care unit admissions with cirrhosis: risk-stratifying patient groups and predicting individual survival. Hepatology 23: 1393 – 1401
23. Wehler M, Kokoska J, Reulbach U, Hahn EG, Strauss R (2001) Short-term prognosis in critically ill patients with cirrhosis assessed by prognostic scoring systems. Hepatology 34: 255 – 261
24. Stadlbauer V, Davies NA, Sen S, Jalan R (2008) Artificial liver support systems in the management of complications of cirrhosis. Semin Liver Dis 28: 96 – 109
25. Hoofnagle JH, Carithers RL Jr, Shapiro C, Asscher N (1995) Fulminant hepatic failure: summary of a workshop. Hepatology 21: 240 – 252
26. Losser MD, Payen D (1996) Mechanisms of liver damage. Sem Liver Dis 16: 357 – 367
27. Shakil AO, Kramer D, Mazariegos GV, Fung JJ, Rakela J (2000) Acute liver failure: clinical features, outcome analysis, and applicability of prognostic criteria. Liver Transpl 6: 163 – 169
28. Stange J, Ramlow W, Mitzner S, Schmidt R, Klinkmann H (1993) Dialysis against a recycled albumin solution enables the removal of albumin-bound toxins. Artif Organs 17: 809 – 813
29. Stange J, Mitzner S (1996) A carrier-mediated transport of toxins in a hybrid membrane. Safety barrier between a patients blood and a bioartificial liver. Int J Artif Organs 19: 677 – 691
30. Rifai K, Ernst T, Kretschmer U, et al (2003) Prometheus--a new extracorporeal system for the treatment of liver failure. J Hepatol 39: 984 – 990
31. Stange J, Mitzner SR, Risler T, et al (1999) Molecular adsorbent recycling system (MARS): clinical results of a new membrane-based blood purification system for bioartificial liver support. Artif Organs 23: 319 – 330
32. Schmidt LE, Sorensen VR, Svendsen LB, Hansen BA, Larsen FS (2001) Hemodynamic changes during a single treatment with the molecular adsorbents recirculating system in patients with acute-on-chronic liver failure. Liver Transpl 7: 1034 – 1039
33. Jalan R, Sen S, Steiner C, Kapoor D, Alisa A, Williams R (2003) Extra-corporeal liver support with molecular adsorbents recirculating system in patients with severe acute alcoholic hepatitis. J Hepatol 38: 24 – 31
34. Di Campli C, Zocco MA, Gaspari R, et al (2005) The decrease in cytokine concentration during albumin dialysis correlates with the prognosis of patients with acute on chronic liver failure. Transplant Proc 37: 2551 – 2553
35. Mitzner SR, Stange J, Klammt S, et al (2000) Improvement of hepatorenal syndrome with extracorporeal albumin dialysis MARS: results of a prospective, randomized, controlled clinical trial. Liver Transpl 6: 277 – 286
36. Heemann U, Treichel U, Loock J, et al (2002) Albumin dialysis in cirrhosis with superimposed acute liver injury: a prospective, controlled study. Hepatology 36: 949 – 958
37. Sen S, Davies NA, Mookerjee RP, et al (2004) Pathophysiological effects of albumin dialysis in acute-on-chronic liver failure: a randomized controlled study. Liver Transpl 10: 1109 – 1119
38. Hassanein TI, Tofteng F, Brown RS Jr, et al (2007) Randomized controlled study of extracorporeal albumin dialysis for hepatic encephalopathy in advanced cirrhosis. Hepatology 46: 1853 – 1862
39. Laleman W, Wilmer A, Evenepoel P, et al (2006) Effect of the molecular adsorbent recirculating system and Prometheus devices on systemic haemodynamics and vasoactive agents in patients with acute-on-chronic alcoholic liver failure. Crit Care 10: R108
40. Skwarek A, Grodzicki M, Nyckowski P, et al (2006) The use Prometheus FPSA system in the treatment of acute liver failure: preliminary results. Transplant Proc 38: 209 – 211
41. Khuroo MS, Farahat KL (2004) Molecular adsorbent recirculating system for acute and acute-on-chronic liver failure: a meta-analysis. Liver Transpl 10: 1099 – 1106
42. Liu JP, Gluud LL, Als-Nielsen B, Gluud C (2004) Artificial and bioartificial support systems for liver failure. Cochrane Database Syst Rev CD003628

43. Banares R, Nevens F, Larsen FS, Jalan R, Albillos A, Dollinger M, RELIEF study group (2010) Extracorporeal liver support with MARS in patients with acute-on-chronic liver failure. The RELIEF trial. J Hepatol 52: S459 (abst)
44. Rifai K, Kribben A, Gerken G, et al (2010) Extracorporeal liver support by fractionated plasma separation and adsorption (prometheus®) in patients with acute-on-chronic liver failure (HELIOS study): a prospective randomized controlled multicenter study. J Hepatol 52: S3 (abst)

XIV Trauma and Emergency Medicine

Cocaine Intoxication

J.E. Hollander and A.M. Chang

Introduction

Medical complications temporally associated with cocaine use may occur in many different organ systems. The most severe cocaine-related toxicity and deaths follow intense sympathetic stimulation (e.g., tachycardia, hypertension, dilated pupils, and increased psychomotor activity) and lead to increased psychomotor activity that generates heat production, which can lead to severe hyperthermia and rhabdomyolysis [1]. Difficult to manage hyperthermia is often associated with cocaine-related deaths [1, 2].

Cardiovascular effects from cocaine are common and include myocardial ischemia, dysrhythmias, and depressed left ventricular (LV) function (sometimes reversible) [3]. Myocardial infarction due to cocaine occurs in approximately 6 % of patients presenting with cocaine-associated chest pain and is increased 24-fold in the hour after cocaine use [3 – 5]. In patients aged 18 to 45 years, 25 % of myocardial infarctions are attributed to cocaine use and they are most common in patients without large cocaine exposures [6]. Cardiac conduction disturbances (e.g., prolonged QRS and QTc) and cardiac dysrhythmias (e.g., sinus tachycardia, atrial fibrillation/flutter, supraventricular tachycardias, idioventricular rhythms, ventricular tachycardia, and ventricular fibrillation) may occur after cocaine use [7].

The neurologic effects of cocaine are varied. Altered mental status and seizures are typically short lived and without serious sequelae but serious conditions, such as cerebral infarction, intracerebral bleeding, subarachnoid hemorrhage, transient ischemic attacks, and spinal infarction, also occur [8, 9]. Cocaine use is associated with a sevenfold increased risk of stroke in women [10].

Pulmonary complications of cocaine include asthma exacerbation, pneumothorax, pneumomediastinum, noncardiogenic pulmonary edema, alveolar hemorrhage, pulmonary infarction, pulmonary artery hypertrophy and acute respiratory failure [8, 11 – 14]. Inhalation of cocaine is typically associated with deep Valsalva maneuvers to maximize drug delivery and can cause pneumothorax, pneumomediastinum, and non-cardiogenic pulmonary edema [12].

The intestinal vascular system is particularly sensitive to the effects of cocaine because the intestinal walls have a wide distribution of alpha-adrenergic receptors, with resulting acute intestinal infarction [1, 8].

Patients who present after ingesting packets filled with cocaine are body packers or body stuffers [15, 16]. Body packers swallow carefully prepared condoms or latex packets filled with large quantities of highly purified cocaine to smuggle it into the country [15]. Body stuffers are typically smaller time drug dealers who

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swallow packets of cocaine while avoiding police [16]. Toxicity occurs when cocaine leaks from the ingested packets. The most severe manifestations of cocaine toxicity are seen in body packers carrying large quantities of cocaine and who have dehiscence of a package [15].

Chronic cocaine use can predispose patients to other medical conditions. Chronic users develop LV hypertrophy that can lead eventually to dilated cardiomyopathy and heart failure [3, 4, 17]. This is in contrast to the acute cardiomyopathy from cocaine that appears to have a reversible component after cessation of cocaine use [3, 17]. Chronic cocaine users who use a large amount of cocaine can present with lethargy and a depressed mental status and may have the cocaine washout syndrome, which is a diagnosis of exclusion [1, 18]. This self-limiting syndrome usually abates within 24 hours but can last for several days and is thought to result from excessive cocaine usage that depletes essential neurotransmitters.

Diagnostic Evaluation

Patients manifesting cocaine toxicity should have a complete evaluation focusing on the history of cocaine use, signs and symptoms of sympathetic nervous system excess, and evaluation of specific organ system complaints. It is important to determine whether signs and symptoms are due to cocaine itself, underlying structural abnormalities, or cocaine-induced structural abnormalities.

Friends or family of patients with altered mental status should be questioned about a history of cocaine usage and the events before presentation.

Laboratory Tests

Since some patients may deny cocaine use, urine testing may be helpful. If the patient manifests moderate or severe toxicity, laboratory evaluation may include a complete blood cell count, serum electrolytes, glucose, blood urea nitrogen, creatinine, creatine kinase (CK), cardiac marker determinations, arterial blood gas analysis, and urinalysis. Hyperglycemia and hypokalemia may results from sympathetic excess. Rhabdomyolysis can be diagnosed by an elevation in CK. Cardiac troponin I or T should be used to identify acute myocardial infarction in symptomatic patients with cocaine use [19].

Imaging and Other Tests

Chest radiography and electrocardiography should be obtained in patients with potential cardiopulmonary complaints. Computed tomography (CT) of the head can be used to evaluate seizure or stroke. Patients with concurrent headache, suspected subarachnoid hemorrhage, or other neurologic manifestations may require lumbar puncture after head CT to rule out other CNS pathology [1, 18, 20].

Treatment

The initial management of cocaine-toxic patients should focus on airway, breathing, and circulation. Treatments are directed at a specific sign, symptom, or organ system affected and are summarized in **Table 1**.

Table 1. Treatment summary for cocaine-related medical conditions

Medical Condition	Treatments
Cardiovascular	
Dysrhythmias	
Sinus tachycardia	Observation Oxygen Diazepam or lorazepam
Supraventricular tachycardia	Oxygen Diazepam or lorazepam Consider diltiazem, verapamil or adenosine If hemodynamically unstable: cardioversion
Ventricular dysrhythmias	Oxygen Diazepam or lorazepam Consider sodium bicarbonate and/or lidocaine If hemodynamically unstable: defibrillation
Acute coronary syndrome	Oxygen Aspirin Diazepam or lorazepam Nitroglycerin Heparin For ST segment elevation (STEMI): Percutaneous intervention (angioplasty and stent placement) preferred. Consider fibrinolytic therapy. Consider morphine sulfate, phentolamine, verapamil or glycoprotein IIb/IIIa inhibitors
Hypertension	Observation Diazepam or lorazepam Consider nitroglycerin, phentolamine and nitroprusside
Pulmonary edema	Furosemide Nitroglycerin Consider morphine sulfate or phentolamine
Hyperthermia	Diazepam or lorazepam Cooling methods If agitated, consider paralysis and intubation
Neuropsychiatric	
Anxiety and agitation	Diazepam or lorazepam
Seizures	Diazepam or lorazepam Consider Phenobarbital
Intracranial hemorrhage	Surgical consultation
Rhabdomyolysis	i.v. hydration Consider sodium bicarbonate or mannitol If in acute renal failure: hemodialysis
Cocaine washout syndrome	Supportive care
Body packers	Activated charcoal Whole-bowel irrigation Laparotomy or endoscopic retrieval

Sympathomimetic Toxidrome/agitation

Patients with sympathetic excess and psychomotor agitation are at risk of hyperthermia and rhabdomyolysis [1, 2, 18]. Management focuses on lowering body temperature, halting further muscle damage and heat production, and ensuring good urinary output. The primary agents used for muscle relaxation and control of agitation are benzodiazepines [1, 18]. Doses beyond those typically used for patients without cocaine intoxication may be required. Antipsychotic agents are useful in mild cases, but their safety in severe cocaine-induced agitation is not clear. Elevations in core body temperature should be treated aggressively with iced water baths or cool water mist with fans. Some cases of severe muscle overactivity may require general anesthesia with non-depolarizing neuromuscular blockade. Non-depolarizing agents are preferred over succinylcholine, because succinylcholine may increase the risk of hyperkalemia in patients with cocaine-induced rhabdomyolysis [1, 18]. Plasma cholinesterase metabolizes both succinylcholine and cocaine; therefore, prolonged clinical effects of either or both agents may occur when both are used.

Hypertension

Patients with severe hypertension can usually be safely treated with benzodiazepines. When benzodiazepines alone are not effective, nitroglycerin, nitroprusside, or phentolamine can be used [21]. Beta-blockers are contraindicated because, in the setting of cocaine intoxication, they cause unopposed alpha adrenergic stimulation with subsequent exacerbation of hypertension [4].

Myocardial Ischemia or Infarction

Patients with cocaine-associated myocardial ischemia or infarction should be treated with aspirin, benzodiazepines, and nitroglycerin as first-line agents. Benzodiazepines decrease the central stimulatory effects of cocaine, thereby indirectly reducing its cardiovascular toxicity [22–24]. Benzodiazepines have a comparable and possibly an additive effect to nitroglycerin with respect to chest pain resolution and hemodynamic parameters for patients with chest pain. Weight-based unfractionated heparin or enoxaparin, as well as clopidogrel are reasonable to use in patients with documented ischemia [4]. Patients who do not respond to these initial therapies can be treated with phentolamine or calcium channel-blocking agents. In the acute setting, beta-blockers are contraindicated, as they can exacerbate cocaine-induced coronary artery vasoconstriction [1, 3, 4, 18].

When patients have ST segment elevation and require reperfusion, primary percutaneous coronary intervention (PCI) is preferred over fibrinolytic therapy due to a high rate of false-positive ST-segment elevations in patients with cocaine-associated chest pain, even in the absence of acute myocardial infarction, as well as the possibility of an increased rate of cerebral complications in patients with repetitive cocaine use [1, 3, 4, 18].

In the absence of electrocardiogram (EKG) changes or elevated cardiac markers, low and intermediate risk patients can be safely managed in a chest pain observation unit for 9 to 12 hours. The likelihood of underlying coronary artery disease or adverse cardiac events in patients in whom myocardial infarction is

ruled out is low [4, 25, 26]. In a study by Weber et al. [25], there were no differences in 30-day outcomes among patients managed with or without stress testing before discharge [25]. The American Heart Association (AHA) recommends stress testing performed at the time of observation or on an outpatient basis [4]. Recent data confirm that coronary CT angiography can also be used during the initial evaluation [27]. Patients with a brief period of observation in the emergency department (ED) found to have normal coronary arteries are at a very low risk of complications and will not require further provocative testing [4, 25].

Dysrhythmias

Supraventricular dysrhythmias may be difficult to treat. Initially, benzodiazepines should be administered. Adenosine can be given, but its effects may be temporary [7]. Use of calcium-channel blockers in association with benzodiazepines appears to be most beneficial [7]. Beta-blockers should be avoided.

Ventricular dysrhythmias can be managed with benzodiazepines, lidocaine or sodium bicarbonate [1]. Bicarbonate is preferred in patients with QRS widening and ventricular dysrhythmias that occur soon after cocaine use, since these dysrhythmias are presumably related to sodium channel-blocking effects of cocaine [3, 7]. Lidocaine can be used when dysrhythmias appear to be related to cocaine-induced ischemia [3, 7].

Seizures

Benzodiazepines and phenobarbital are the first- and second-line drugs, respectively, for seizure management [20]. Phenytoin is not recommended in cases associated with cocaine. Although no studies have compared barbiturates to phenytoin for control of cocaine-induced seizures, barbiturates are theoretically preferable because they also produce central nervous system (CNS) sedation and are generally more effective for toxin-induced convulsions [1, 20]. Newer agents have not been well studied in the setting of cocaine intoxication.

Cerebrovascular Infarction

A recent study at a tertiary stroke center identified 96 patients with cocaine use; almost half were given a diagnosis of ischemic stroke or transient ischemic attack, a quarter with intracerebral hemorrhage (ICH), and another quarter with subarachnoid hemorrhage. Stroke type differed significantly between active and prior users with active users more likely to have ICH compared with previous users (37.7 % *v* 8.6 %) and less likely to have ischemic stroke or transient ischemic attack (36.1 % *v* 65.7 %) [9]. An epidemiologic study from Texas indicated that cocaine abuse was associated with both hemorrhagic (OR, 2.33; 95 % CI, 1.74 – 3.11) and ischemic (OR, 2.03; 95 % CI, 1.48 – 2.79) stroke [9].

Some patients with neurological complaints have predisposing cerebrovascular disease (for example, aneurysms or arteriovenous malformations), most have not. Multiple hypotheses exist regarding the mechanism of cocaine-related ischemic stroke including vasospasm, enhanced platelet aggregation, cerebral vasculitis, and cardioembolism from cocaine-induced myocardial infarction and cardiomyopathy. Hypertensive surges causing a disturbance of cerebral autoregulation and blood flow may play a part in cocaine-induced hemorrhagic stroke [18].

Cocaine can lead to both ischemic and hemorrhagic strokes. Most of these patients should be managed similarly to patients with non-cocaine-associated cerebrovascular infarctions with two exceptions: The utility of tissue plasminogen activator (t-PA) in patients with recent cocaine-associated cerebrovascular events is unknown; blood pressure management should follow the recommendations above.

Aortic Dissection

Cocaine use can lead to aortic dissection. Stanford types A and B aortic dissection have both been reported with cocaine use. Although aortic dissection occurs in only 2.6–3.5 per 100,000 patient years, cocaine may be a causative factor in up to 37 % of cases [28, 29]. Untreated, the mortality rate climbs to 33 % within 24 hours and 90 % at 1 year [30–32]. Treatment is similar to other patients with aortic dissection but medical management should be adjusted to try and avoid beta-blockade.

Abdominal Ischemia

In the abdomen, cocaine has been reported to induce gastric and intestinal perforations, mesenteric ischemia, and ischemic colitis [8]. In a review by Linder et al, the average age of patients with cocaine-induced ischemic colitis was 32.6 years with a mortality of 28.5 % [33]. Patients had about one day of symptoms prior to presentation. As in other acute abdominal processes, CT is useful to make the diagnosis [33].

Body Stuffers and Packers

Body stuffers who manifest clinical signs of toxicity should be treated similarly to other cocaine-intoxicated patients. Gastrointestinal decontamination with activated charcoal should be performed [1, 15]. Assessment for unruptured cocaine packages should be considered. In some cases, whole-bowel irrigation may be necessary [15].

Body packers are typically asymptomatic at the time of detention when passing immigration. In patients who present with symptoms or develop symptoms of cocaine toxicity or rapidly deteriorate because of exposure to huge doses of cocaine, immediate surgical removal of the ruptured packages may be necessary [15].

Prognosis

Patient prognosis is dependent on the type of complication the patient has related to the cocaine use. Continued cocaine usage, however, is associated with an increased likelihood of recurrent symptoms and, therefore, aggressive drug rehabilitation may be useful. Cessation of cocaine use is the hallmark of secondary prevention. Recurrent chest pain is less common and myocardial infarction and death are rare in patients who discontinue cocaine [3, 25, 34]. Aggressive risk factor modification is indicated in patients with myocardial infarction or with evidence of premature atherosclerosis, coronary artery aneurysm or ectasia. This

includes smoking cessation, hypertension control, diabetes control and aggressive lipid lowering therapy. While these strategies have not been tested specifically for patients with cocaine, they are standard of care for patients with underlying coronary artery disease [4].

Patients with evidence of atherosclerosis may be candidates for long-term antiplatelet therapy with aspirin with or without clopidogrel for patients who receive stent placement [4]. The role of nitrates and calcium channel blockers remains speculative and should be used for symptomatic relief. The use of beta-adrenergic antagonists, although useful in patients with previous myocardial infarction and cardiomyopathy, needs special consideration in the setting of cocaine abuse. Since recidivism is high in patients with cocaine associated chest pain (60 % admit to cocaine use in the subsequent year) [35], beta-blocker therapy should probably be avoided in many of these patients [4].

Conclusion

Cocaine use continues worldwide. Emergency physicians and intensivists will treat cocaine intoxicated patients and should understand the differences in management of patients with various diseases when they present in temporal proximity to cocaine use compared to when cocaine has not been used. The mainstays of treatment of the cocaine intoxicated patient are benzodiazepines and supportive care, with other complaint-driven treatments as detailed above.

References

1. Hollander JE (2004) Cocaine. In: Dart RC (ed) Dart's Medical Toxicology (3rd ed). Lippincott Williams and Wilkins, Philadelphia, pp 1083 – 1096
2. Ruttenber AJ, McAnally HB, Wetli CV (1999) Cocaine-associated rhabdomyolysis and excited delirium: different stages of the same syndrome. Am J Forensic Med Pathol 20: 120 – 127
3. Hollander JE (1995) The management of cocaine-associated myocardial ischemia. N Engl J Med 333: 1267 – 1272
4. McCord J, Jneid H, Hollander JE, et al (2008) American Heart Association Acute Cardiac Care Committee of the Council on Clinical Cardiology. Management of cocaine-associated chest pain and myocardial infarction: a scientific statement from the American Heart Association Acute Cardiac Care Committee of the Council on Clinical Cardiology. Circulation 117: 1897 – 1907
5. Hollander JE, Hoffman RS, Gennis P, et al (1994) Prospective multicenter evaluation of cocaine-associated chest pain. Cocaine Associated Chest Pain (COCHPA) Study Group. Acad Emerg Med 1: 330 – 339
6. Qureshi AI, Suri MF, Guterman LR, Hopkins LN (2001) Cocaine use and the likelihood of nonfatal myocardial infarction and stroke: data from the Third National Health and Nutrition Examination Survey. Circulation 103: 502 – 506
7. Hoffman RS (2010) Treatment of patients with cocaine-induced arrhythmias: bringing the bench to the bedside. Br J Clin Pharmacol 69: 448 – 457
8. Glauser J, Queen JR (2007) An overview of non-cardiac cocaine toxicity. J Emerg Med 32: 181 – 186
9. Toossi S, Hess CP, Hills NK, Josephson SA (2010) Neurovascular complications of cocaine use at a tertiary stroke center. J Stroke Cerebrovasc Dis 19: 273 – 278
10. Sacco RL, Benjamin EJ, Broderick JP, et al (1997) American Heart Association Prevention Conference. IV. Prevention and Rehabilitation of Stroke. Risk factors. Stroke 28: 1507 – 1517
11. Devlin RJ, Henry JA (2008) Clinical review: Major consequences of illicit drug consumption. Crit Care 12: 202

12. Haim DY, Lippmann ML, Goldberg SK, Walkenstein MD (1995) The pulmonary complications of crack cocaine. A comprehensive review. Chest 107: 233–240
13. Alnas M, Altayeh A, Zaman M (2010) Clinical course and outcome of cocaine-induced pneumomediastinum. Am J Med Sci 339: 65–67
14. Restrepo CS, Carrillo JA, Martínez S, Ojeda P, Rivera AL, Hatta A (2007) Pulmonary complications from cocaine and cocaine-based substances: imaging manifestations. Radiographics 27: 941–956
15. Traub SJ, Hoffman RS, Nelson LS (2003) Body packing--the internal concealment of illicit drugs. N Engl J Med 349: 2519–2526
16. Sporer KA, Firestone J (1997) Clinical course of crack cocaine body stuffers. Ann Emerg Med 29: 596–601
17. Diercks DB, Fonarow GC, Kirk JD, et al (2008) Illicit stimulant use in a United States heart failure population presenting to the emergency department (from the Acute Decompensated Heart Failure National Registry Emergency Module). Am J Cardiol 102: 1216–1219
18. Hoffman RS (2006) Cocaine. In: Flomembaum N, Goldfrank L, Hoffman R, Howland MA, Lewin N, Nelson L (eds) Goldfrank's Toxicology (8th ed). McGraw-Hill, New York, pp 1133–1146
19. Hollander JE, Levitt MA, Young GP, Briglia E, Wetli CV, Gawad Y (1998) Effect of recent cocaine use on the specificity of cardiac markers for diagnosis of acute myocardial infarction. Am Heart J 135: 245–252
20. Winbery S, Blaho K, Logan B, Geraci S (1998) Multiple cocaine-induced seizures and corresponding cocaine and metabolite concentrations. Am J Emerg Med 16: 529–533
21. Hollander JE (2008) Cocaine intoxication and hypertension. Ann Emerg Med 51:S18–20
22. Hollander JE, Hoffman RS (1992) Cocaine induced myocardial infarction: an analysis and review of the literature. J Emerg Med 10: 169–177
23. Baumann BM, Perrone J, Hornig SE, Shofer FS, Hollander JE (2000) Randomized, double-blind, placebo-controlled trial of diazepam, nitroglycerin, or both for treatment of patients with potential cocaine-associated acute coronary syndromes. Acad Emerg Med 7: 878–885
24. Honderick T, Williams D, Seaberg D, Wears R (2003) A prospective, randomized, controlled trial of benzodiazepines and nitroglycerine or nitroglycerine alone in the treatment of cocaine-associated acute coronary syndromes. Am J Emerg Med 21: 39–42
25. Weber JE, Shofer FS, Larkin GL, Kalaria AS, Hollander JE (2003) Validation of a brief observation period for patients with cocaine-associated chest pain. N Engl J Med 348: 510–517
26. Kontos MC, Schmidt KL, Nicholson CS, Ornato JP, Jesse RL, Tatum JL (1999) Myocardial perfusion imaging with technetium-99m sestamibi in patients with cocaine-associated chest pain. Ann Emerg Med 33: 639–645
27. Walsh K, Chang AM, Perrone J, et al (2009) Coronary computerized tomography angiography for rapid discharge of low-risk patients with cocaine-associated chest pain. J Med Toxicol 5: 111–119
28. Singh S, Trivedi A, Adhikari T, Molner J, Arora R, Khosla S (2007) Cocaine-related acute aortic dissection: patient demographics and clinical outcomes. Can J Cardiol 23: 1131–1134
29. Singh A, Khaja A, Alpert MA (2010) Cocaine and aortic dissection. Vasc Med 15: 127–133
30. Hagan PG, Nienaber CA, Isselbacher EM, et al (2000) The International Registry of Acute Aortic Dissection (IRAD). New insights into an old disease. JAMA 283: 897
31. Nienaber CA, Eagle KA (2003) Aortic dissection: new frontiers in diagnosis and management: Part I: from etiology to diagnostic strategies. Circulation 108: 628–635
32. Suzuki T, Mehta RH, Ince H, et al (2003) Clinical profiles and outcomes of acute type B aortic dissection in the current era: lessons from the International Registry of Aortic Dissection (IRAD). Circulation 108 (Suppl 1): II312–317
33. Linder JD, Mönkemüller KE, Raijman I, Johnson L, Lazenby AJ, Wilcox CM. (2000) Cocaine-associated ischemic colitis. South Med J 93: 909–913
34. Hollander JE, Hoffman RS, Burstein J, Shih RD, Thode HC, and the Cocaine Associated Myocardial Infarction Study (CAMI) Group (1995) Cocaine associated myocardial infarction. Mortality and complications. Arch Intern Med 155: 1081–1086
35. Hollander JE, Hoffman RS, Gennis P, et al (1995) Cocaine-associated chest pain: one-year follow-up. Acad Emerg Med 2: 179–184

Airway Management for Major Trauma

C. Hommers and J. Nolan

Introduction

Airway control and ensuring adequate respiratory function are priorities in managing any seriously-injured patient. Failure to maintain a patent airway remains a significant cause of preventable death and disability. In these circumstances, emergency tracheal intubation is a potentially life-saving procedure to optimize oxygenation, maintain ventilation and reduce the risk of aspiration. Early tracheal intubation has been promoted and adopted increasingly in many trauma systems. However, much controversy surrounds this practice, particularly in the pre-hospital setting where high complication rates have been reported, and current evidence suggests that tracheal intubation may not be universally beneficial [1]. Airway management of patients with major injuries is challenging, even within hospital. This chapter will review four controversial topics relating to airway management in severely injured patients: Pre-hospital intubation, protection of the cervical spine, the use of cricoid pressure, and the choice of induction drug.

Pre-hospital Intubation

Despite being promoted as a standard of care, the timing, benefit, and relationship of intubation to outcome from major trauma remain undetermined. Few studies have shown improved outcome from pre-hospital intubation, whereas many others have reported no benefit or an association with increased mortality [1, 2]. Existing evidence comes largely from uncontrolled retrospective studies that often included heterogeneous patient populations (blunt and penetrating trauma) and multiple confounding factors, which makes reliable risk adjustment and meaningful interpretation extremely difficult. A recent systematic review of emergency intubation in acutely ill and injured patients identified just three eligible randomized controlled trials from the 452 studies reviewed [3]. Heterogeneity and methodological limitations prevented any of the studies of adult trauma patients from meeting the inclusion criteria and the authors concluded that there was insufficient high-quality evidence to comment on the efficacy of emergency intubation.

Given the procedural complexity of intubation in the seriously injured patient and the uncontrolled nature of the pre-hospital environment it is plausible that, in inexperienced hands, adverse events may contribute to the worse outcome observed with pre-hospital intubation. Many of the available data about intubation complications relate to paramedic-based emergency medical services (EMS)

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systems in the United States. Success rates ranging from 60 – 90 % have been described widely but are as low as 50 % in rescuers who perform the procedure only rarely [1, 4]. Many of these data relate to intubation without the use of neuromuscular blocking drugs or sedatives and higher rates of success have been associated with drug-assisted intubation. There remains considerable concern about the high number of complications, the most serious being unrecognized esophageal intubation, rates of which range from 0.4 % to 12 % [2, 4]. Given that most of these data are self-reported, this is likely to represent the best-case scenario. When emergency physicians evaluated, on admission to hospital, 108 paramedic intubations (non-drug-assisted), the unrecognized esophageal intubation rate was 16.7 %, with trauma patients being significantly more likely than medical patients to have misplaced tubes (37 % versus 14 %) [5]. Other serious complications have been reported commonly. In a study from San Diego, hypoxemia (SaO_2 < 90 %) occurred in 31 of 54 (57 %) patients undergoing paramedic rapid sequence induction (RSI) and intubation. Over half of these events lasted more than 3 minutes; despite this, the paramedic documented the intubation as 'easy' in 84 % of cases [6].

In Europe, pre-hospital intubation is undertaken more commonly by physicians. When attempted by an experienced anesthesiologist or emergency physician, success rates approaching 100 % have been reported in several studies from France, Germany and the UK [7]. Reduced complication rates and improved survival have also been demonstrated [8, 9]. This lends weight to the argument that experience and skill are key factors in ensuring safe and effective pre-hospital advanced airway management. Although there is no clear consensus on acquisition and maintenance of intubation skill, current paramedic training in many parts of the world would be considered inadequate by most in-hospital standards. Training programs consist variably of didactic teaching modules, simulation using manikins and cadavers, and limited operating room experience, with paramedic students in the US attempting a median of seven intubations during their entire training [2, 10]. Notably, amongst anesthetic trainees in Switzerland, a mean of 57 intubation attempts was required to reach a success rate of 90 % [11]. Beyond baseline competence, maintaining skills requires regular clinical experience. A figure of one intubation a month or 10 per year has been proposed but few pre-hospital practitioners attain this level of clinical exposure without access to additional training opportunities.

When interpreting all of these results it must be remembered that intubation is just one aspect of pre-hospital care and other clinical interventions are often taking place concurrently. It is inevitable that these interventions will interact, affecting physiological processes adversely and influencing overall patient outcome [1]. For example, unintended hyperventilation occurs frequently after pre-hospital RSI for traumatic brain injury, and has been associated with increased mortality [12]. Other aspects of care may have similar unquantifiable effects. Examples include fluid administration, ventilation strategies and the use of sedative drugs. Studies, such as the Ontario Pre-hospital Advanced Life Support (OPALS) Major Trauma Study, have evaluated the overall effect of implementing paramedic advanced life support programs and found no difference in survival. Indeed, a subgroup of patients with Glasgow Coma Scale scores (GCS) < 9 had a worse outcome [13].

It seems unrealistic to expect paramedics to achieve high success rates given their current level of training. Some paramedic-based aero medical systems have

demonstrated good results. This may reflect strong medical leadership, the use of small, targeted paramedic groups to improved training and clinical exposure, strict RSI protocols, use of waveform capnography for verification of intubation, and optimization of post-intubation care. As no protocol can compensate for good clinical judgment, some authorities have suggested that only experienced hospital practitioners have the ability to provide safe pre-hospital anesthesia [7]. The Association of Anaesthetists of Great Britain and Ireland (www.aagbi.org) has produced guidance stating that healthcare personnel providing pre-hospital anesthesia should have the same level of training and competence that would allow them to provide unsupervised RSI and intubation in the hospital environment – currently a minimum of 2 years training in emergency specialities and 1 year of anesthesia.

These ideals will remain an impossible target for many EMS systems worldwide and, in the absence of convincing evidence of benefit for pre-hospital intubation, and the indisputable potential for harm, alternative approaches must be considered. Basic airway maneuvers may be sufficient for those involved rarely in airway management. However, supraglottic airway devices have been proposed as an appropriate first line for personnel not highly skilled in tracheal intubation [14]. While offering advantages of improved ventilation and oxygenation and reduced risk of gastric inflation and regurgitation, these devices are simpler to use, require less training and have the advantage of being generally fail safe in inexperienced hands [14].

In-hospital Airway Management

Even in the relatively controlled environment of the hospital, many factors contribute to the challenge of airway management in severely injured patients. Screening tests are of limited value to predict difficult airways in emergencies [15]. Time restraints, uncooperative patients, hemodynamic instability, risk of aspiration, the need for cervical spine protection, and facial and neck injuries, all add to potential difficulties. Recognizing the importance of airway management and identifying a substantial variation in practice occurring from center to center, the Eastern Association for the Surgery of Trauma (EAST) undertook an evidence-based literature review in 2002 [16]. It published a list of indications for early intubation. These included airway obstruction, hypoventilation, severe hypoxemia (despite supplemental oxygen), severe cognitive impairment (GCS < 8), severe hemorrhagic shock and cardiac arrest.

A recent retrospective review of 1000 consecutive intubations at a level 1 trauma center in San Diego found that 9.9 % of trauma patients required intubation within 2 hours of arrival [17]. The range of intubation rates reported previously was between 8.7 – 27 %, with a suggestion that lower rates may reflect more widespread use of pre-hospital intubation. The San Diego group reported that the EAST indications did not identify adequately all patients who benefited from early intubation. Altered mental state (GCS > 8), combativeness and preoperative pain management were among the most common additional discretionary indications [17].

RSI and intubation using direct laryngoscopy has become the standard approach to securing the airway in major trauma and has been associated consistently with high levels of success in emergency intubation [18]. Success rates of

97 – 99 % (within 3 attempts) have been reported widely by both emergency physicians and anesthesiologists [19]. The largest series published to date reviewed 10 years of experience at a major trauma referral center in Baltimore [20]. Of 57,529 admissions, 6,088 (10.6 %) required intubation within the first hour, and the success rate was 99.7 %. A rescue surgical airway was performed in 21 patients (0.3 %). The commonest reasons for failed intubation and need for cricothyroidotomy were pre-morbid anatomical variations and direct trauma to the face and neck. The authors cite the use of a simple RSI-based protocol with a small selection of familiar rescue devices (bougie and laryngeal mask airway [LMA]), and the presence of an experienced anesthesiologist at each admission, as the basis for their success. Complication rates and number of attempts at intubation were not reported in this study. In another study, success at first attempt was lower amongst less experienced operators (residents) and the complication rate was significantly higher when more junior staff were involved in the intubation (14.2 % vs. 9.7 %; $p< 0.05$) [17]. The association of complications with number of intubation attempts has been well documented previously [21].

Although experiences at busy trauma centers may not be universally representative, several aspects of care have emerged as key factors in ensuring timely, safe and effective airway management. These include adherence to a simple RSI protocol and failed intubation drill [22], the application of monitoring standards in the operating room, particularly the use of end-tidal CO_2 ($ETCO_2$) [23], and the availability of experienced personnel at all emergency intubations [17].

Cervical Spine Protection

Estimated rates of secondary neurological damage occurring after cervical spine injury have decreased significantly since the introduction of spinal immobilization in the 1970s [24]. Concerns that cervical movement during airway management was a significant contributing factor to this damage, resulted in manual in-line stabilization (MILS) during direct laryngoscopy becoming a standard of care for acute trauma patients. Although intuitively appealing, the evidence base for this practice is extremely limited with data originating from studies on uninjured volunteers, cadaveric models and small, uncontrolled case series. Appreciation of the potential detrimental effect of MILS has been emerging gradually and many commentators have called for reappraisal of the practice [25, 26].

Early data in healthy anesthetized volunteers showed that MILS reduced cervical spine movement by as much as 50 % [27]. However, the evidence that externally limiting head and neck movement minimizes the pathological motion of the cervical spine at unstable segments is weak. Cadaveric studies modeling varieties of cervical instability have reported conflicting results ranging from reduced, to unchanged or even increased subluxation with the application of MILS [26]. The suggested explanation for increased displacement of the cervical spine with immobilization is the greater force that must be applied by the operator to obtain an acceptable view [28]. This theory has been borne out in a small case series of volunteers in which a doubling of laryngoscopic force was observed with application of MILS [29]. As the biomechanics of laryngoscopy are poorly understood, it is unclear which aspects of applied pressure, if any, are clinically relevant.

More concerning is the adverse effect of MILS on glottic view: Several investigators have reported significant worsening of laryngoscopic view, increased time

to intubation and increased likelihood of failed intubation [26]. The resultant hypoxemia observed is particularly worrying given the high incidence of traumatic brain injury in this population.

As only 4 % of trauma patients have cervical spine injuries, and unstable injuries with recoverable cord function occur in only a minority of these, neurological deterioration during airway manipulation is likely to be extremely rare. Animal data indicate that compression in excess of 50 % of the cord diameter for greater than one hour is required for permanent injury to occur [30]. This may

Table 1. Techniques for reducing cervical spine movement and improving ease of intubation.

Study	Subjects	Airway management	Design	Findings
Takahasi et al. [31]	33 residents using manikin in semi-rigid collar	AWS Macintosh	Clinical observation	AWS fewer attempts and 100 % success (2 esophageal tubes with Mac). No difference in speed.
Aoi et al. [32]	36 elective patients in semi-rigid collar	AWS Macintosh	Clinical observation Randomized	AWS improved ease and grade of intubation. No difference in speed.
Takenaka et al. [33]	30 elective patients	AWS +/– bougie	Fluoroscopy Randomized	AWS in combination with bougie reduced extension of cervical spine between occiput and the fourth cervical vertebra (6.5 vs 16.0 degrees, $p < 0.01$)
Turkstra et al. [34]	24 elective patients with MILS	Airtraq Macintosh	Fluoroscopy Crossover	Airtraq reduced cervical spine motion by 66 % ($p < 0.01$). No difference in speed.
Maharaj et al. [35]	40 elective patients with MILS	Airtraq Macintosh	Clinical observation Randomized	Airtraq reduced duration of intubation and need for additional maneuvers. Fewer blood pressure and heart rate changes with Airtraq.
Robitaille et al. [36]	20 elective patients	Glidescope Macintosh	Fluoroscopy Crossover	Glidescope improved view. No difference in cervical spine motion.
Gercek et al. [37]	48 elective patients with MILS	Macintosh, ILMA and fibreoptic (oral and nasal)	Ultrasound Crossover	ILMA and fiberoptic techniques reduced cervical spine movement (17.57 vs 4.6 degrees). Significantly prolonged intubation times with fiberoptic.
Maruyama et al. [38]	45 elective patients	AWS Macintosh McCoy	Fluoroscopy Randomized	AWS reduced cervical spine movement compared with both Mac and McCoy (22.3 vs 32.3 vs 36.5 degrees respectively). AWS intubation time longer.
Wahlen et al. [39]	48 elective patients	Macintosh, Bullard, Bonfils and ILMA	Fluoroscopy Crossover	Bullard, Bonfils and ILMA all reduced cervical spine movement (3.4, 5.5, 4.9 degrees respectively; Mac 22.5 degrees) Longer intubation times with Bonfil and ILMA.

AWS: Airway Scope; MILS: manual in-line stabilization; ILMA: intubating laryngeal mask airway

explain why, in 25 years of practice, there have been few, if any, reliable reports of intubation causing a secondary spinal cord injury [26]. It may be that maintenance of spinal cord perfusion pressure and tissue oxygenation are more important factors in preventing secondary injury than minor degrees of cervical spine movement. In any case, ethical and logistical barriers preclude the possibility of a large-scale controlled trial ever taking place. Research has, therefore, focused more recently on alternative approaches to improving safety in trauma airway management.

Several strategies have been evaluated to reduce cervical spine movement and improve ease of intubation (**Table 1**) [31–39]. Some of these strategies, including nasotracheal intubation and flexible fiberoptic laryngoscopy, have limited application in the acute trauma setting. However, intubating supraglottic airways, video laryngoscopes and optical stylets have produced more promising results. The latter do not require a direct line of sight for glottic visualization and several of the available devices have been found to reduce cervical spine movement when compared to standard laryngoscopy. The Airtraq, Airway Scope (AWS) – particularly when used in combination with a bougie – Trachlight and intubating LMA, have all been found to have significant beneficial effects on cervical spine motion and in some cases to improve laryngeal visualization and ease of intubation [31, 32, 35]. All of these studies have again been conducted on healthy volunteers and what remains to be assessed is the effect of airway soiling on the performance of these devices.

Given the lack of high-quality evidence, clinicians must weigh up the issues in any given circumstance, balancing any beneficial effect of MILS against the risks of suboptimal laryngoscopic views. It seems pragmatic to apply MILS, providing it does not compromise rapid intubation. If the view is poor, some degree of flexion or extension should be permitted and early consideration given to the use of an alternative supraglottic device.

The Cricoid Pressure Controversy

Cricoid pressure was described originally by Sellick (1961) as a method of reducing the risk of regurgitation and aspiration of gastric contents during the induction of anesthesia. Initially tested on cadavers, Sellick subsequently tried out the maneuver on 26 human subjects at high risk of aspiration. None of the patients regurgitated with cricoid pressure applied and three patients had immediate reflux upon release. Sellick's maneuver subsequently gained widespread acceptance and cricoid pressure has since become an essential element of RSI.

Subsequent reports of regurgitation and aspiration despite application of cricoid pressure prompted criticism of this practice and raised questions about its efficacy and safety [40]. All of the available supporting evidence again comes from small, uncontrolled studies and cadaveric models, the clinical relevance of which is poorly defined [41]. Whether failure of the maneuver clinically is attributable to the technique itself or improper application is impossible to determine. The optimal method, timing and force applied remain unclear and are often quoted as technical barriers to the success of cricoid pressure [41]. In fact, the only consistent data relating to cricoid pressure indicate that the majority of personnel apply it incorrectly. This incorrect application of force is of vital impor-

tance as it can result in either incomplete occlusion or airway compression and limited laryngeal visualization. The ability of individuals to apply cricoid pressure correctly has been tested using models and these indicate that it is applied with a very variable force (0–120 N) [42].

Variable head position and anatomy also impact the efficacy of cricoid pressure. Studies using computed tomography (CT) have demonstrated lateral displacement of the esophagus in 49 % of individuals. This was found to increase to 90.5 % with cricoid pressure [43]. More recent magnetic resonance imaging (MRI) indicates that cricoid pressure occludes the hypophayrnx, which makes the position of the esophagus irrelevant for the success of cricoid pressure in preventing regurgitation [44]. Even with cricoid pressure applied correctly, airway compression was observed in 81 % of subjects [43].

Several studies have shown that cricoid pressure reduces gastric inflation during mask ventilation. This may be particularly relevant in pediatric practice where it has been found to prevent inflation effectively up to airway pressures of 40 cmH_2O. However, this finding must be interpreted in the light of further data that indicate that cricoid pressure increases difficulty with mask ventilation, reduces tidal volumes, increases peak inspiratory pressures, and may even prevent ventilation by obstructing the airway [41].

Evidence on the effect of cricoid pressure on laryngeal view is contradictory [40]. However, combining cricoid pressure with MILS, as commonly occurs in the setting of major trauma, has been demonstrated to cause a significant deterioration in grade of view at laryngoscopy [2]. Cricoid pressure also impedes effective placement of an LMA reducing the success of insertion from 94 % to 67 % and hindering tracheal intubation via the LMA. The current Difficult Airway Society guidelines (www.das.uk.com) indicate that in an emergency the cricoid pressure should be released to aid the passage of an LMA.

Other serious complications reported with cricoid pressure include esophageal rupture and cricoid fracture with displacement of laryngeal fragments. Several studies have considered directly the effect of cricoid pressure on the cervical spine; two have suggested significant movement associated with cricoid pressure [41]. A retrospective review of intubation in 73 cervical spine injured patients undergoing RSI did not demonstrate any adverse neurological sequelae from cricoid pressure [45]. This calls into question the clinical relevance of minor degrees of movement.

The risk of aspiration with anesthesia has been decreasing over time, but the contribution of cricoid pressure to this improvement is uncertain. Significant advances in anesthesia and airway management are likely to be responsible for the current very low aspiration rate amongst elective patients. In the emergency setting, the picture is less clear because aspiration often occurs before attempted tracheal intubation and widely varying rates have been reported that range from 0 % to 22 % [41]. It is likely that higher rates of aspiration are associated with repetitive attempts at laryngoscopy. In a review of 2,833 emergency airways, an incidence of 1.9 % was reported, increasing to 22 % with three or more attempts [21]; the frequently poor application of cricoid pressure may well contribute to these multiple attempts.

A risk-benefit analysis has to be considered in any given clinical situation. The effect of cricoid pressure on view and its effectiveness in preventing regurgitation is likely to vary from patient to patient. Many of the reported problems with cricoid pressure probably relate to incorrect application and unless reliability in its

performance can be improved, consideration of efficacy is of secondary importance. The risk of aspiration versus the risk of hypoxemia should be considered case-by-case and if there is difficulty with intubation or ventilation, consider removing the cricoid pressure.

Induction Drugs in the Hemodynamically Compromised Trauma Patient

The ideal induction drug does not exist and individual practice is determined often by operator experience. Etomidate has long been considered safe and reliable for emergency intubation and has become one of the most widely used drugs for RSI in trauma patients worldwide. Emergency physicians readily adopted etomidate because of its favorable hemodynamic profile, easy dosing and rapid onset. Debate about the effect of etomidate on adrenal function and the clinical significance of this effect in critically ill patients has brought its use into question.

It has been known for many years that etomidate suppresses adrenal function transiently by reversible inhibition of 11b hydroxylase, the enzyme involved in the final pathway of cortisol production. The clinical significance of this effect was first recognized in the early 1980s when an excess mortality was observed in intubated trauma patients sedated with etomidate infusions on the intensive care unit (ICU). Numerous reports have linked etomidate to adrenal insufficiency, reduced cortisol levels and inadequate responses to corticotropin in the critically ill [46]. Although continuous infusions for sedation have long been abandoned, it is the direct effect of a single bolus dose that has become the focus of attention more recently.

It is well know that adrenal insufficiency, which is common in the critically ill, is associated with poorer prognosis, particularly in patients with septic shock. Recent data now indicate that etomidate, even when injected as a single bolus dose, may be associated with more sustained adrenal suppression in the critically ill, lasting at least 24 hours and possibly up to 72 hours [47]. Although the adverse effect of etomidate on adrenal dysfunction in the critically ill is in little doubt, the clinical significance of this is less clear. The CORTICUS study group reconfirmed the association between etomidate and a reduced response to corticotropin (60.4 % versus 43.4 %, $p = 0.004$). There was a higher 28-day mortality in the etomidate group (40 % versus 29.6 %, $p = 0.03$), a difference that was interestingly unaffected by the addition of supplemental hydrocortisone [48]. Unsupported conclusions were appropriately avoided on the basis of the non-randomized, retrospective analysis. All other studies claiming to show an increased mortality have been based also on retrospective analyses often involving very small numbers. No study specifically designed to compare mortality has yet demonstrated any difference [46].

A recent randomized controlled trial compared the use of etomidate and ketamine for RSI in 655 acutely ill patients [49]. There were no differences between groups in the mean maximum sequential organ failure assessment (SOFA) score, in intubating conditions, or in early or late (28 day) mortality. The effect of etomidate on adrenal function was demonstrated, with adrenal insufficiency in 86 % of the etomidate group compared with 48 % of the ketamine group (OR 6.7, 3.5 – 12.7). The authors concluded that ketamine is a safe and valuable alternative to etomidate and should be considered, particularly in patients with severe sepsis who are most at risk from adrenal insufficiency.

Although no causal link to increased morbidity or mortality has ever been established, the weight of observational and biochemical data indicating potential harm has resulted in numerous investigators calling for etomidate to be withdrawn. As alternative induction drugs are available, it is increasingly difficult to justify the use of etomidate in the critically ill. Unfortunately none of the alternative drugs are devoid of side effects and few high-quality studies comparing safety profiles have been conducted.

Ketamine has been emerging as the most favorable alternative to etomidate in the treatment of the hemodynamically compromised patient because its sympathomimetic action maintains cardiovascular stability. Initial concerns about the use of ketamine in traumatic brain injury have been re-evaluated [50]. During spontaneous ventilation, ketamine increases cerebral blood flow and intracranial pressure because of cerebral vasodilation but this can be obviated by controlled ventilation and adequate sedation. Any potential increase in intracranial pressure will be offset by an increase in mean arterial pressure and decrease in cerebral oxygen consumption ($CMRO_2$). An increasing body of experimental evidence indicates a possible protective anti-inflammatory effect in sepsis and a neuroprotective effect in ischemia; this may strengthen the argument in favor of ketamine in the future.

Conclusion

Tracheal intubation of the seriously injured, critically ill patient is a high-risk procedure in any setting. The increased incidence of difficult intubation and poor physiological reserve are associated with numerous complications, even in experienced hands. In the particularly challenging pre-hospital environment, standards of care should reflect best hospital practice and it should be undertaken only by personnel highly trained in drug-assisted intubation, who maintain their skills with regular practice. Less skilled practitioners may cause considerable harm by repeated attempts at larynoscopy and there is a risk of unrecognized esophageal intubation. Supraglottic airway devices such as the LMA, are often familiar as rescue devices, but may be taught more appropriately as a first line airway management technique for those less experienced in tracheal intubation.

RSI with cricoid pressure, MILS of the cervical spine and direct laryngoscopy remain the procedures of choice for airway control in major trauma. Careful use of a cardiostable induction drug minimizes the hemodynamic complications of induction. Ketamine appears to have the most favorable profile of the currently available drugs. Awareness of the limited evidence for use of cricoid pressure and MILS and an appreciation of the potential harmful effects on glottic view and management should ensure the best chance of successful and safe tracheal intubation.

References

1. Wang HE, Yealy DM (2006) Out-of-hospital endotracheal intubation: where are we? Ann Emerg Med 47: 532–541
2. Nolan JD (2001) Prehospital and resuscitative airway care: should the gold standard be reassessed? Curr Opin Crit Care 7: 413–421
3. Lecky F, Bryden D, Little R, Tong N, Moulton C (2008) Emergency intubation for acutely ill and injured patients. Cochrane Database Syst Rev: CD001429

4. Cobas MA, De la Peña MA, Manning R, Candiotti K, Varon AJ (2009) Prehospital intubations and mortality: a level 1 trauma center perspective. Anesth Analg 109: 489–493
5. Katz SH, Falk JL (2001) Misplaced endotracheal tubes by paramedics in an urban emergency medical services system. Ann Emerg Med 37: 32–37
6. Dunford JV, Davis DP, Ochs M, Doney M, Hoyt DB (2003) Incidence of transient hypoxia and pulse rate reactivity during paramedic rapid sequence intubation. Ann Emerg Med 42: 721–728
7. Herff H, Wenzel V, Lockey D (2009) Prehospital intubation: the right tools in the right hands at the right time. Anesth Analg 109: 303–305
8. Garner AA (2004) The role of physician staffing of helicopter emergency medical services in prehospital trauma response. Emerg Med Australas 16: 318–323
9. Newton A, Ratchford A, Khan I (2008) Incidence of adverse events during prehospital rapid sequence intubation: a review of one year on the London Helicopter Emergency Medical Service. J Trauma 64: 487–492
10. Wang HE, Seitz SR, Hostler D, Yealy DM (2005) Defining the learning curve for paramedic student endotracheal intubation. Prehosp Emerg Care 9: 156–162
11. Konrad C, Schupfer G, Wietlisbach M, Gerber H (1998) Learning manual skills in anesthesiology: Is there a recommended number of cases for anesthetic procedures? Anesth Analg 86: 635–639
12. Davis DP, Dunford JV, Poste JC, et al (2004) The impact of hypoxia and hyperventilation on outcome after paramedic rapid sequence intubation of severely head-injured patients. J Trauma 57: 1–8
13. Stiell IG, Nesbitt LP, Pickett W, et al (2008) The OPALS Major Trauma Study: impact of advanced life-support on survival and morbidity. CMAJ 178: 1141–1152
14. Cook TM, Hommers C (2006) New airways for resuscitation? Resuscitation 69: 371–387
15. Levitan RM, Everett WW, Ochroch EA (2004) Limitations of difficult airway prediction in patients intubated in the emergency department. Ann Emerg Med 44: 307–313
16. Dunham CM, Barraco RD, Clark DE, et al (2003) Guidelines for emergency tracheal intubation immediately after traumatic injury. J Trauma 55: 162–179
17. Sise MJ, Shackford SR, Sise CB, et al (2009) Early intubation in the management of trauma patients: indications and outcomes in 1,000 consecutive patients. J Trauma 66: 32–39
18. Sakles JC, Laurin EG, Rantapaa AA, Panacek EA (1998) Airway management in the emergency department: a one-year study of 610 tracheal intubations. Ann Emerg Med 31: 325–332
19. Levitan RM, Rosenblatt B, Meiner EM, Reilly PM, Hollander JE (2004) Alternating day emergency medicine and anesthesia resident responsibility for management of the trauma airway: a study of laryngoscopy performance and intubation success. Ann Emerg Med 43: 48–53
20. Stephens CT, Kahntroff S, Dutton RP (2009) The success of emergency endotracheal intubation in trauma patients: a 10-year experience at a major adult trauma referral center. Anesth Analg 109: 866–872
21. Mort TC (2004) Emergency tracheal intubation: complications associated with repeated laryngoscopic attempts. Anesth Analg 99: 607–613
22. Casey ZC, Smally AJ, Grant RJ, McQuay J (2007) Trauma intubations: can a protocol-driven approach be successful? J Trauma 63: 955–960
23. Donald MJ, Paterson B (2006) End tidal carbon dioxide monitoring in prehospital and retrieval medicine: a review. Emerg Med J 23: 728–730
24. Crosby ET (1992) Tracheal intubation in the cervical spine-injured patient. Can J Anaesth 39: 105–109
25. Crosby ET (2006) Airway management in adults after cervical spine trauma. Anesthesiology 104: 1293–1318
26. Manoach S, Paladino L (2007) Manual in-line stabilization for acute airway management of suspected cervical spine injury: historical review and current questions. Ann Emerg Med 50: 236–245
27. Watts AD, Gelb AW, Bach DB, Pelz DM (1997) Comparison of the Bullard and Macintosh laryngoscopes for endotracheal intubation of patients with a potential cervical spine injury. Anesthesiology 87: 1335–1342

28. Manoach S, Paladino L (2009) Laryngoscopy force, visualization, and intubation failure in acute trauma: should we modify the practice of manual in-line stabilization? Anesthesiology 110: 6–7
29. Santoni BG, Hindman BJ, Puttlitz CM, et al (2009) Manual in-line stabilization increases pressures applied by the laryngoscope blade during direct laryngoscopy and orotracheal intubation. Anesthesiology 110: 24–31
30. Delamarter RB, Sherman J, Carr JB (1995) Pathophysiology of spinal cord injury. Recovery after immediate and delayed decompression. J Bone Joint Surg Am 77: 1042–1049
31. Takahashi K, Morimura N, Sakamoto T, et al (2010) Comparison of the airway scope and macintosh laryngoscope with in-line cervical stabilization by the semisolid neck collar: Manikin study. J Trauma 68: 363–366
32. Aoi Y, Inagawa G, Nakamura K, Sato H, Kariya T, Goto T (2010) Airway scope versus macintosh laryngoscope in patients with simulated limitation of neck movements. J Trauma 69: 838–842
33. Takenaka I, Aoyama K, Iwagaki T, Ishimura H, Takenaka Y, Kadoya T (2009) Approach combining the airway scope and the bougie for minimizing movement of the cervical spine during endotracheal intubation. Anesthesiology 110: 1335–1340
34. Turkstra TP, Pelz DM, Jones PM (2009) Cervical spine motion: a fluoroscopic comparison of the AirTraq Laryngoscope versus the Macintosh laryngoscope. Anesthesiology 111: 97–101
35. Maharaj CH, Buckley E, Harte BH, Laffey JG (2007) Endotracheal intubation in patients with cervical spine immobilization: a comparison of macintosh and airtraq laryngoscopes. Anesthesiology 107: 53–59
36. Robitaille A, Williams SR, Tremblay MH, Guilbert F, Theriault M, Drolet P, (2008) Cervical spine motion during tracheal intubation with manual in-line stabilization: direct laryngoscopy versus GlideScope videolaryngoscopy. Anesth Analg 106: 935–941
37. Gercek E, Wahlen BM, Rommens PM (2008) In vivo ultrasound real-time motion of the cervical spine during intubation under manual in-line stabilization: a comparison of intubation methods. Eur J Anaesthesiol 25: 29–36
38. Maruyama K, Yamada T, Kawakami R, Kamata T, Yokochi M, Hara K (2008) Upper cervical spine movement during intubation: fluoroscopic comparison of the AirWay Scope, McCoy laryngoscope, and Macintosh laryngoscope. Br J Anaesth 100: 120–124
39. Wahlen BM, Gercek E (2004) Three-dimensional cervical spine movement during intubation using the Macintosh and Bullard laryngoscopes, the bonfils fibrescope and the intubating laryngeal mask airway. Eur J Anaesthesiol 21: 907–913
40. El-Orbany M, Connolly LA (2010) Rapid sequence induction and intubation. Anesth Analg 110: 1318–1325
41. Ellis DY, Harris T, Zideman D (2007) Cricoid pressure in emergency department rapid sequence tracheal intubations: a risk-benefit analysis. Ann Emerg Med 50: 653–665
42. Clark RK, Trethewy CE (2005) Assessment of cricoid pressure application by emergency department staff. Emerg Med Australas 17: 376–381
43. Smith KJ, Dobranowski J, Yip G, Dauphin A, Choi PT (2003) Cricoid pressure displaces the esophagus: an observational study using magnetic resonance imaging. Anesthesiology 99: 60–64
44. Rice MJ, Mancuso AA, Gibbs C, Morey TE, Gravenstein N, Deitte LA (2009) Cricoid pressure results in compression of the postcricoid hypopharynx: the esophageal position is irrelevant. Anesth Analg 109: 1546–1552
45. Criswell JC, Parr MJ, Nolan JP (1994) Emergency airway management in patients with cervical spine injuries. Anaesthesia 49: 900–903
46. Hohl CM, Kelly-Smith CH, Yeung TC, Sweet DD, Doyle-Waters MM, Schulzer M, (2010) The effect of a bolus dose of etomidate on cortisol levels, mortality, and health services utilization: A systematic review. Ann Emerg Med 56: 105–113
47. Cuthbertson BH, Sprung CL, Annane D, et al (2009) The effects of etomidate on adrenal responsiveness and mortality in patients with septic shock. Intensive Care Med 35: 1868–1876
48. Lipiner-Friedman D, Sprung CL, Laterre PF, et al (2007) Adrenal function in sepsis: the retrospective Corticus cohort study. Crit Care Med 35: 1012–1018

49. Jabre P, Combes X, Lapostolle F, et al (2009) Etomidate versus ketamine for rapid sequence intubation in acutely ill patients: a multicentre randomised controlled trial. Lancet 374: 293 – 300
50. Morris C, Perris A, Klein J, Mahoney P (2009) Anaesthesia in haemodynamically compromised emergency patients: does ketamine represent the best choice of induction agent? Anaesthesia 64: 532 – 539

Goal-directed Coagulation Management in Major Trauma

H. Schoechl, W. Voelckel, and C. Solomon

Introduction

Severe tissue trauma is frequently associated with hemorrhagic shock and subsequent pronounced coagulopathy [1]. Uncontrolled bleeding is the second most common cause of death, and hemorrhage is directly responsible for 40 % of all trauma-related deaths [2]. Coagulopathy can be detected with standard coagulation tests immediately after arrival in the emergency room (ER) in approximately 25 – 35 % of all trauma patients [1, 2]. Moreover, early trauma-induced coagulopathy is associated with a 4-fold increase in mortality [1]. Blood coagulation monitoring is essential in order to assess the underlying coagulation disorder and to tailor hemostatic treatment. Thromboelastometry (TEM) and thrombelastography (TEG) are promising point-of-care technologies providing rapid information on the initiation process of clot formation, clot quality, and stability of the clot [3].

The primary aims in the treatment of hemorrhagic shock patients are control of ongoing bleeding, restoration of intravascular volume, and early, aggressive therapy of underlying coagulopathy. Experiences mainly derived from military trauma care (**Table 1**) suggest a high fresh frozen plasma (FFP) to red blood cell (RBC) ratio as treatment strategy in major bleeding patients. Such a strategy can be employed in combination with the administration of coagulation factor concentrates if these products are available to physicians. This combined coagulation therapy can be guided by TEM and TEG test results, allowing the optimization of hemostasis in trauma cases on an individualized basis [4]. These strategies focus on the same therapeutic goal: A quick and substantial increase in coagulation factors to fight coagulopathy, to reduce blood loss, and to improve survival.

Table 1. Studies describing the administered ratios of fresh frozen plasma: red blood cell (FFP:RBC) in trauma-related bleeding. This list is not intended to be exhaustive.

Author, year [ref]	Type of study	Country	Patient numbers
Borgman, 2007 [73]	Retrospective chart review	USA (Military)	246
Gunter, 2008 [74]	Retrospective	USA (Civilian)	259
Maegele, 2008 [75]	Retrospective trauma registry	Germany (Civilian)	713
Spinella, 2008 [76]	Retrospective	USA (Military)	708
Teixeira, 2009 [77]	Retrospective trauma registry	USA (Civilian)	383
Zink, 2009 [78]	Retrospective	USA (Civilian)	466
Kashuk, 2008 [79]	Retrospective	USA (Civilian)	133
Sperry, 2008 [80]	Prospective cohort study	USA (Civilian)	415

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Pathophysiology of Coagulopathy in Trauma

In hemorrhagic shock caused by tissue trauma and vascular injury, an "endogenous" anticoagulant pathway is activated [5]. In shock, high amounts of tissue plasminogen activator (tPA) are released from endothelial cells and thrombomodulin is expressed on their surface. Thrombomodulin binds thrombin and subsequently activates the protein C pathway. Protein C together with its cofactor, protein S, slows down the accelerators of the coagulation process by inactivating FVIIIa and FVa. Furthermore, high amounts of protein C consume plasminogen activator inhibitor 1 (PAI-1), the major antagonist of t-PA. As a consequence, overwhelming amounts of t-PA are available, creating a profibrinolytic state [5]. The overall incidence of hyperfibrinolysis is still unclear. Fibrinolysis, according to TEM/TEG test results in two small studies, was observed in 2.5 % and 8.7 %, respectively, of all trauma patients [6, 7]. However, in major trauma the incidence seems to be higher. This is especially true in patients with severe shock who require catecholamines or vasopressin for blood pressure stabilization and are prone to hyperfibrinolysis. In summary, hyperfibrinolysis is more common than previously assumed and associated with a poor outcome [8].

Volume therapy plays an essential role in restoring intravascular fluid deficit. It is undisputed that dilution of the remaining coagulation factors is an inevitable consequence when intravascular volume is restored. Data from the German trauma registry revealed that 34 % of trauma patients suffer from severe coagulopathy on arrival in the emergency room [9]. This is in part related to aggressive pre-hospital volume replacement. Patients from this study received a mean of 2200 ml of fluid, but 50 % of patients received more than 3000 ml [9]. Whereas volume resuscitation using crystalloids may result in dilutional coagulopathy, *in vitro* studies revealed that colloids impair the fibrin polymerization process to an extent which is greater than the dilutional effect alone [10, 11].

Major trauma results in substantial tissue factor (TF) exposure with subsequent early fibrin formation. Consequently, consumption of coagulation factors primarily affects fibrinogen. Fibrinogen is not only the precursor of fibrin but also an important ligand between activated platelets and of paramount importance for the whole coagulation process [12]. In elective surgery, it was demonstrated that fibrinogen was the first coagulation factor reaching critical levels [13]. In severe trauma patients with a mean injury severity score (ISS) of 35, fibrinogen concentration decreased from 1.6 g in the field to 0.95 g on admission to the emergency room [14]. In an observational study (n = 161), Carroll and colleagues reported that 11 % of patients had a fibrinogen concentration of less than 1.0 g on admission to the ER, but contributed 31 % of all fatalities [6]. Since fibrinogen plays a central role in hemostasis it is obvious that a decrease in fibrinogen concentrations results in decreased clot stability and increased bleeding [15].

Hypothermia

Hypothermia is a common problem in trauma victims and correlates with a poor outcome. Wang and collaborators reported data from more than 38,000 trauma patients and found that admission hypothermia was independently associated with an increased odds of death in patients admitted with low core temperature

(odds ratio [OR] 3.03; 95 % confidence interval [CI] 2.62 – 3.51) [16]. An explanation for this finding could be that body temperature of less than 34 °C is associated with increased bleeding. Jurkovic et al. found that mortality of hypothermic patients was significantly higher than those who remained warm. In patients, who arrived in the ER with a core temperature of less than 32 °C 100 % mortality was observed [17]. Hypothermia compromises primary as well as secondary hemostasis and enhances clot lysis. However, these effects are of clinical relevance only at temperatures of less than 34 °C. At temperatures of 33 °C thrombin generation is markedly affected and platelet adhesion is diminished in the range of 33 % of normal [18].

Acidosis

Hypoperfusion and shock are further associated with increased base deficit, lactate concentration and acidosis. Several reports independently revealed that acidosis was related to poor outcome in trauma patients [19]. One reason for this finding is that acidosis affects the activity of coagulation factors, impairs thrombin generation and alters platelet function. Meng et al. showed in an *in vitro* model that the activity of the prothrombinase complex was reduced by approximately 70 % at pH 7.0 compared with pH 7.4 ($p < 0.05$) [20]. Martini reported that acidosis, induced by infusion of 0.2 M HCL accelerated fibrinogen degradation [21]. Platelet aggregation is also enhanced by acidosis [18].

Diagnosis

Due to the complex nature of acute trauma-induced coagulopathy, real time and reliable laboratory testing should be available in order to support a targeted therapeutic approach based on test results. The availability of such a 'theranostic' regime means that rapid diagnostic testing and drug therapy can be combined, with a real time feedback loop improving drug efficiency and minimizing side-effects. Theranostics will reach its full potential when drug discovery and development can be done on an individual basis, providing a truly personalized approach to treatment. The key questions that testing procedures should address when treating trauma victims with severe bleeding are: Why is the patient bleeding? and Is it due to surgical or coagulopathic bleeding?

When trying to answer these questions, the main hindrance is the time taken to receive test results from the clinical laboratories (29 – 295 minutes) [22, 23]. Although no single coagulation test can mirror the whole picture of coagulopathy, the standard coagulation tests, like prothrombin time (PT), activated partial thromboplastin time (aPTT) and fibrinogen plasma concentration, are widely used in the perioperative setting. However, these tests were not developed to assess coagulation in acute bleeding situations [24] and the time needed to conduct these assays is incompatible with the prompt correction of coagulopathy which is required in the trauma setting [22]. Currently, point-of-care devices which are capable of monitoring PT and aPTT (CoaguChek® S and XS) have been employed in the emergency room and operating room (OR) [25]. However, measurements taken using these instruments have been shown to deviate from laboratory testing. The degree to which this variation has tangible clinical impact has

yet to be established [26]. However, irrespective of the need for faster testing procedures, these tests may have limited value for the assessment of coagulopathy and for guidance of hemostatic therapy. *In vivo* coagulation occurs primarily on the surface of platelets and TF-bearing cells [27]. Fibrinogen and platelets are tightly interwoven and RBCs also play a significant role in hemostasis [28]. However, these cells are removed by the centrifugation process. In addition, conventional tests stop with the formation of the first fibrin strands, when only approximately 5 % of thrombin has been generated [29]. These assays only provide information about the beginning of clotting and do not assess the quality and strength of the clot. Furthermore, the influence of (hyper)fibrinolysis on clot stability cannot be evaluated by routine coagulation tests [30]. Preoperative PT and aPTT testing has little predictive value for bleeding, while tests performed intraoperatively and postoperatively are of little value for identifying the cause of bleeding [24]. Obtaining test results, including fibrinogen concentration, is time consuming and of little use for the guidance of emergency hemostatic therapy. Furthermore, Fenger-Eriksen et al. demonstrated that different automated coagulation analyzers revealed significantly different levels of fibrinogen [31]. The presence of colloid plasma expander gave rise to erroneously high levels of fibrinogen recorded by some coagulation analyzers employing the Clauss method, overestimating levels by 80 % and 110 % in cases of 30 % and 50 % dilution, respectively (though in the absence of such confounders this method is reliable) [31, 32].

Taken together, standard coagulation tests do not offer useful information about the nature of the coagulopathy; their prognostic value for a potential bleeding tendency and transfusion of allogeneic blood products is poor. These limitations apply not only to preoperative testing, but also lead to limited usefulness of standard laboratory methods for the intraoperative and intensive care unit (ICU) periods in situations that are complicated by acute bleeding.

In recent years, attention has focused upon viscoelastic methods as point-of-care tests for coagulation in massive blood loss [22, 33]. TEM measures the viscoelastic changes of clot formation in whole blood under low shear conditions. In contrast to standard coagulation tests, TEM/TEG provides information on the rapidity of coagulation initiation, kinetics of clot growth, clot strength and breakdown. ROTEM® (TEM International® GmbH, Munich, Germany) utilizes a newer and improved technique, using a plastic pin supported by a ball bearing, which rotates slowly backwards and forwards through an angle of 4.75°. This method is more stable and less sensitive to shock and vibration. The pin is vertically immersed into a cup containing the blood sample. In contrast, TEG® uses a torsion wire and the cup is rotating.

After re-calcification of the blood sample and addition of an activator, the coagulation process in the test cup starts. Following generation of the first fibrin filaments between the pin and the wall of the test cup, the rotation range of the pin is reduced. The movement of the pin is converted into an optical signal and transferred to a graphical display, which plots the changes in the viscoelastic properties of the clot over time. A set of standard reagents is used to discriminate between several potential causes of bleeding. Two basic tests that use intrinsic activation (INTEM) and extrinsic activation (EXTEM) provide information on the general coagulation status (impaired, normal, and hypercoagulable) through the following parameters: Clotting time (CT), clot formation time (CFT), alpha angle, maximum clot firmness (MCF) and clot lysis (CL) (**Fig. 1**).

In the FIBTEM test (**Fig. 1**), platelets are inhibited by cytochalasin D, therefore this test provides information on the fibrin component of the clot separately. In the APTEM assay, an antifibrinolytic (aprotinin) is added to the EXTEM assay. If this yields an improvement in all parameters (CT, CFT, α-angle, MCF) then this indicates hyperfibrinolysis, before there is any indicative breakdown in EXTEM (**Fig. 2**).

TEM and TEG can be carried out at the patient's bedside. The measurements are performed in whole blood, not in plasma. Also, without the need for centrifu-

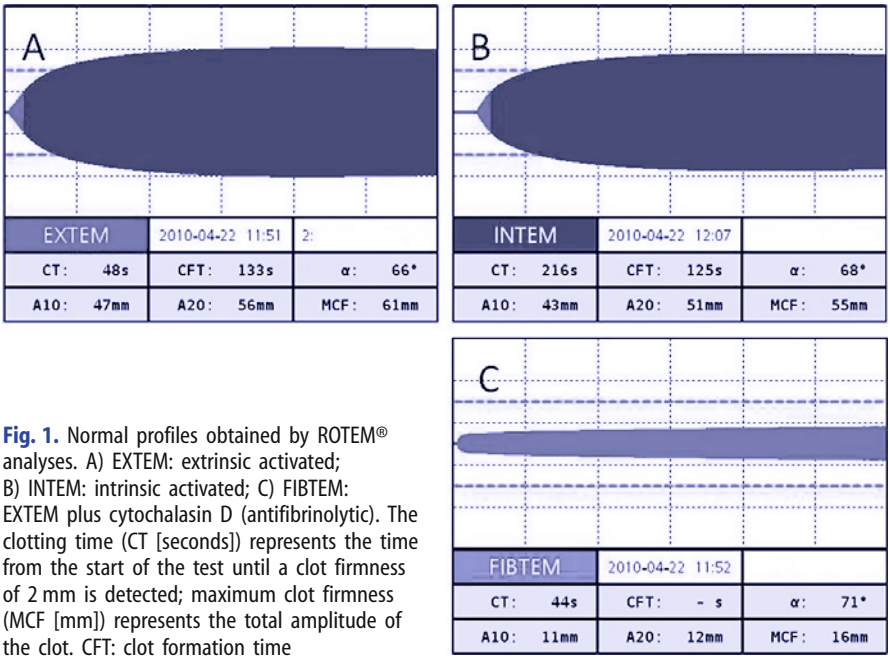

Fig. 1. Normal profiles obtained by ROTEM® analyses. A) EXTEM: extrinsic activated; B) INTEM: intrinsic activated; C) FIBTEM: EXTEM plus cytochalasin D (antifibrinolytic). The clotting time (CT [seconds]) represents the time from the start of the test until a clot firmness of 2 mm is detected; maximum clot firmness (MCF [mm]) represents the total amplitude of the clot. CFT: clot formation time

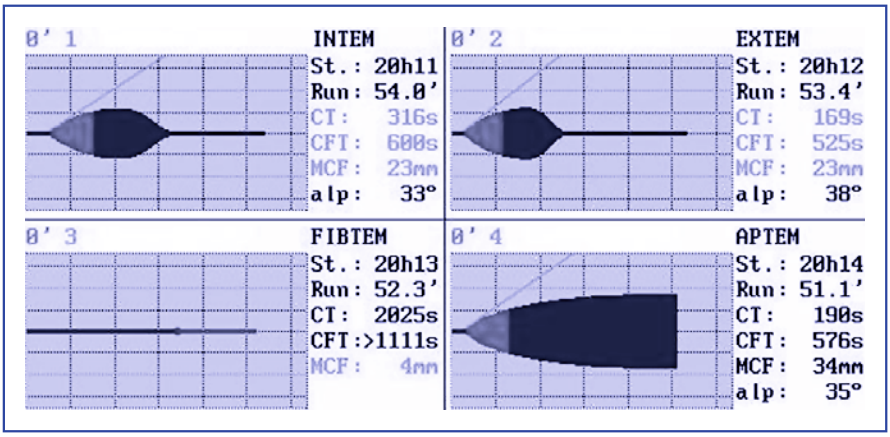

Fig. 2. Hyperfibrinolysis in ROTEM®. Clot breakdown is seen using INTEM and EXTEM, no clot formation is observed in FIBTEM, stable clots are seen in APTEM.

gation, the time taken to receive test results is much shorter (approximately 10 minutes) compared with conventional laboratory testing (mean 88 minutes, 29 – 295 minutes) [23]. Recent data suggest that viscoelastic devices are superior to routine coagulation tests in detecting trauma-induced coagulopathy [3, 33]. Kashuk et al. showed that FFP would have been administered to significantly more patients based on conventional transfusion triggers compared to TEG® test results (61.5 % by international normalized ratio [INR] versus 26.9 % by TEG $p = 0.003$), suggesting that TEG® might be useful in guiding transfusion therapy and reducing FFP transfusion [3].

In a study that included 69 trauma patients, Kaufmann et al. showed that only the ISS and TEG® results were predictive of early transfusion requirements [34]. Plotkin et al. reported that only the maximum amplitude and not standard coagulation tests, like PT and aPTT, was predictive for blood product transfusions [35]. In addition, hyperfibrinolysis may influence the coagulation process in major trauma and is associated with high mortality [8]. The ROTEM remains the only tool for detecting hyperfibrinolysis in acutely bleeding patients, since all laboratory based techniques used to detect hyperfibrinolysis (e.g., euglobulin lysis time [ELT], plasmin-antiplasmin, PAI-1) are complex and too time-consuming [7].

Treatment of Coagulation Disorders

Hypothermia is a common problem in trauma victims and correlates with a significantly worse prognosis [19]. Thus, no efforts should be spared to maintain adequate body temperature. During the initial evaluation phase in the ER the patient should be kept dry and covered. Consequent warming of fluids and blood components prior to infusion is mandatory. Intraoperative use of patient warming devices is strongly recommended [36]. In bleeding patients it is important to fight against the vicious cycle of hypothermia, acidosis and coagulopathy.

The concept of ‘damage-control surgery’ is an accepted and well proven strategy in the treatment of exsanguinating trauma patients and is adopted worldwide. Abdominal packing as well as external fixation of extremity fractures shortens operation time and minimizes exposure of the patient to a cold environment. It has been demonstrated that the concept of ‘damage-control surgery’ reduces the total amount of blood loss and improves survival in major trauma patients [37].

In pre-hospital care, identification of bleeding trauma patients and rapid transport to a definitive care facility is of paramount importance. In the pre-hospital phase, fluid resuscitation should be minimized to what is necessary to maintain adequate vital signs and avoid hypovolemic cardiac arrest. The concept of deliberated hypotension is well accepted although the scientific basis is poor and only very limited data are available in the literature. Fluid resuscitation should preserve vital functions without increasing the risk of further rebleeding. Experimental studies employing an uncontrolled bleeding model revealed improved survival in animals that were fluid resuscitated to low blood pressure thresholds [38]. In a pig study of uncontrolled bleeding, an aortotomy of 2 mm was performed in the infrarenal aorta. With a drop in blood pressure, initial hemorrhage stopped spontaneously. Fluid resuscitation resulted in rebleeding with an increase

in blood pressure (average systolic pressure of 94 ± 3 mmHg) [39]. In one pre-hospital study, restrictive fluid replacement in patients with penetrating trauma resulted in improved outcome [40]. Dutton et al. reported that an intra-operative targeted systolic blood pressure as low as 70 mmHg reduced the time of active bleeding compared with a systolic blood pressure around 100 mmHg (2.4 h vs. 2.9 h, respectively) in severely injured patients. However, mortality rates were comparable in both groups [41]. In summary, the lowest acceptable blood pressure level and how long such a targeted low blood pressure can be tolerated are still unknown. This level is also influenced by pre-existing conditions, like coronary artery disease or stroke, which have to be taken into account.

Coagulation Therapy

Ratio driven 'damage-control resuscitation'

In current clinical practice, FFP is most frequently used to replace lost coagulation factors. However, the appropriate use of FFP continues to be a controversial topic [42]. The 'damage-control resuscitation' concept proposes early and aggressive strategies with a predetermined fixed ratio of blood components for treatment of trauma-induced coagulopathy [43]. Recent studies suggest that use of a ratio driven concept of FFP:RBC in a 1:1 ratio improves survival in severe bleeding in military and civilian trauma (**Table 1**). The results of these studies are conflicting and most of the trials are retrospective.

Recently, Murad et al. published a meta-analysis of 10 observational studies in order to assess the effects of high volume plasma transfusion on outcome and adverse effects in trauma and surgical patients (**Table 2**) [44]. The majority of bleeding patients suffered from penetrating trauma. All except two studies demonstrated improved survival. Five studies demonstrated that a higher ratio of FFP:RBC was associated with increased survival. A dose-response relationship was observed, although the relationship was not linear. A significant reduction in morality was revealed in patients receiving FFP:RBC in ratios greater than 1:3. (OR 0.38; 95 % CI 0.24 – 0.60; $I^2 = 85$ %; p value for Q test = 0.01). However, a dose dependent relationship could not be observed in other studies.

Table 2. Mortality in patients undergoing massive transfusion. (Adapted from [44])

Author, year [ref]	Odds ratio	Lower limit	Upper limit	Plasma (events/total)	Control (events/total)
Borgman, 2007 [73]	0.29	0.16	0.51	31/162	38/84
Cotton, 2009 [81]	0.46	0.28	0.75	54/125	88/141
Holcomb, 2008 [82]	0.58	0.40	0.84	87/252	102/214
Kashuk, 2008 [79]	0.44	0.22	0.88	23/59	44/74
Maegele, 2008 [75]	0.59	0.42	0.81	76/229	222/484
Teixeira, 2009 [77]	0.18	0.12	0.28	58/226	103/157
Scalea, 2006 [48]	1.49	0.63	3.53		
Snyder, 2009 [49]	0.84	0.47	1.50		
Duchesne, 2008 [83]	0.05	0.02	0.13	19/71	56/64
Dente, 2009 [84]	0.12	0.02	0.67	7/50	4/7
	0.38	**0.24**	**0.60**		

Heterogeneity: $p = 0.01$; $I^2 = 85$ %

Limitations of the ratio driven concept

It has been shown that large amounts of FFP are needed in order to sufficiently increase coagulation factor activity [45]. This strategy requires immediate access to large volumes of thawed universal donor FFP. Prior to infusion, FFP has to be thawed, which takes at least 30 minutes. To negate this time delay, pre-thawing of FFP could be carried out. However, this is unfeasible anywhere other than busy trauma centers because of the likely waste and potential overuse that would occur [46]. In the future, lyophilized plasma, immediately available in the ER could solve these logistic problems [47].

Most of the studies addressing an early formula-driven hemostatic resuscitation with different FFP:RBC ratios are retrospective (**Table 1**).

Survivor bias

The evidence for a beneficial effect of ratio driven plasma transfusion on the survival of trauma patients undergoing massive transfusion is of very low quality and at high risk of bias as patients with the highest survival chance were treated with the maximum of resources. Additionally a survivor bias must be considered. Patients with massive, uncontrollable bleeding died before large amounts of FFP could be infused. Therefore, non-survivors received a lower FFP:RBC. In the only prospective study, Scalea et al, reported no survival benefit for higher FFP:RBC ratios when early deaths were excluded [48]. In another study, Snyder et al. [49] calculated regression models to correct survivorship bias. Mortality in the group with high FFP:RBC ratios (> 1:2) was compared with that in the group with low ratios (< 1:2). The high ratio resulted in better survival at 24 hours when a fixed FFP:RBC ratio was given. This survival advantage disappeared when the ratio was treated as a time-dependent variable (relative risk = 0.84, 95 % CI = 0.47 to 1.5) (**Table 2**). These studies highlight a problem regarding how the length of time taken to administer RBC or FFP affects the real ratios of transfused products. It is incumbent upon the scientific community to define a period of time in which it is acceptable to assume a ratio of 1:1 RBC:FFP administration. The authors believe that for units of these products to be considered equal they must be transfused within 30 minutes of each other.

Potential harms

Although the incidences of transfusion-related acute lung injury (TRALI) are typically reported, of more clinical significance is acute lung injury (ALI), which occurs more often in those patients receiving allogeneic products. There is growing evidence that large amounts of FFP transfusion are associated with an increased risk of ALI and acute respiratory distress syndrome (ARDS) [50, 51]. In the meta-analysis by Murad and collaborators, there was a threefold increase in ALI in patients receiving high volume FFP therapy (OR 2.92; 95 % CI 1.99 – 4.29) (**Table 3**) [44]. Chaiwat et al. also reported a dose dependent increase in ARDS following FFP transfusion [50]. Transfusion of more than 5 units of FFP was identified as an independent predictor of ARDS. In critically ill patients, a multivariate analysis revealed that transfusion of FFP was associated with an increase in infectious complications or of infection per unit of FFP transfused (OR 1.039, CI 1.013 – 1.067) [51].

Table 3. Incidence of ALI in patients receiving high volumes of fresh frozen plasma (FFP). Adapted from [44]

Author name, year [ref]	Odds ratio	Lower limit	Upper limit	Plasma (events/total)	Control (events/total)
Leese,1987 [85]	0.78	0.30	2.07	8/99	10/99
Leese, 1991 [86]	0.97	0.22	4.23	4/35	4/34
van der Werff, 1997 [87]	4.30	1.29	14.30		
Martin, 2003 [88]	4.10	1.55	10.85	12/83	7/177
Gajic, 2004 [89]	2.28	1.15	4.54		
Dara, 2005 [90]	5.04	1.26	20.16	8/44	3/71
Khan, 2007 [91]	2.48	1.29	4.75		
	2.32	**1.46**	**3.71**		

Heterogeneity: $p = 0.14$; $I^2 = 38\ \%$

Timing of Coagulation Therapy

A key element in the sufficient treatment of trauma-induced coagulopathy is the early administration of coagulation factors. Snyder et al. reported that the first unit of FFP was administered in trauma patients a mean of 93 min after admission, while the first unit of RBCs was administered after 18 min (mean) [49]. A massive time delay in FFP transfusion was also reported by Riskin and colleagues [53]. These authors reviewed data on trauma patients requiring 10 or more RBC units during the first 24 hours of admission for a period of two years before and after the establishment of a massive transfusion protocol. The FFP:RBC ratios were identical in the two phases (1:1.8 and 1:1.8, $p = 0.97$). Despite the similar FFP:RBC ratios and overall mean numbers of transfusions, mortality decreased from 45 % to 19 % ($p = 0.02$). A significant finding in this study was that the mean time to the administration of the first FFP was decreased from 254 to 169 minutes ($p = 0.04$) in the second part of the study. This study highlighted a significant reduction in mortality despite unchanged FFP:RBC ratios and equivalent overall mean numbers of transfusions, which underscores the importance of timely substitution of coagulation factors. The low volume of clotting factor concentrates offers the benefit of significant time savings when supplementing clotting factors. For example, fibrinogen concentrates are able to provide up to 6 g of fibrinogen in 1 – 2 minutes [54], which would be impossible to achieve using FFP.

Individualized Goal-directed Coagulation Therapy

During the past few years, new insights into the pathophysiology of trauma-induced coagulopathy and the widespread use of viscoelastic coagulation monitoring has boosted the development of alternative treatment strategies. The basic concept of individualized goal-directed coagulation therapy is based on a quick and reliable diagnostic tool for assessment of the patient's current coagulation status. For this approach, point-of-care diagnostic tools like TEM or TEG are essential. Coagulation therapy can be tailored to the actual patients needs according to the test results [55].

The concept of goal-directed coagulation therapy primarily focuses on improvement of clot strength. Data from combat trauma revealed that a low max-

imum amplitude in TEG was predictive for blood product requirements, suggesting that clot quality is an important determinate of bleeding tendency [35]. Fibrinogen, platelets and FXIII are the major components of clot firmness. Thus, fibrinogen concentration appears to be a determining factor to guarantee the quality of blood clots in normal individuals and in trauma patients [56, 57]. Evaluation of fibrinogen should be a cornerstone in all transfusion algorithms, especially if used in patients with excessive bleeding. Regular monitoring of fibrinogen levels is strongly recommended.

The optimal level of fibrinogen that should be administered to trauma patients with life-threatening bleeding is still unknown. Plasma fibrinogen concentrations of less than 1 g/l, which are proposed in older guidelines are considered insufficient to prevent significant blood loss. Current recommendations suggest the critical fibrinogen concentration in the range of 1.5 – 2 g/l [36]. The total amount of fibrinogen administered seems to correlate with outcome. Stinger et al. reported in combat trauma patients receiving massive transfusions, that the amount of fibrinogen (calculated from all blood products) infused correlated with survival. Patients receiving a RBC:fibrinogen ratio > 0.2 g were more likely to survive when compared with the lower ratio groups [58].

Improvement in clot quality

The first step in goal-directed coagulation therapy is to improve clot quality by increasing the fibrinogen concentration. This can be achieved by either administering large volumes of FFP [45] or *via* the infusion of cryoprecipitate or fibrinogen concentrate. Cryoprecipitate is used as a therapeutic option in congenital fibrinogen deficiency; however, it was withdrawn from most European countries some years ago on the basis of safety concerns, though it remains available in the UK and the USA [57]. Fibrinogen concentrate (trade name: RiaSTAP®) is licensed in all European countries and the USA, but only for congenital fibrinogen deficiency. For acquired bleeding, a pasteurized fibrinogen concentrate (trade name: Haemocomplettan P/HS®) is licensed in Austria, Brazil, Bulgaria, Germany, the Czech Republic, Hungary, Kuwait, the Netherlands, Portugal, Romania, Switzerland, Taiwan and Turkey [56]. Recently a triple virus-inactivated fibrinogen concentrate (trade name: Clottafact®) received a national license in France for use in acquired bleeding.

Fibrinogen concentrates are immediately available, contain a defined amount of fibrinogen, and enjoy a favorable safety profile with respect to transmission of infectious diseases or TRALI [59]. In order to increase the fibrinogen concentration by approximately 1 g/l in a patient with a body weight of 70 kg, the administration of approximately 3 g of fibrinogen concentrate is necessary. It is possible to utilize both EXTEM and FIBTEM to monitor improvements in clot quality after fibrinogen concentrate administration (**Fig. 3**), and thus guide dosing. Fibrinogen concentrates have been used with success as standard replacement therapy in major surgery and trauma patients [4, 60, 61]. However, more trials of this kind need to be undertaken to firmly establish treatment protocols in which fibrinogen concentrate is used as primary hemostatic therapy in cases of bleeding trauma patients.

As platelets are important determinates of clot quality and serve as a matrix for coagulation factors, the platelet count in trauma patients should be kept above 50,000/μl [36]. Notably, the platelet count provides no information about possible platelet dysfunction. In trauma patients, recent intake of aspirin and to

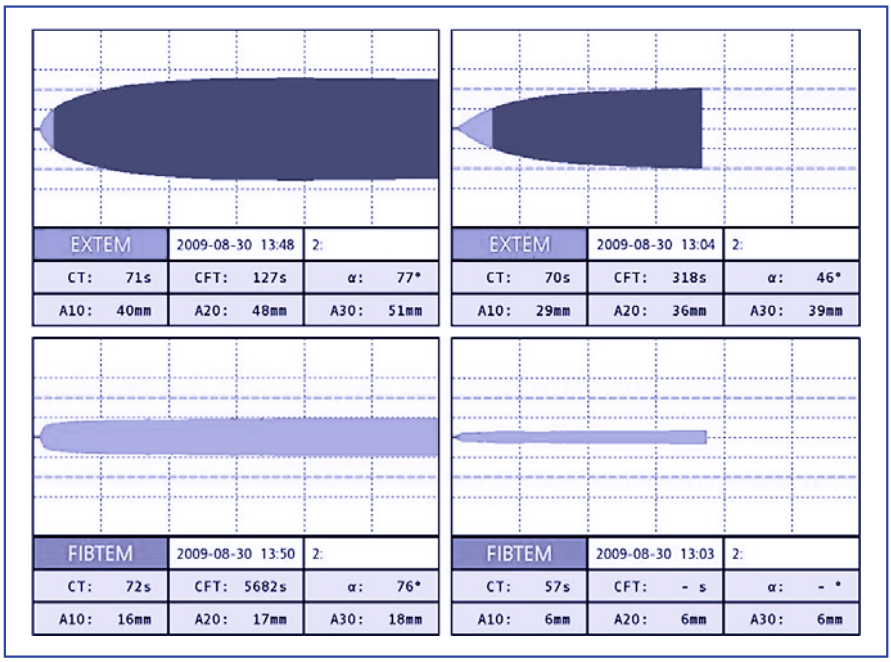

Fig. 3. Increase in maximum clot firmness can be observed using EXTEM and FIBTEM. Measurements recorded before and after the administration of 8 g fibrinogen concentrate are shown.

a greater extent adenosine diphosphate (ADP) receptor antagonists can create severe bleeding tendency. The potential compensatory role of high dose fibrinogen in thrombocytopenia and platelet dysfunction requires further investigation [28, 62, 63].

Improvement of thrombin generation

Measurement of endogenous thrombin potential showed that thrombin generation was markedly increased following trauma, even in patients with prolonged standard coagulation tests [64]. Accordingly thrombin generation *per se* is not an initial problem at the early stage of injury but later on in the course of trauma management [65]. An improvement in thrombin generation can be achieved by administration of FFP, rFVIIa and prothrombin complex concentrates (PCCs). PCC is a virally-inactivated plasma product containing the vitamin K-dependent coagulation factors (II, VII, IX, X), the inhibitor proteins, C, S and Z, and small amounts of antithrombin. To prevent activation of the coagulation factors, most PCCs contain heparin as well. PCCs may be beneficial in patients with massive bleeding who require immediate therapy of the coagulation defect. In situations where prothrombin complex factors are deficient, such as patients receiving vitamin K antagonist therapy, PCCs should be administered in line with current guidelines [66, 67]. The products are well standardized and are licensed in Europe for use in the reversal of vitamin K antagonist therapy, the treatment of acquired bleeding and as prophylactic therapy for perioperative bleeding. Although this broad range of indications can be treated with PCCs, only a small number of

studies have been carried out to establish their efficacy outside of anticoagulation reversal [4, 68, 69]. To date there is no PCC in the USA licensed for vitamin K antagonist reversal; all available PCCs are only 3-factor concentrates and are only indicated for treatment of hemophilia B.

Schöchl et al reported recently that TEM-guided goal-directed coagulation therapy using coagulation factor concentrate (PCC and fibrinogen concentrate) was associated with increased survival rates compared to those predicted by the trauma injury severity score (TRISS 32.4 %) and by the revised injury severity classification (RISC) score of the German trauma registry [4].

Recombinant activated factor VII (rFVIIa) is an analog to the naturally occurring serine protease factor VIIa, which reflects approximately 1 % of the total circulating factor VII usually present in plasma [27]. rFVIIa exerts its function by binding to exposed tissue factor at the site of injury, thus causing a massive increase in thrombin generation. Thrombin production can be further accelerated on the surface of activated platelets by rFVIIa. However, in cases of depleted levels of factor II (FII), such as dilutional coagulopathy, the substrate required for thrombin generation is lacking and a beneficial effect of rFVIIa administration is mitigated. rFVIIa initially requires available FII and subsequently fibrinogen and platelets to stimulate coagulation. rFVIIa is currently licensed for the management of patients with hemophilia A and B who develop inhibitors to exogenously administered factor concentrates, and in some countries for deficiencies of FVII and Glanzmanns thrombasthenia. The results of two randomized controlled trials in bleeding trauma patients treated with rFVIIa are available. In the first study a reduction of 2.6 RBC transfusions was observed when rFVIIa had been administered [70]. In penetrating trauma patients, rFVIIa resulted only in a reduction of 1 RBC transfusion [70]. The second study was terminated after inclusion of 573 of 1502 planned patients because of unexpected low mortality in the placebo group and difficulties in the enrolment of patients [71]. The data collected to this point showed a mortality of 11.0 % (rFVIIa group) versus 10.7 % (placebo group) ($p = 0.93$) in blunt trauma and 18.2 % (rFVIIa group) versus 13.2 % (placebo group) ($p = 0.40$) after penetrating injuries. rFVIIa patients with blunt trauma received a mean of 7.8 ± 10.6 RBC units and 19.0 ± 27.1 total allogeneic units through 48 hours, whereas placebo patients received 9.1 ± 11.3 RBC units ($p = 0.04$) and 23.5 ± 28.0 total allogeneic units ($p = 0.04$). Thrombotic adverse events were similar across study cohorts [71]. In both studies, the cumulative dosage of rFVIIa was high (400 μg/kg)

XIV

Improvement in clot stability

Hyperfibrinolysis contributes to coagulopathy to an unknown degree. According to the studies of Brohi and co-workers, a profibrinolytic state can be triggered by severe tissue trauma and hypovolemic shock [1]. When clot stability is impaired by premature breakdown, antifibrinolytics may be indicated [8]. Data from the recently published Crash-2 trial, where early use of tranexamic acid (1g over 10 min followed by an infusion of 1 g over 8 h) was tested against placebo, a survival benefit of 1.5 % was shown (relative risk 0.91, 95 % CI 0.85 – 0.97, $p = 0.0035$) in the tranexamic acid group. Thromboembolic side effects were similar in both groups. Surprisingly, blood product transfusion was not different between the groups ($p = 0.21$) [72].

Conclusion

Coagulopathy following severe trauma is a common problem and associated with high mortality. TEM/TEG are promising diagnostic tools in the management of severely bleeding patients. The main therapeutic options in the treatment of coagulopathic patients are damage-control-surgery, permissive hypotension in uncontrolled bleeding and consequent maintenance of normal body temperature. Ratio driven resuscitation protocols with a high ratio of FFP:RBC revealed improved survival in military and civilian trauma care. In contrast, goal-directed coagulation therapy focuses on the actual demand of the patient and individualizes coagulation therapy. A modern monitoring device delivering prompt and reliable data about the actual coagulation status of the patient is essential for this approach. Hence, it follows that the most modern therapeutics available, coagulation factor concentrates, would be used predominantly. Fibrinogen is the most vulnerable coagulation factor and should be replaced early in the course of bleeding. An improvement in thrombin generation can be achieved by PCC, FFP and rFVIIa.

In the case of tranexamic acid, a large randomly controlled trial revealed improved survival rates and this drug should be considered as a therapeutic option. No data from large prospective randomized studies are currently available regarding ratio driven standard therapy using FFP and platelet concentrates. Growing evidence suggests that early aggressive supplementation of coagulation factors is crucial. If this is confirmed in future randomly controlled trials, coagulation factor concentrates would be faster and more effective than allogeneic products to increase the coagulation potential and could become the standard for point-of-care-guided, targeted treatment for trauma-induced coagulopathy.

References

1. Brohi K, Cohen MJ, Davenport RA (2007) Acute coagulopathy of trauma: mechanism, identification and effect. Curr Opin Crit Care 13: 680 – 685
2. Sauaia A, Moore FA, Moore EE, et al (1995) Epidemiology of trauma deaths: a reassessment. J Trauma 38: 185 – 193
3. Kashuk JL, Moore EE, Le T, et al (2009) Noncitrated whole blood is optimal for evaluation of postinjury coagulopathy with point-of-care rapid thrombelastography. J Surg Res 156: 133 – 138
4. Schochl H, Nienaber U, Hofer G, et al (2010) Goal-directed coagulation management of major trauma patients using thromboelastometry (ROTEM(R))-guided administration of fibrinogen concentrate and prothrombin complex concentrate. Crit Care 14: R55
5. Brohi K, Cohen MJ, Ganter MT, et al (2007) Acute traumatic coagulopathy: initiated by hypoperfusion: modulated through the protein C pathway? Ann Surg 245: 812 – 818
6. Carroll RC, Craft RM, Langdon RJ, et al (2009) Early evaluation of acute traumatic coagulopathy by thrombelastography. Transl Res 154: 34 – 39
7. Levrat A, Gros A, Rugeri L, et al (2008) Evaluation of rotation thrombelastography for the diagnosis of hyperfibrinolysis in trauma patients. Br J Anaesth 100: 792 – 797
8. Schochl H, Frietsch T, Pavelka M, Jambor C (2009) Hyperfibrinolysis after major trauma: differential diagnosis of lysis patterns and prognostic value of thrombelastometry. J Trauma 67: 125 – 131
9. Maegele M, Lefering R, Yucel N, et al (2007) Early coagulopathy in multiple injury: an analysis from the German Trauma Registry on 8724 patients. Injury 38: 298 – 304
10. Fries D, Innerhofer P, Reif C, et al (2006) The effect of fibrinogen substitution on reversal of dilutional coagulopathy: an in vitro model. Anesth Analg 102: 347 – 351

11. Fenger-Eriksen C, Tonnesen E, Ingerslev J, Sorensen B (2009) Mechanisms of hydroxyethyl starch-induced dilutional coagulopathy. J Thromb Haemost 7: 1099 – 1105
12. Lowe GD, Rumley A, Mackie IJ (2004) Plasma fibrinogen. Ann Clin Biochem 41: 430 – 440
13. Hiippala ST, Myllyla GJ, Vahtera EM (1995) Hemostatic factors and replacement of major blood loss with plasma-poor red cell concentrates. Anesth Analg 81: 360 – 365
14. Lampl L, Seifried E, Tisch M, et al (1992) [Hemostatic disorders following polytrauma-- the role of physiologic coagulation inhibitors during the preclinical phase]. Anasthesiol Intensivmed Notfallmed Schmerzther 27: 31 – 36
15. Fries D, Martini WZ (2010) Role of fibrinogen in trauma-induced coagulopathy. Br J Anaesth 105: 116 – 121
16. Wang HE, Callaway CW, Peitzman AB, Tisherman SA (2005) Admission hypothermia and outcome after major trauma. Crit Care Med 33: 1296 – 1301
17. Jurkovich GJ, Greiser WB, Luterman A, Curreri PW (1987) Hypothermia in trauma victims: an ominous predictor of survival. J Trauma 27: 1019 – 1024
18. Wolberg AS, Meng ZH, Monroe DM, 3rd, Hoffman M (2004) A systematic evaluation of the effect of temperature on coagulation enzyme activity and platelet function. J Trauma 56: 1221 – 1228
19. Cosgriff N, Moore EE, Sauaia A, et al (1997) Predicting life-threatening coagulopathy in the massively transfused trauma patient: hypothermia and acidoses revisited. J Trauma 42: 857 – 861
20. Meng ZH, Wolberg AS, Monroe DM, 3rd, Hoffman M (2003) The effect of temperature and pH on the activity of factor VIIa: implications for the efficacy of high-dose factor VIIa in hypothermic and acidotic patients. J Trauma 55: 886 – 891
21. Martini WZ (2009) Coagulopathy by hypothermia and acidosis: mechanisms of thrombin generation and fibrinogen availability. J Trauma 67: 202 – 208
22. Kashuk JL, Moore EE, Sawyer M, et al (2010) Postinjury coagulopathy management: goal directed resuscitation via POC thrombelastography. Ann Surg 251: 604 – 614
23. Toulon P, Ozier Y, Ankri A, et al (2009) Point-of-care versus central laboratory coagulation testing during haemorrhagic surgery. A multicenter study. Thromb Haemost 101: 394 – 401
24. Dzik WH (2004) Predicting hemorrhage using preoperative coagulation screening assays. Curr Hematol Rep 3: 324 – 330
25. Dempfle CE, Borggrefe M (2008) Point of care coagulation tests in critically ill patients. Semin Thromb Hemost 34: 445 – 450
26. Christensen TD, Larsen TB, Jensen C, Maegaard M, Sorensen B (2009) International normalised ratio (INR) measured on the CoaguChek S and XS compared with the laboratory for determination of precision and accuracy. Thromb Haemost 101: 563 – 569
27. Hoffman M, Monroe DM, 3rd (2001) A cell-based model of hemostasis. Thromb Haemost 85: 958 – 965
28. Lang T, Johanning K, Metzler H, et al (2009) The effects of fibrinogen levels on thromboelastometric variables in the presence of thrombocytopenia. Anesth Analg 108: 751 – 758
29. Mann KG, Brummel K, Butenas S (2003) What is all that thrombin for? J Thromb Haemost 1: 1504 – 1514
30. Luddington RJ (2005) Thrombelastography/thromboelastometry. Clin Lab Haematol 27: 81 – 90
31. Fenger-Eriksen C, Moore GW, Rangarajan S, Ingerslev J, Sorensen B (2010) Fibrinogen estimates are influenced by methods of measurement and hemodilution with colloid plasma expanders. Transfusion 50: 2571 – 2576
32. Adam S, Karger R, Kretschmer V (2010) Photo-optical methods can lead to clinically relevant overestimation of fibrinogen concentration in plasma diluted with hydroxyethyl starch. Clin Appl Thromb Hemost 16: 461 – 471
33. Schochl H, Forster L, Woidke R, Solomon C, Voelckel W (2010) Use of rotation thromboelastometry (ROTEM) to achieve successful treatment of polytrauma with fibrinogen concentrate and prothrombin complex concentrate. Anaesthesia 65: 199 – 203
34. Kaufmann CR, Dwyer KM, Crews JD, Dols SJ, Trask AL (1997) Usefulness of thrombelastography in assessment of trauma patient coagulation. J Trauma 42: 716 – 720

35. Plotkin AJ, Wade CE, Jenkins DH, et al (2008) A reduction in clot formation rate and strength assessed by thrombelastography is indicative of transfusion requirements in patients with penetrating injuries. J Trauma 64: S64 – 68
36. Rossaint R, Bouillon B, Cerny V, et al (2010) Management of bleeding following major trauma: an updated European guideline. Crit Care 14: R52
37. Higa G, Friese R, O'Keeffe T, et al (2010) Damage control laparotomy: a vital tool once overused. J Trauma 69: 53 – 59
38. Kowalenko T, Stern S, Dronen S, Wang X (1992) Improved outcome with hypotensive resuscitation of uncontrolled hemorrhagic shock in a swine model. J Trauma 33: 349 – 353
39. Sondeen JL, Coppes VG, Holcomb JB (2003) Blood pressure at which rebleeding occurs after resuscitation in swine with aortic injury. J Trauma 54: S110 – 117
40. Bickell WH, Wall MJ, Jr., Pepe PE, et al (1994) Immediate versus delayed fluid resuscitation for hypotensive patients with penetrating torso injuries. N Engl J Med 331: 1105 – 1109
41. Dutton RP, Mackenzie CF, Scalea TM (2002) Hypotensive resuscitation during active hemorrhage: impact on in-hospital mortality. J Trauma 52: 1141 – 1146
42. Nascimento B, Callum J, Rubenfeld G, et al (2010) Clinical review: Fresh frozen plasma in massive bleedings – more questions than answers. Crit Care 14: 202
43. Holcomb JB (2007) Damage control resuscitation. J Trauma 62: S36 – 37
44. Murad MH, Stubbs JR, Gandhi MJ, et al (2010) The effect of plasma transfusion on morbidity and mortality: a systematic review and meta-analysis. Transfusion 50: 1370 – 1383
45. Chowdhury P, Saayman AG, Paulus U, Findlay GP, Collins PW (2004) Efficacy of standard dose and 30 ml/kg fresh frozen plasma in correcting laboratory parameters of haemostasis in critically ill patients. Br J Haematol 125: 69 – 73
46. Shander A, Hofmann A, Ozawa S, et al (2010) Activity-based costs of blood transfusions in surgical patients at four hospitals. Transfusion 50: 753 – 765
47. Shuja F, Shults C, Duggan M, et al (2008) Development and testing of freeze-dried plasma for the treatment of trauma-associated coagulopathy. J Trauma 65: 975 – 985
48. Scalea TM, Bochicchio KM, Lumpkins K, et al (2008) Early aggressive use of fresh frozen plasma does not improve outcome in critically injured trauma patients. Ann Surg 248: 578 – 584
49. Snyder CW, Weinberg JA, McGwin G Jr, et al (2009) The relationship of blood product ratio to mortality: survival benefit or survival bias? J Trauma 66: 358 – 362
50. Chaiwat O, Lang JD, Vavilala MS, et al (2009) Early packed red blood cell transfusion and acute respiratory distress syndrome after trauma. Anesthesiology 110: 351 – 360
51. Watson GA, Sperry JL, Rosengart MR, et al (2009) Fresh frozen plasma is independently associated with a higher risk of multiple organ failure and acute respiratory distress syndrome. J Trauma 67: 221 – 227
52. Sarani B, Dunkman WJ, Dean L, et al (2008) Transfusion of fresh frozen plasma in critically ill surgical patients is associated with an increased risk of infection. Crit Care Med 36: 1114 – 1118
53. Riskin DJ, Tsai TC, Riskin L, et al (2009) Massive transfusion protocols: the role of aggressive resuscitation versus product ratio in mortality reduction. J Am Coll Surg 209: 198 – 205
54. Solomon C, Pichlmaier U, Schoechl H, et al (2010) Recovery of fibrinogen after administration of fibrinogen concentrate to patients with severe bleeding after cardiopulmonary bypass surgery. Br J Anaesth 104: 555 – 562
55. Brenni M, Worn M, Bruesch M, Spahn DR, Ganter MT (2010) Successful rotational thromboelastometry-guided treatment of traumatic haemorrhage, hyperfibrinolysis and coagulopathy. Acta Anaesthesiol Scand 54: 111 – 117
56. Fenger-Eriksen C, Ingerslev J, Sorensen B (2009) Fibrinogen concentrate--a potential universal hemostatic agent. Expert Opin Biol Ther 9: 1325 – 1333
57. Sorensen B, Bevan D (2010) A critical evaluation of cryoprecipitate for replacement of fibrinogen. Br J Haematol 149: 834 – 843
58. Stinger HK, Spinella PC, Perkins JG, et al (2008) The ratio of fibrinogen to red cells transfused affects survival in casualties receiving massive transfusions at an army combat support hospital. J Trauma 64: S79 – 85

59. Dickneite G, Pragst I, Joch C, Bergman GE (2009) Animal model and clinical evidence indicating low thrombogenic potential of fibrinogen concentrate (Haemocomplettan P). Blood Coagul Fibrinolysis 20: 535 – 540
60. Fenger-Eriksen C, Jensen TM, Kristensen BS, et al (2009) Fibrinogen substitution improves whole blood clot firmness after dilution with hydroxyethyl starch in bleeding patients undergoing radical cystectomy: a randomized, placebo-controlled clinical trial. J Thromb Haemost 7: 795 – 802
61. Karlsson M, Ternstrom L, Hyllner M, et al (2009) Prophylactic fibrinogen infusion reduces bleeding after coronary artery bypass surgery. A prospective randomised pilot study. Thromb Haemost 102: 137 – 144
62. Schochl H, Posch A, Hanke A, Voelckel W, Solomon C (2010) High-dose fibrinogen concentrate for haemostatic therapy of a major trauma patient with recent clopidogrel and aspirin intake. Scand J Clin Lab Invest 70: 453 – 457
63. Velik-Salchner C, Haas T, Innerhofer P, et al (2007) The effect of fibrinogen concentrate on thrombocytopenia. J Thromb Haemost 5: 1019 – 1025
64. Dunbar NM, Chandler WL (2009) Thrombin generation in trauma patients. Transfusion 49: 2652 – 2660
65. Schreiber MA, Differding J, Thorborg P, Mayberry JC, Mullins RJ (2005) Hypercoagulability is most prevalent early after injury and in female patients. J Trauma 58: 475 – 480
66. Baglin TP, Keeling DM, Watson HG (2006) Guidelines on oral anticoagulation (warfarin): third edition – 2005 update. Br J Haematol 132: 277 – 285
67. Hirsh J, Guyatt G, Albers G, Harrington R, Schunemann H (2008) Antithrombotic and Thrombolytic Therapy. American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 133: 110S–112S
68. Bruce D, Nokes TJ (2008) Prothrombin complex concentrate (Beriplex P/N) in severe bleeding: experience in a large tertiary hospital. Crit Care 12: R105
69. Schick KS, Fertmann JM, Jauch KW, Hoffmann JN (2009) Prothrombin complex concentrate in surgical patients: retrospective evaluation of vitamin K antagonist reversal and treatment of severe bleeding. Crit Care 13: R191
70. Boffard KD, Riou B, Warren B, et al (2005) Recombinant factor VIIa as adjunctive therapy for bleeding control in severely injured trauma patients: two parallel randomized, placebo-controlled, double-blind clinical trials. J Trauma 59: 8 – 15
71. Hauser CJ, Boffard K, Dutton R, et al (2010) Results of the CONTROL trial: efficacy and safety of recombinant activated Factor VII in the management of refractory traumatic hemorrhage. J Trauma 69: 489 – 500
72. Shakur H, Roberts I, Bautista R, et al (2010) Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. Lancet 376: 23 – 32
73. Borgman MA, Spinella PC, Perkins JG, et al (2007) The ratio of blood products transfused affects mortality in patients receiving massive transfusions at a combat support hospital. J Trauma 63: 805 – 813
74. Gunter OL, Jr., Au BK, Isbell JM, et al (2008) Optimizing outcomes in damage control resuscitation: identifying blood product ratios associated with improved survival. J Trauma 65: 527 – 534
75. Maegele M, Lefering R, Paffrath T, et al (2008) Red-blood-cell to plasma ratios transfused during massive transfusion are associated with mortality in severe multiple injury: a retrospective analysis from the Trauma Registry of the Deutsche Gesellschaft für Unfallchirurgie. Vox Sang 95: 112 – 119
76. Spinella PC, Perkins JG, Grathwohl KW, et al (2008) Effect of plasma and red blood cell transfusions on survival in patients with combat related traumatic injuries. J Trauma 64: S69 – 77
77. Teixeira PG, Inaba K, Shulman I, et al (2009) Impact of plasma transfusion in massively transfused trauma patients. J Trauma 66: 693 – 697
78. Zink KA, Sambasivan CN, Holcomb JB, Chisholm G, Schreiber MA (2009) A high ratio of plasma and platelets to packed red blood cells in the first 6 hours of massive transfusion improves outcomes in a large multicenter study. Am J Surg 197: 565 – 570

79. Kashuk JL, Moore EE, Johnson JL, et al (2008) Postinjury life threatening coagulopathy: is 1:1 fresh frozen plasma:packed red blood cells the answer? J Trauma 65: 261 – 270
80. Sperry JL, Ochoa JB, Gunn SR, et al (2008) An FFP:PRBC transfusion ratio >/=1:1.5 is associated with a lower risk of mortality after massive transfusion. J Trauma 65: 986 – 993
81. Cotton BA, Au BK, Nunez TC, et al (2009) Predefined massive transfusion protocols are associated with a reduction in organ failure and postinjury complications. J Trauma 66: 41 – 48
82. Holcomb JB, Wade CE, Michalek JE, et al (2008) Increased plasma and platelet to red blood cell ratios improves outcome in 466 massively transfused civilian trauma patients. Ann Surg 248: 447 – 458
83. Duchesne JC, Hunt JP, Wahl G, et al (2008) Review of current blood transfusions strategies in a mature level I trauma center: were we wrong for the last 60 years? J Trauma 65: 272 – 276
84. Dente CJ, Shaz BH, Nicholas JM, et al (2009) Improvements in early mortality and coagulopathy are sustained better in patients with blunt trauma after institution of a massive transfusion protocol in a civilian level I trauma center. J Trauma 66: 1616 – 1624
85. Leese T, Holliday M, Heath D, Hall AW, Bell PR (1987) Multicentre clinical trial of low volume fresh frozen plasma therapy in acute pancreatitis. Br J Surg 74: 907 – 911
86. Leese T, Holliday M, Watkins M, et al (1991) A multicentre controlled clinical trial of high-volume fresh frozen plasma therapy in prognostically severe acute pancreatitis. Ann R Coll Surg Engl 73: 207 – 214
87. van der Werff YD, van der Houwen HK, Heijmans PJ, et al (1997) Postpneumonectomy pulmonary edema. A retrospective analysis of incidence and possible risk factors. Chest 111: 1278 – 1284
88. Martin RC, 2nd, Jarnagin WR, Fong Y, et al (2003) The use of fresh frozen plasma after major hepatic resection for colorectal metastasis: is there a standard for transfusion? J Am Coll Surg 196: 402 – 409
89. Gajic O, Rana R, Mendez JL, et al (2004) Acute lung injury after blood transfusion in mechanically ventilated patients. Transfusion 44: 1468 – 1474
90. Dara SI, Rana R, Afessa B, Moore SB, Gajic O (2005) Fresh frozen plasma transfusion in critically ill medical patients with coagulopathy. Crit Care Med 33: 2667 – 2671
91. Khan H, Belsher J, Yilmaz M, et al (2007) Fresh-frozen plasma and platelet transfusions are associated with development of acute lung injury in critically ill medical patients. Chest 131: 1308 – 1314

XV Neurological Aspects

Understanding Posterior Reversible Encephalopathy Syndrome

S. Legriel, F. Pico, and E. Azoulay

Introduction

Posterior reversible encephalopathy syndrome (PRES) [1, 2] is a clinicoradiological entity that was well described by Hinchey et al. [3] in 1996 based on 15 cases, shortly after two other small case-series were published [4, 5]. This condition has been designated by a variety of names (reversible posterior leukoencephalopathy syndrome, reversible posterior cerebral edema syndrome, and reversible occipital parietal encephalopathy). PRES is now the accepted term [1, 2, 6] but has been challenged recently based on the risk of neurological impairment and up to 15 % mortality rate [7, 8]. PRES is characterized by variable associations of seizure activity, consciousness impairment, headaches, visual abnormalities, nausea/vomiting, and focal neurological signs. The cerebral imaging abnormalities are often symmetric and predominate in the posterior white matter (**Fig. 1**). Recognition of PRES has evolved with increasing availability of magnetic resonance imaging (MRI).

PRES can develop in association with a vast array of conditions. However, regardless of the underlying cause, the main abnormality is cerebral vasogenic edema, the pathogenesis of which is still under debate [1, 2]. PRES is typically reversible once the cause is removed. However, patients with severe manifestations of PRES, such as coma and/or status epilepticus, may require admission to the intensive care unit (ICU) [9, 10]. Moreover, permanent neurological impairment or death occurs in a minority of patients [5, 7, 8].

The objective of this chapter is to provide clinicians with guidance for diagnosing and treating patients with PRES. The diagnostic criteria are described in detail and management recommendations are given with an algorithm.

Epidemiology

The global incidence of PRES is unknown. The only epidemiological data come from retrospective studies of patients seen between 1988 and 2008 [3, 6–8, 10–13]. PRES has been reported in patients aged 4 to 90 years, although most cases occur in young to middle-aged adults, the mean age ranging across case-series from 39 to 47 years. There is a marked female predominance that may reflect some of the causes. Many patients with PRES have comorbidities, which may be severe conditions, such as bone marrow or solid organ transplantation, chronic renal failure, and chronic hypertension.

Mechanical ventilation is required in 35 % to 40 % of patients with PRES, for 3 to 7 days [7, 8]. Status epilepticus may require ICU admission [10]. No epidemi-

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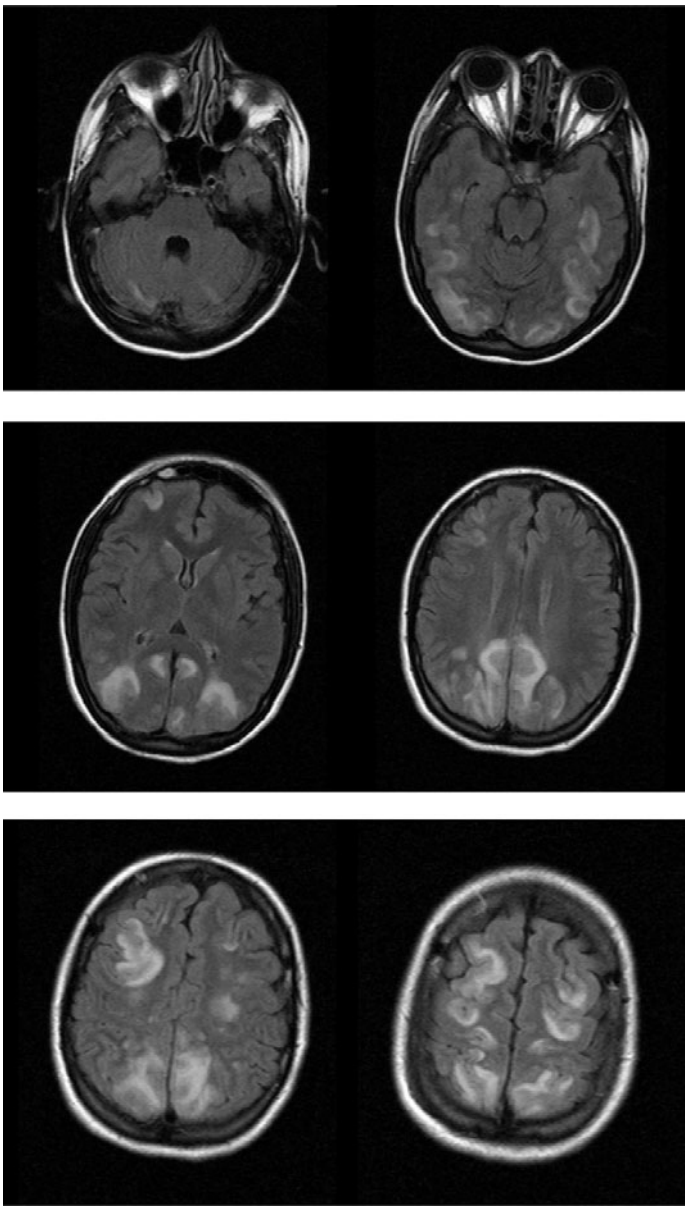

Fig. 1. Cerebral magnetic resonance imaging in a patient with posterior reversible encephalopathy syndrome (PRES). Fluid-attenuated inversion recovery (FLAIR) sequence showing bilateral high-signal foci in the cerebellum, basal ganglia, and occipital, parietal, frontal, and temporal lobes

ological data are available on the subgroup of patients with PRES requiring ICU admission. Mean hospital length of stay was 20 days [7, 8].

Diagnosis

PRES is a clinicoradiological entity. The intensity and severity of clinical manifestations vary and may require ICU admission. Imaging findings also vary in severity. Thorough familiarity with the imaging criteria is crucial to the diagnosis. The combination of suggestive clinical manifestations and radiological criteria establishes the diagnosis of PRES. In doubtful cases, the clinical and radiological improvement that occurs once appropriate treatment is given confirms the diagnosis. Nevertheless, there are no consensual guidelines to validate diagnosis of PRES.

Clinical Manifestations of PRES

Typical presenting manifestations

The typical features of PRES consist of consciousness impairment, seizure activity, headaches, visual abnormalities, nausea/vomiting, and focal neurological signs (**Table 1**). Consciousness impairment may range in severity from confusion, somnolence, and lethargy to encephalopathy or coma. Consciousness impairment has been reported in 13 % [14] to 90 % [8] of cases. Seizure activity occurs in up to 92 % of cases [7]. The seizures are rarely isolated (23 %-28 %) [7, 8]. Secondary generalized seizures are common (53 – 62 %) [3, 8]. Status epilepticus, defined as

Table 1. Topographic distribution of clinical and radiological features in cohort studies of posterior reversible encephalopathy syndrome (PRES)

	Hinchey 1996 [3] n = 15	Casey 2000 [6] n = 16	Bartynski 2007 [11] n = 136	McKinney 2007[14] n = 76	Lee 2008 [7] n = 36	Burnett 2010 [8] n = 79
Clinical Features of PRES						
Consciousness impairment	10 (67 %)	NR	39 (26 %)	10 (13 %)	34 (94 %)	76 (90 %)
Seizure activity	11 (73 %)	NR	97 (71 %)	58 (76 %)	33 (92 %)	56 (70 %)
Headaches	8 (53 %)	NR	39 (26 %)	3 (4 %)	19 (53 %)	26 (31 %)
Visual abnormalities	10 (67 %)	NR	39 (26 %)	3 (4 %)	13 (36 %)	24 (29 %)
Nausea/vomiting	8 (53 %)	NR	39 (26 %)	NR	NR	NR
Focal neurological signs	NR	NR	NR	2 (3 %)	1 (3 %)	14 (17 %)
Acute hypertension	12 (80 %)	NR	91 (67 %)	NR	NR	62 (78 %)
Radiological Features of PRES						
Bilateral	15 (100 %)	11 (69 %)	> 98 (> 72 %)	NR	36 (100 %)	NR
Asymmetric	10 (67 %)	NR	21 (15 %)	2 (3 %)	NR	NR
Confluent	NR	2 (13 %)	31 (23 %)	44 (58 %)	2 (13 %)	12 (16 %)
Gray matter	4 (27 %)	NR	NR	22 (29 %)	16 (44 %)	NR
Posterior > anterior	14 (93 %)	15 (94 %)	30 (22 %)	NR	NR	NR
Occipital	14 (93 %)	NR	134 (99 %)	75 (99 %)	NR	NR
Parietal	13 (87 %)	8 (50 %)	134 (99 %)	75 (99 %)	NR	50 (67 %)
Frontal	7 (47 %)	14 (88 %)	93 (68 %)	60 (89 %)	22 (61 %)	61 (81 %)
Temporal	9 (60 %)	16 (100 %)	55 (40 %)	52 (68 %)	NR	62 (83 %)
Brainstem	2 (13 %)	NR	17 (13 %)	14 (18 %)	21 (58 %)	NR
Cerebellum	1 (7 %)	NR	41 (30 %)	26 (34 %)	21 (58 %)	NR
Basal ganglia	1 (7 %)	3 (19 %)	19 (14 %)	9 (12 %)	NR	NR

NR: None reported

ongoing continuous seizure activity for at least 5 minutes (continuous) or as more than two motor seizures without full recovery of consciousness in the interval (intermittent), has been described in 3 % [7] to 13 % [10] of patients. Visual abnormalities were found in 26 % [11] to 67 % [3] of patients and consisted of blurred vision (7 % [3]-18 % [8]), visual neglect (4 % [8]-27 % [3]), homonymous hemianopsia (4 % [8]-20 % [3]), visual hallucinations (3 % [7]-5 % [8]), and cortical blindness (8 % [8]-33 % [3]). Headaches and nausea/vomiting were reported in 26 % [11] to 53 % [3] of patients. Focal neurological signs were either not mentioned at all or reported in only 3 % [7, 14] to 17 % [8] of cases.

A frequently associated sign: Acute hypertension
Acute hypertension is not usually described among the main signs of PRES. However, hypertension has been reported in most studies [3–5, 7, 8, 11, 12], in 67 % [11] to 80 % [3] of patients. In one study, mean systolic blood pressure reached 187 (80–240) mm Hg [7]. It is worth noting that mean blood pressure defined as [systolic blood pressure +2(diastolic blood pressure)/3] reflects cerebral autoregulation of blood flow. Acute hypertensive emergency was not significantly associated with the intensity of the clinical or radiological manifestations of PRES [11]. Therefore, high mean blood pressure is often observed in PRES but its level is not correlated to the severity of PRES.

Radiological Characteristics of PRES

The topographic distribution of radiological features reported in cohort studies is given in **Table 1** [3, 6–8, 11, 14].

The four radiological patterns of PRES [11]
Until recently, PRES was believed to consistently produce bilateral and symmetric regions of edema typically located in the white matter and predominating in the posterior parietal and occipital lobes. Occasionally, edema has been described in the frontal lobes, temporal, basal ganglia or cerebellum and brainstem in the posterior fossa, and cortical gray matter.

In a study of 136 patients, however, this pattern was found in only 26 % of cases [11]: Three radiological patterns were found in 99 patients, and incomplete forms of these three patterns in the remaining 37 patients (**Fig. 2**):

a. Holohemispheric watershed pattern (23 %) (Fig. 2a)
A swath of confluent vasogenic edema extends through the frontal, parietal, and occipital lobes. Involvement of the temporal lobes is less marked. This topography matches the watershed zone between the anterior and posterior cerebral arteries, on the one hand, and the middle cerebral artery, on the other.

b. Superior frontal sulcus pattern (27 %) (Figure 2b)
Patchy edema predominates in the frontal lobes along the superior frontal sulci. The parietal and occipital lobes are variably involved.

c. Dominant parietal-occipital pattern (22 %) (Fig. 2c)
In this pattern previously thought to be typical of PRES, the posterior part of the parietal and occipital lobes is predominantly involved. The edema varies in severity from mild to extensive.

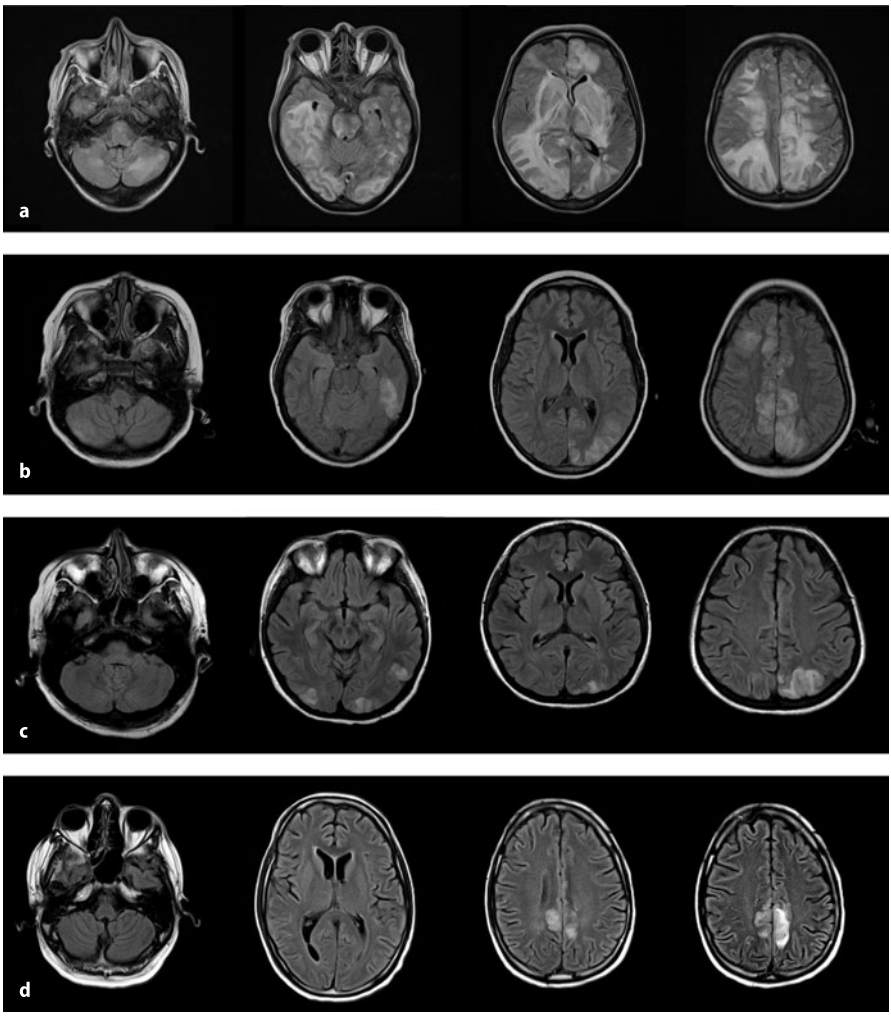

Fig. 2. Four main magnetic resonance imaging patterns of posterior reversible encephalopathy syndrome (PRES).
2a. Holohemispheric watershed pattern. Fluid-attenuated inversion recovery (FLAIR) sequences showing bilateral vasogenic edema in a linear pattern involving the white matter of the cerebellum, brainstem, and occipital, parietal, frontal, and temporal lobes. This pattern was found in 23 % of patients.
2b. Superior frontal sulcus pattern. Fluid-attenuated inversion recovery (FLAIR) sequences showing bilateral vasogenic edema in a non-confluent pattern involving the frontal sulcus area and, to a lesser degree, the white matter of the parietal, occipital, and temporal lobes. This pattern was found in 27 % of patients.
2c. Dominant parietal-occipital pattern. Fluid-attenuated inversion recovery (FLAIR) sequences showing bilateral vasogenic edema in the white matter of the occipital and parietal lobes. This so-called 'classic' pattern was found in 22 % of patients.
2d. Partial expression of the three primary patterns. Fluid-attenuated inversion recovery (FLAIR) sequences showing bilateral vasogenic edema in the white matter of the parietal and frontal lobes but not in the occipital lobes. This pattern can also be asymmetric. Partial and/or asymmetric forms of the three primary patterns were found in 28 % of patients.

d. Partial or asymmetric expression of the primary patterns (28 %) (Fig. 2d)
The partial form is defined as bilateral absence of edema in either the parietal or the occipital lobes. The frontal lobes are often involved. The asymmetric form is characterized by unilateral absence of edema in either a parietal or an occipital lobe. Finally, in the partial and asymmetric form, there is both absence of involvement of either the parietal or the occipital lobes and asymmetric abnormalities in the affected parietal or occipital lobes.

Roles for computed tomography and magnetic resonance imaging in the diagnosis of PRES

- Computed tomography (CT): In retrospective reviews, CT scans were available for review in 65 % [11] to 100 % [7] of cases. CT findings are often normal or nonspecific [11]. Hypodensities in a suggestive topographic distribution suggest PRES (Fig. 3).
- MRI: Cerebral MRI is the key investigation for the diagnosis of PRES. Proton-density and T2-weighted images show regions of high signal indicating edema. Fluid-attenuated inversion recovery (FLAIR) sequences also visualize the lesions. The use of FLAIR has been shown to improve the diagnosis of PRES and the detection of subcortical and cortical lesions in PRES [6]. T1-weighted images show low-intensity foci. Diffusion-weighted imaging (DWI) is normal but the apparent diffusion coefficient is increased [13]. Finally, enhancement is seen in about half the cases [11].

MRI is superior to CT for the diagnosis of PRES. Of 67 patients who had both CT and MRI at least 2 days after the clinical onset of PRES [11], 22 had both investigations on the same day and of these, only 7 (32 %) had contributive CT findings. Interestingly, the proportion of patients with contributive CT findings was 74 % on day 2, suggesting that repeated CT scanning may be helpful when MRI is unavailable. MRI has been performed in 84 % [11] to 100 % [7] of patients with PRES and both MRI and CT in 49 % [11] to 87 % [6].

Complications diagnosed radiologically at presentation of PRES

- Cerebral ischemia: Cerebral infarction is seen as high DWI signal intensity with a decrease in the apparent diffusion coefficient below 20 %. Cerebral infarction is among the early signs of non-reversible damage associated with adverse outcomes [13]. This complication was present at the acute phase of PRES in 9 (10 %) of the 82 patients with available DWI in one study [11] and in 5 (23 %) of 22 patients in another [13]. In this setting, every effort must be taken to exclude a reversible cerebral vasoconstriction syndrome defined as at least two narrowings per artery on two different cerebral arteries at brain magnetic resonance angiography (MRA) or at conventional angiography [15]. Ducros et al. reported a 9 % incidence of PRES in reversible cerebral vasoconstriction syndrome [15].
- Cerebral hemorrhage: Cerebral hemorrhage is uncommon in PRES (5 % [7] to 17 % [14] of patients). Reported cases were about evenly distributed in three categories, parenchymal hematoma, subarachnoid hemorrhage, and focal intraparenchymal hemorrhage measuring less than 5 mm in diameter [14, 16]. Cerebral hemorrhage may be more common among patients with allogeneic bone marrow transplantation or anticoagulant treatment, whereas

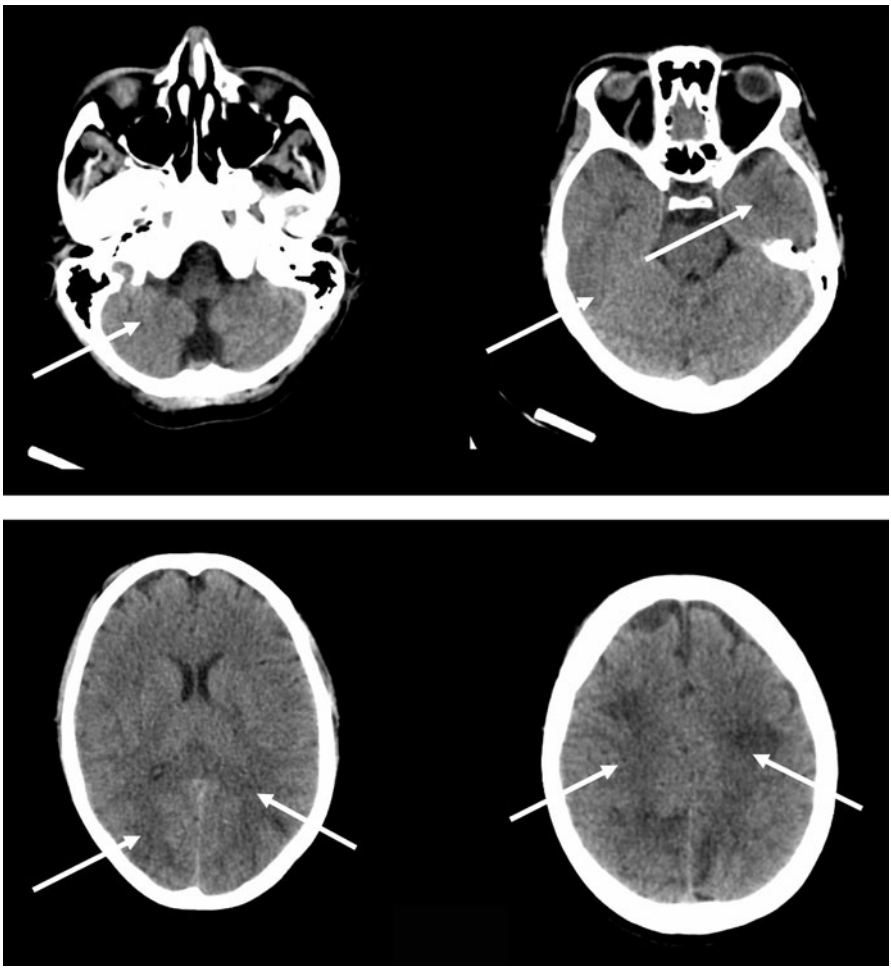

Fig. 3. Cerebral computed tomography in a patient with occipital, parietal, frontal, and temporal abnormalities suggesting posterior reversible encephalopathy syndrome (PRES). Several low-density areas are visible in the occipital, parietal, frontal and temporal lobes (white arrows).

blood pressure levels may have no influence on the bleeding risk [16]. A statistically significant association has been reported between edema severity on FLAIR sequences and bleeding risk [14].

In the presence of cerebral or subarachnoid hemorrhage, vascular imaging must rule out cerebral aneurysm and reversible cerebral vasoconstriction syndrome.

- Cerebral herniation: Posterior edema, particularly when located in the cerebellum and brainstem, may cause transtentorial cerebral herniation [17].

Retrospective Diagnosis of PRES after Regression of the Initial Clinical and Radiological Abnormalities

In some cases, the diagnosis of PRES remains in doubt. In this situation, regression of the clinical and radiological abnormalities with appropriate treatment supports the diagnosis. Thus, repeated brain imaging is helpful.

Differential Diagnosis

The non-specific clinical manifestations and multiplicity of radiological patterns raise diagnostic challenges. Many conditions may resemble PRES, including ictal or post-ictal state (with or without status epilepticus), progressive multifocal leukoencephalopathy (PML), severe leukoaraiosis, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), infectious encephalitis, acute disseminated encephalomyelitis, mitochondrial myopathy encephalopathy lactacidosis and stroke-like episodes syndrome (MELAS), vasculitis, Creutzfeld-Jakob disease, cerebral venous sinus thrombosis, and ischemic stroke (watershed or posterior cerebral artery territory) [18, 19]. The MRI characteristics of these conditions are reported in **Table 2**.

Pathophysiology

The pathophysiology of PRES remains controversial. The two main hypotheses contradict each other. One involves impaired cerebral autoregulation responsible for an increase in cerebral blood flow (CBF), whereas the other involves endothelial dysfunction with cerebral hypoperfusion. This hypoperfusion hypothesis may be most relevant to cases of PRES associated with cytotoxic therapy. Under both hypotheses, the result of the cerebral blood perfusion abnormalities is blood-brain barrier dysfunction with cerebral vasogenic edema [2] (**Fig. 4**).

Cerebral Hyperperfusion Results in Vasogenic Edema by Exceeding the Capacity for Autoregulation of Perfusion Pressure

When mean arterial blood pressure (MAP) is within the 60–120 mmHg range, cerebral autoregulation via variations in vasoconstriction and vasodilatation keeps the CBF at about 50 ml/100 g/min in healthy individuals. To overcome this autoregulation mechanism, MAP must exceed 170 mmHg (systolic/diastolic blood pressure of 220/110 mmHg). However, a smaller MAP increase of only 50 mm Hg (systolic/diastolic blood pressure of 160/100 mmHg) in a patient with *de novo* hypertension is sufficient to trigger severe vasoconstriction [31].

Cerebral hyperperfusion leads to the release of the vasodilators nitric oxide (NO) and prostacyclin under the influence of endothelial agonists such as acetylcholine, norepinephrine, and substance P. Concomitantly, there is overproduction of catecholamines, vasopressin, thromboxane, and endothelin 1. These substances increase vasoreactivity and activate the renin-angiotensin-aldosterone system. Angiotensin II activates the gene expression of pro-inflammatory cytokines such as interleukin (IL)-6 and the transcription of nuclear factor-kappa B (NF-κB), leading to direct cytotoxic effects on the blood vessel wall. This damage to the

Table 2. Differential diagnosis of cerebral magnetic resonance imaging (MRI) findings in patients with white matter abnormalities mimicking posterior reversible encephalopathy syndrome (PRES)

	T1	T2	FLAIR	DWI	ADC	Gd	GMD/WMD	Other characteristics
PRES [1–5, 11]	↓	↑	↑	↑ or →	↓ or →	0 or +	WMD >>> GMD	Typically bilateral and symmetric, located in the white matter of the posterior parietal-occipital lobes; but also involves the frontal lobes, temporal posterior fossa, or brainstem
Ictal/Post-ictal state [20]	↓	↑	↑	↑	↓	+	GMD >>> WMD	Theoretically, complete resolution of MRI changes in the area involved in the seizure activity
Progressive multifocal leuko-encephalopathy (PML) [21]	↓	↑	↑	↑ (newer or active lesion) ↓ (older lesion)	↓ (newer or active lesion) ↑ (older lesion)	0 or +	WMD + cortical GMD – WMD junc-tion (U fibers)	Multifocal lesions
Severe leukoaraiosis [22]	↓	↑	↑	↑	↑	0	WMD	Diffuse, confluent white matter abnormality around the frontal horn and/or the posterior part of the lateral ventricles (parieto-occipital) and in the centrum semiovale
Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalo-pathy (CADASIL) [23]	↓	↑	↑	↑	↓	0	WMD	Symmetric involvement of white matter and basal ganglia, dilated perivascular spaces
Infectious encephalitis [24]	↓	↑	↑	↑ or →	↓ or →	+	WMD and/or GMD	Depend on the stage of the disease and type of microorganism
Acute disseminated encepha-lomyelitis (ADEM) [25]	↓ or →	↑	↑	→	↑	+	WMD	Asymmetric multifocal lesions of less than 5 cm, confluent multifocal lesions of more than 5 cm, and multifocal lesions involving the basal ganglia

Table 2. (*continued*)

	T1	T2	FLAIR	DWI	ADC	Gd	GMD/WMD	Other characteristics
Mitochondrial myopathy encephalopathy lactacidosis and stroke-like episodes syndrome (MELAS) [26]	↑	↓	↓	→ or ↓	→ or ↑	0 or +	WMD + GMD	Lesions in parieto-occipital regions and cortex of the cerebrum, cerebellum, and adjacent white matter
CNS vasculitis [27]	↓	↑	↑	↓	↑	+	WMD + GMD	Depend on the underlying disease. Usefulness of brain perfusion MRI.
Creutzfeld-Jakob disease [28]	→	↑	↑	↑	↓	0	GMD	Lesions of basal ganglia, caudate nucleus, striatum, and/or thalamus
Cerebral venous sinus thrombosis [29]	↑	↑	↑	↑ or → or ↓ depends on association with cerebral ischemia	↑ or ↓ depends on association with cerebral ischemia	0	GMD +/- WMD	Venous thrombus is seen on T2 echogradient as hypoT2 in the first day and as hyperT2 and hyperT1 signal in venous sinus between day 3 and day 30
Acute ischemic stroke (1–7 days) [30]	↓	↑	↑	↑	↓	0	WMD + GMD	
Subacute ischemic stroke (1–4 weeks) [30]	↓	↑	↑	↑ or →	↑	+	WMD + GMD	
Old ischemic stroke (> 1 month) [30]	↓	↑	↑	↑ or →	↑	0	WMD + GMD	

T1: T1-weighted imaging; T2: T2-weighted imaging; FLAIR: fluid attenuated inversion recovery; DWI: diffusion-weighted imaging; Gd: gadolinium enhancement; GMD: gray matter disease; WMD: white matter disease; CNS, central nervous system; →: isosignal; ↑: hypersignal; ↓: hyposignal

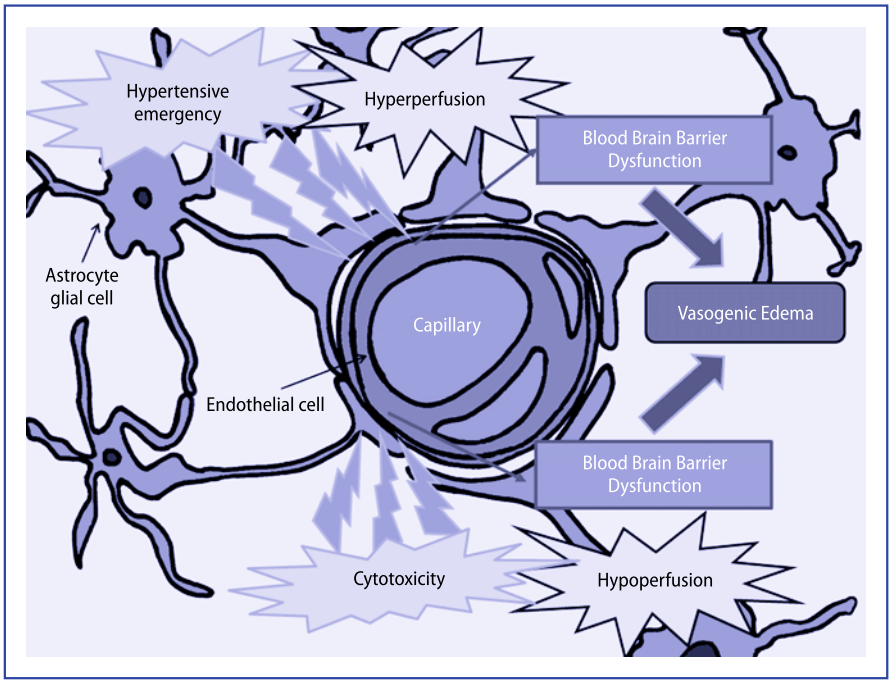

Fig. 4. This figure shows the two main hypotheses of posterior reversible encephalopathy syndrome (PRES) pathophysiology. One involves impaired cerebral autoregulation responsible for cerebral hyperperfusion and blood brain barrier dysfunction. The other is related to cytotoxicity and involves endothelial dysfunction, blood brain barrier alteration and cerebral hypoperfusion. Under both hypotheses, the result of the cerebral blood perfusion abnormalities is cerebral vasogenic edema.

vascular endothelium causes blood-brain barrier dysfunction and cerebral vasogenic edema [31].

Data supporting the hyperperfusion hypothesis have been reported. Thus, irrespective of the cause of PRES, hypertension is a feature in 67 % [11] to 80 % [3] of cases. In addition, a study involving single photon emission CT (SPECT) 99mTc-HMPAO imaging showed regional hyperperfusion in the occipital lobe and cerebellum [4].

Cerebral Hypoperfusion Related to Disruption of the Blood-brain Barrier Results in Vasogenic Edema

Not all patients with PRES have hypertension. In patients with PRES and normal blood pressure, cytotoxicity has been hypothesized to be the mechanism underlying the brain edema [2]. Causes of PRES without hypertension include eclampsia/preeclampsia, cyclosporine toxicity, and infection/sepsis/septic shock. The potential mechanisms vary with the cause. Immune system (T-cell) activation leads to endothelial cell activation with the release of various mediators such as histamine, free radicals, NO, bradykynin, and arachidonic acid [32]. These mediators activate the production of pro-inflammatory cytokines (e.g., tumor necrosis factor [TNF]-α, IL-1, IL-6, and interferon [IFN]-γ) [33–37]. Leukocyte trafficking

increases via the release of adhesion molecules (e.g., intercellular adhesion molecule [ICAM]-1, P-selectin, E-selectin, and cell adhesion molecule [CAM]-1) [2, 38]. Upregulation of endothelial surface antigens and the release of endothelin affect the local vascular tone [39]. All these changes result in vascular instability with vasoconstriction and downstream hypoperfusion. Blood-brain barrier dysfunction occurs, leading to vasogenic cerebral edema [2, 40].

This hypothesis is supported by studies involving catheter angiography, MRA, and MR perfusion imaging, which show cerebral hypoperfusion [41–43].

Pathophysiology of Complications of PRES: Cerebral Ischemia and Cerebral Hemorrhage

Ischemia following vasogenic edema may involve conversion to cytotoxic edema and may result from longer exposure to the initial source of toxicity [40]. However, the distinction between vasogenic and cytotoxic edema may be somewhat artificial, as both forms of edema probably co-exist in many conditions. Cytotoxic edema is defined as a pre-morbid cellular process characterized by induction of swelling of all cellular elements of the brain (neurons, glia, astrocytes, and endothelial cells) [44]. The swelling is indirectly related to ATP depletion with failure of the ATP-dependent Na^+/K^+ channel and diffusion of extracellular water according to the osmotic gradient into the intracellular sector. Cells in both the white and the gray matter are affected, and swelling is more severe in the astrocytes than in the neurons [44]. Compensatory mechanisms induce calcium overload and activation of proteases (cathepsin B, calpain, serine proteases), nucleases, and phospholipases (cytosolic Ca^{2+}-dependent phospholipase A2), leading to necrosis and apoptosis [45]. These phenomena are potentiated by mitochondrial damage related to ATP depletion [45].

Bleeding related to reperfusion injury is another potential complication of blood-brain-barrier dysfunction and cerebral edema. Oxidative stress with overproduction of reactive oxygen species (ROS) and oxidative damage to lipid membranes in the blood-brain-barrier causes vessels within ischemic foci to leak or rupture [44]. Leukocyte trafficking with endothelial cell adhesion and activation leads to proteolysis of catenin, a component of the endothelial cell-cell junction [46]. The resulting damage to microvascular endothelial cells causes edema and bleeding [44]. Proteolysis by matrix metalloproteinases and proteases secreted by activated leukocytes may cause bleeding after reperfusion injury [44].

Conditions Most Commonly Associated With PRES

The list of conditions associated with PRES is increasing steadily.

Toxic Agents

Exposure to toxic agents is the most common condition associated with PRES, in 11 % [7] to 61 % [14] of cases. **Box 1** shows an exhaustive list of toxic agents known to be associated with PRES. This etiology has been the focus of specific studies. In a study of cyclosporine neurotoxicity in 16 patients, exposure duration at symptom onset ranged from 6 days to 5 years and the plasma cyclosporine levels were within the therapeutic range at diagnosis [5]. All patients had hypertension. Symptomatic treatment and cyclosporine withdrawal was followed by a full

Box 1. List of toxic agents known to be associated with posterior reversible encephalopathy syndrome (PRES)

- Cancer chemotherapy agents (in combination) [8, 12, 14]
- Cytotoxic agents
  - Alkylating agents
    - Cisplatin [48]
    - Oxaliplatin [49]
    - Carboplatin [50]
  - Anti-metabolites
    - Gemcitabine [48]
    - Cytarabine [51]
    - Methotrexate [52]
  - Mitotic inhibitors
    - Vincristine [53]
    - Irinotecan hydrochloride [54]
  - Others
    - L-asparaginase [14]
- Anti-angiogenic agents
  - Bevacizumab [54]
  - Sunitinib [55]
  - RAF kinase inhibitor BAY 43 – 9006 [56]
- Immunomodulatory cytokines
  - Interferon-alpha [3, 57]
  - Interleukin-2 [58]
- Monoclonal antibodies
  - Rituximab (anti-CD20) [59]
  - Infliximab (anti-TNF-α) [60]
- Intravenous immunoglobulins [61]
- Anti-TNF-α protein
  - Etanercept [62]
- Anti-lymphocyte globulin [63]
- Immunosuppressive agents
  - Anticalcineurin agents [8]
    - Cyclosporine A [3, 5, 10, 12, 14]
    - Tacrolimus (FK 506) [3, 12, 14]
  - Sirolimus [64]
  - High-dose corticosteroid therapy (e.g., dexamethasone and methylprednisolone) [14]
- Blood transfusion [65]
- Other agents
  - Granulocyte-stimulating factor [66]
  - Antiretroviral agents [67]
  - Linezolid [68]
  - Erythropoeitin [69]
  - Cocaine [14]
  - Ephedra sinica (traditional Chinese remedy) [70]
  - Intravenous contrast agents [14]
  - Lysergic acid amide [19]
  - Carbamazepine [71]
  - Intravenous caffeine [72]

TNF: tumor necrosis factor

recovery in 14 patients. One patient with an occipital lobe hemorrhage had permanent visual field impairment and another had severe bleeding with transtentorial herniation and died shortly after diagnosis.

Transplantation patients are at risk for PRES, as they are exposed to cancer chemotherapy and/or immunosuppressive therapy. PRES has been reported after bone marrow or stem cell transplantation and after solid organ transplantation. In a study of 27 patients with PRES after liver or kidney transplantation, the time from transplantation to PRES diagnosis was 2 months in liver transplant recipients and 1 year in kidney transplant recipients [47]. Common concomitants of PRES were cytomegalovirus or bacterial infection and moderately severe transplant rejection. Hypertension was a feature and was more severe in the kidney transplant group than in the liver transplant group.

Hypertension

Hypertension is the second most common condition associated with PRES, being present in 6 % [12] to 72 % [7] of cases. The first case-series, published in 1992, had 14 patients, all of whom recovered fully within 2 weeks after blood pressure control was achieved [4]. The main cause of hypertension was acute or chronic kidney failure. Cases associated with hypertension due to autoimmune disease or toxic exposures have been reported [19].

Infection/Sepsis/Septic Shock

Infections have been reported in 8 % [14] to 24 % of cases [12]. The most common situation was PRES onset within 2 weeks after a Gram-positive bloodstream infection, often with hypertension at diagnosis [12]. PRES has also been reported in patients with *Escherichia coli* bloodstream infection [73].

Preeclampsia/Eclampsia

Pre-eclampsia/eclampsia [3, 7, 8, 12, 14, 74] was present in 7 % [14] to 20 % [3] of patients with PRES. The outcome was usually favorable. Hypertension was a prominent feature at presentation. PRES onset occurred from 28 weeks' gestational age [74] to day 13 postpartum [3].

Autoimmune Disease

Autoimmune disease has been encountered in 8 % [14] to 10 % [12] of cases. PRES has been reported in patients with systemic lupus erythematosus [75, 76], systemic sclerosis [76], polyarteritis nodosa [77], Wegener's granulomatosis [78], thrombotic microangiopathy [79], polyangiitis [80], Takayasu arteritis [81], Hashimoto encephalopathy [82], and Crohn's disease [83].

Other Conditions

There are myriad conditions associated with PRES, sometimes only anecdotally. They include sickle cell disease [12], Guillain-Barré syndrome [84], hypomagnesemia [3], hypercalcemia [85], tumor lysis syndrome [86], porphyria [87], pheochromocytoma [88], and Cushing syndrome [89].

Outcomes

As indicated by the name of this syndrome, appropriate treatment is expected to ensure a full recovery. However, permanent complications and fatal cases have been reported, leading some authors to suggest that a better name may be "potentially reversible encephalopathy syndrome" [90]. Clinical findings returned to baseline in 35 % [8] to 100 % [3] of patients. Radiological recovery is more difficult to document, as all published studies were retrospective and repeated brain imaging was performed in only 44 % [8] to 87 % [11] of cases. Among patients with follow-up imaging studies, 49 % [6] to 75 % [3] had resolution of the initial abnormalities within 5 days [7] to 17 months [3]. Permanent neurological abnormalities are related to ischemia and/or bleeding. Recurrences have been reported in 6 % of cases [8].

Limited data are available on functional outcomes. In one study, the median modified Rankin Scale score was 2.5 at discharge, indicating mild-to-moderate disability [8]. Mild disability is defined as being capable of handling one's own affairs without help but not of carrying out all previous activities; and moderate disability is defined as requiring help for some activities but being able to walk unassisted.

Death has been reported in up to 15 % [7, 8] of patients. However, the relative contributions of PRES and of associated factors to the fatal outcomes are unclear.

Management of PRES

PRES must be diagnosed early and investigations must be performed to identify the causative factors. Symptomatic treatment should be given immediately and the causative factors corrected without delay. ICU admission and life-supporting treatments may be required [9, 10].

Diagnostic Strategy

The diagnostic strategy for PRES is fairly well standardized (**Fig. 5**). After a careful history and thorough physical examination, investigations should be performed as appropriate, starting with the simplest and moving to the more sophisticated.

CT may be easier to obtain first. However, MRI must be performed, either as the first or as the second imaging study. MRI is considerably better than CT for the diagnosis of PRES and can provide information regarding many of the causes of PRES [1–3, 6, 7, 11, 13]. MRA must be added to MRI to identify an associated cerebral reversible vasoconstriction syndrome.

Electroencephalography (EEG) should be performed routinely to look for non-convulsive status epilepticus. Patients most likely to have non-convulsive status epilepticus are those in a deep coma or prolonged post-ictal state [10]. Lumbar puncture findings are not specific in PRES [7]. However, the cerebrospinal fluid (CSF) must be examined in patients with a fever or clinical suspicion of meningitis and when deemed appropriate by the attending physicians. Laboratory tests should be obtained routinely. Plasma anticonvulsant drug assays (including magnesemia dosage) and qualitative tests for toxic agents or medications associated with seizures and other symptoms of PRES should be performed at the discretion of the attending physicians.

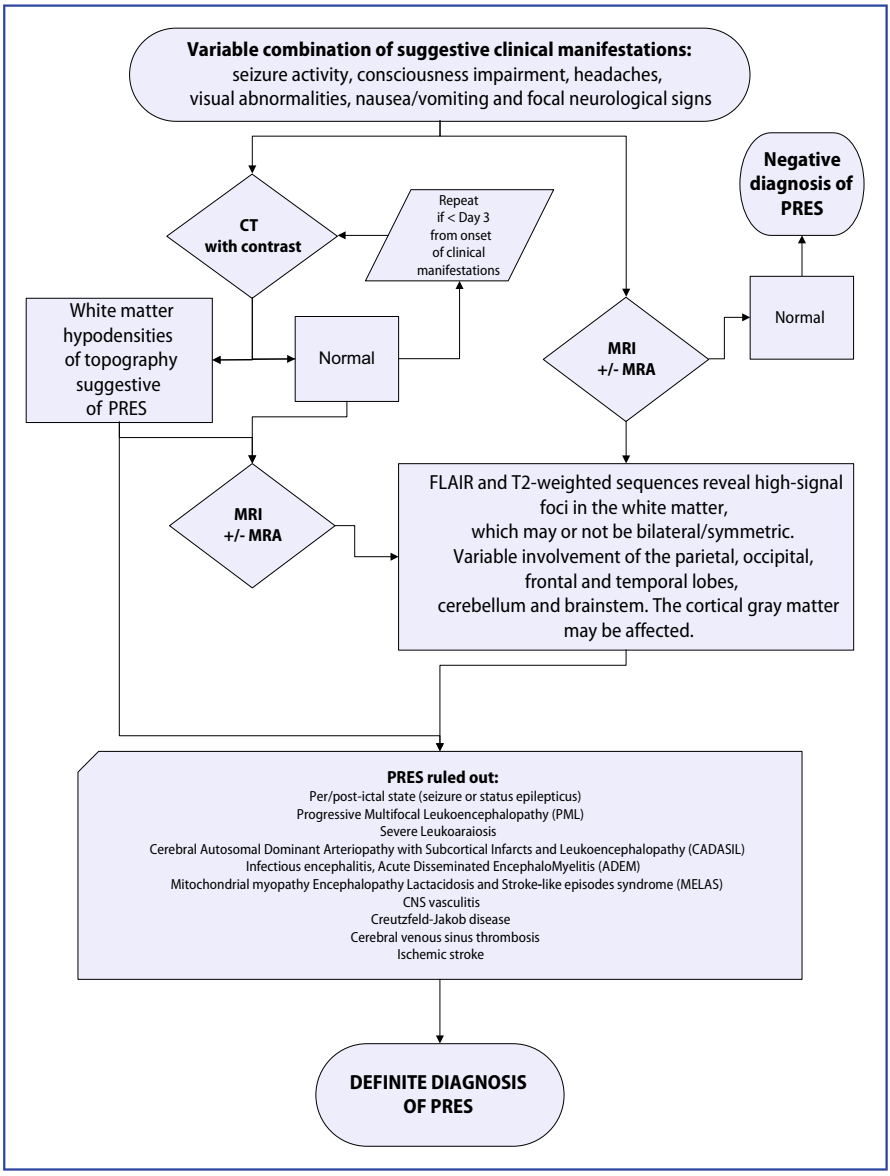

Fig. 5. Diagnostic strategy for posterior reversible encephalopathy syndrome (PRES). MRI: magnetic resonance imagery; MRA: magnetic resonance angiography; CT: computed tomography

A neurosurgical biopsy should be performed in patients who fail to respond to appropriate treatment and whose cerebral imaging studies show focal lesions of unknown or doubtful nature. Brain biopsy may show non-specific white matter changes consistent with vasogenic edema (activated astrocytes, scattered macrophages, and rare lymphocytes). Findings at a later stage include demyelination and anoxic neuronal alterations, sometimes with bleeding in the white and gray matter [91].

Treatment

The treatment strategy associates general measures with correction of the underlying cause of PRES (**Fig. 6**).

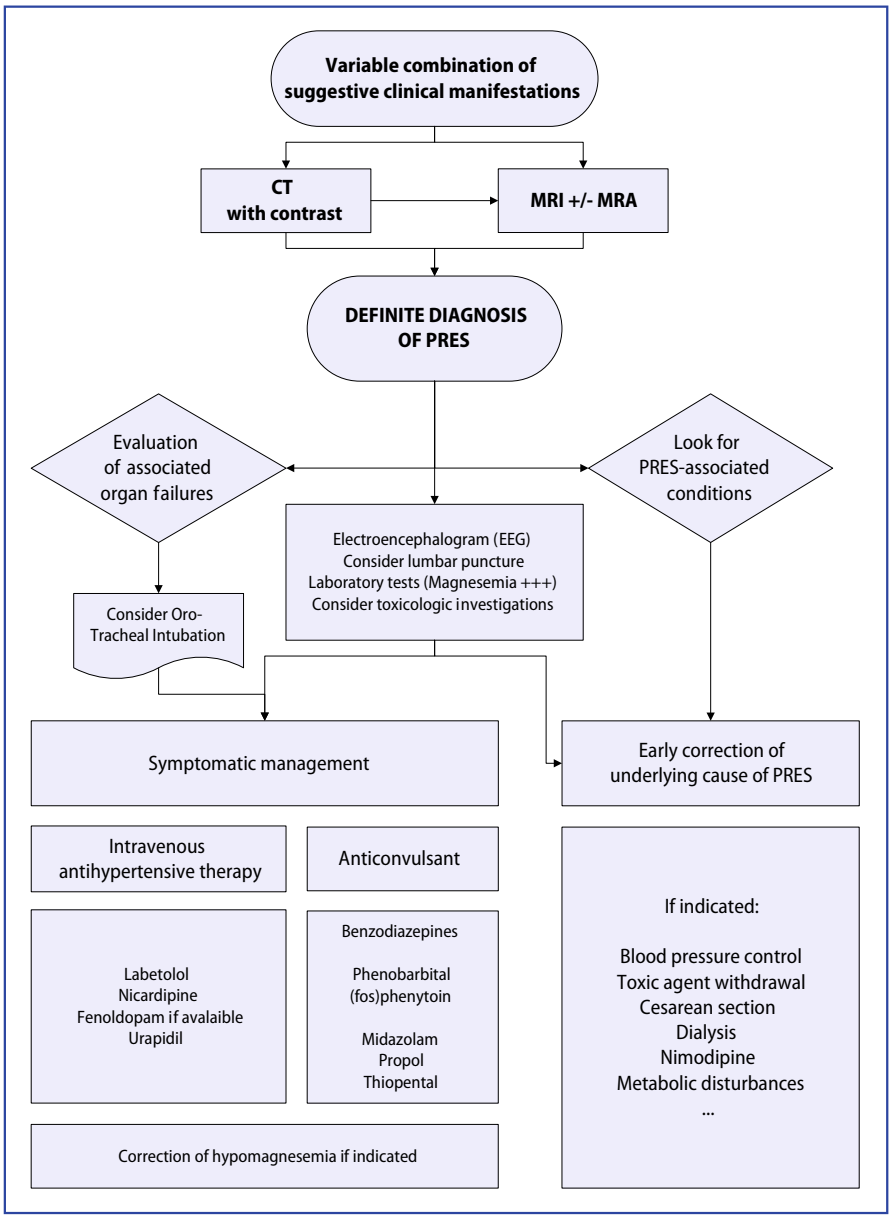

Fig. 6. Treatment of posterior reversible encephalopathy syndrome (PRES). MRI: magnetic resonance imaging; MRA: magnetic resonance angiography; CT: computed tomography

General measures

Patients with PRES require the symptomatic measures usually taken in the ICU. Although most patients have stable hemodynamics, catecholamines are required occasionally. The need for upper airway protection should be evaluated continuously in patients with marked consciousness impairment or seizure activity. If endotracheal intubation is performed, rapid-sequence induction with etomidate and succinylcholine can be used, provided there is no evidence of hyperkalemia. Propofol or thiopental are also good choices, since they have anticonvulsant effects. Neuromuscular blocking agents may transiently mask seizures.

Hypoglycemia should be looked for routinely and corrected. If glucose is given, 100 mg of thiamine should be administered concomitantly, most notably when there is evidence of vitamin B1 deficiency. Patients should be routinely evaluated for hyperthermia and metabolic disturbances, in particular hypomagnesemia, which require prompt correction. Aspiration pneumonia may complicate the initial consciousness disorders.

Antiepileptic treatment, appropriate for the electrical and clinical pattern in the patient, should be initiated on an emergency basis and according to current guidelines. Patients with persistent seizure activity at ICU admission should be given intravenous benzodiazepines (clonazepam 1 mg or diazepam 10 mg) either before ICU admission or in the ICU. The dose can be repeated up to three times if necessary. Patients with continuing seizure activity despite intravenous benzodiazepines should receive standard complementary intravenous anticonvulsant drugs (phenobarbital 10 to 15 mg/kg, phenytoin 18 mg/kg, or equivalent dose of fosphenytoin). Patients with refractory status epilepticus need midazolam, propofol, or thiopental in titrated doses until remission of the clinical seizure activity. When the EEG reveals electrical status epilepticus, these anesthetic drugs are given in titrated doses to induce EEG burst suppression then as a continuous infusion for at least 12 hours [92].

Control of hypertensive emergency, if present, is an important part of the symptomatic management. The aim is not to normalize the blood pressure but rather to decrease the MAP by 20–25 % within the first 2 hours and to bring the blood pressure down to 160/100 mmHg within the first 6 hours [31, 93]. More rapid blood pressure reduction is not recommended since it can aggravate the cerebral perfusion pressure alterations and promote ischemia [94]. Intravenous antihypertensive drugs are necessary. Appropriate choices include labetolol, nicardipine, or fenoldopam if available [31, 94]. Urapidil has been suggested as a second-line agent, perhaps in combination with another agent [95].

Correction of the underlying cause of PRES

An early etiologic diagnosis allows prompt correction of the cause of PRES. Patients may require blood pressure control, withdrawal of cancer chemotherapy or immunosuppressive agents, Cesarean section, dialysis, or other interventions. Prompt correction of the cause is crucial to decrease the risk of ischemia or bleeding and therefore to avoid permanent disability or death [3].

Conclusion

This review highlights recent advances in the diagnosis, pathophysiological understanding, and management of PRES. Although the clinical presentation is

non-specific, most patients have a suggestive combination of symptoms. MRI is crucial for diagnosing PRES, monitoring the course, and assessing treatment effectiveness. MRA performed during MRI can be useful to identify associated cerebral vasoconstriction. Repeated cerebral imaging helps to support the diagnosis and identifies complications potentially responsible for permanent impairments. The pathophysiology of PRES remains controversial. However, the list of conditions known to be associated with PRES is increasing steadily. Early recognition and resolution of the underlying cause is the keystone of management. Persistence of the cause carries a risk of ischemia, bleeding, and death. Finally, studies are needed to identify factors of adverse prognostic significance and to develop neuroprotective strategies.

References

1. Bartynski WS (2008) Posterior reversible encephalopathy syndrome, part 1: fundamental imaging and clinical features. AJNR Am J Neuroradiol 29: 1036 – 1042
2. Bartynski WS (2008) Posterior reversible encephalopathy syndrome, part 2: controversies surrounding pathophysiology of vasogenic edema. AJNR Am J Neuroradiol 29: 1043 – 1049
3. Hinchey J, Chaves C, Appignani B, et al (1996) A reversible posterior leukoencephalopathy syndrome. N Engl J Med 334: 494 – 500
4. Schwartz RB, Jones KM, Kalina P, et al (1992) Hypertensive encephalopathy: findings on CT, MR imaging, and SPECT imaging in 14 cases. AJR Am J Roentgenol 159: 379 – 383
5. Schwartz RB, Bravo SM, Klufas RA, et al (1995) Cyclosporine neurotoxicity and its relationship to hypertensive encephalopathy: CT and MR findings in 16 cases. AJR Am J Roentgenol 165: 627 – 631
6. Casey SO, Sampaio RC, Michel E, Truwit CL (2000) Posterior reversible encephalopathy syndrome: utility of fluid-attenuated inversion recovery MR imaging in the detection of cortical and subcortical lesions. AJNR Am J Neuroradiol 21: 1199 – 1206
7. Lee VH, Wijdicks EF, Manno EM, Rabinstein AA (2008) Clinical spectrum of reversible posterior leukoencephalopathy syndrome. Arch Neurol 65: 205 – 210
8. Burnett MM, Hess CP, Roberts JP, Bass NM, Douglas VC, Josephson SA (2010) Presentation of reversible posterior leukoencephalopathy syndrome in patients on calcineurin inhibitors. Clin Neurol Neurosurg 112: 886 – 889
9. Servillo G, Striano P, Striano S, et al (2003) Posterior reversible encephalopathy syndrome (PRES) in critically ill obstetric patients. Intensive Care Med 29: 2323 – 2326
10. Kozak OS, Wijdicks EF, Manno EM, Miley JT, Rabinstein AA (2007) Status epilepticus as initial manifestation of posterior reversible encephalopathy syndrome. Neurology 69: 894 – 897
11. Bartynski WS, Boardman JF (2007) Distinct imaging patterns and lesion distribution in posterior reversible encephalopathy syndrome. AJNR Am J Neuroradiol 28: 1320 – 1327
12. Bartynski WS, Boardman JF, Zeigler ZR, Shadduck RK, Lister J (2006) Posterior reversible encephalopathy syndrome in infection, sepsis, and shock. AJNR Am J Neuroradiol 27: 2179 – 2190
13. Covarrubias DJ, Luetmer PH, Campeau NG (2002) Posterior reversible encephalopathy syndrome: prognostic utility of quantitative diffusion-weighted MR images. AJNR Am J Neuroradiol 23: 1038 – 1048
14. McKinney AM, Short J, Truwit CL, et al (2007) Posterior reversible encephalopathy syndrome: incidence of atypical regions of involvement and imaging findings. AJR Am J Roentgenol 189: 904 – 912
15. Ducros A, Boukobza M, Porcher R, Sarov M, Valade D, Bousser MG (2007) The clinical and radiological spectrum of reversible cerebral vasoconstriction syndrome. A prospective series of 67 patients. Brain 130: 3091 – 3101
16. Hefzy HM, Bartynski WS, Boardman JF, Lacomis D (2009) Hemorrhage in posterior reversible encephalopathy syndrome: imaging and clinical features. AJNR Am J Neuroradiol 30: 1371 – 1379

17. Belogolovkin V, Levine SR, Fields MC, Stone JL (2006) Postpartum eclampsia complicated by reversible cerebral herniation. Obstet Gynecol 107: 442–445
18. Lamy C, Mas JL (2001) [Reversible posterior leukoencephalopathy. A new syndrome or a new name for an old syndrome?]. Presse Med 30: 915–920
19. Legriel S, Bruneel F, Spreux-Varoquaux O, et al (2008) Lysergic acid amide-induced posterior reversible encephalopathy syndrome with status epilepticus. Neurocrit Care 9: 247–252
20. Cole AJ (2004) Status epilepticus and periictal imaging. Epilepsia 45 (Suppl 4): 72–77
21. Thurnher MM, Post MJ, Rieger A, Kleibl-Popov C, Loewe C, Schindler E (2001) Initial and follow-up MR imaging findings in AIDS-related progressive multifocal leukoencephalopathy treated with highly active antiretroviral therapy. AJNR Am J Neuroradiol 22: 977–984
22. O'Sullivan M (2008) Leukoaraiosis. Pract Neurol 8: 26–38
23. Chabriat H, Joutel A, Dichgans M, Tournier-Lasserve E, Bousser MG (2009) Cadasil. Lancet Neurol 8: 643–653
24. Gilman S (1998) Imaging the brain. First of two parts. N Engl J Med 338: 812–820
25. Sonneville R, Klein IF, Wolff M (2010) Update on investigation and management of post-infectious encephalitis. Curr Opin Neurol 23: 300–304
26. Matthews PM, Tampieri D, Berkovic SF, et al (1991) Magnetic resonance imaging shows specific abnormalities in the MELAS syndrome. Neurology 41: 1043–1046
27. Pomper MG, Miller TJ, Stone JH, Tidmore WC, Hellmann DB (1999) CNS vasculitis in autoimmune disease: MR imaging findings and correlation with angiography. AJNR Am J Neuroradiol 20: 75–85
28. Kallenberg K, Schulz-Schaeffer WJ, Jastrow U, et al (2006) Creutzfeldt-Jakob disease: comparative analysis of MR imaging sequences. AJNR Am J Neuroradiol 27: 1459–1462
29. Stam J (2005) Thrombosis of the cerebral veins and sinuses. N Engl J Med 352: 1791–1798
30. Culebras A, Kase CS, Masdeu JC, et al (1997) Practice guidelines for the use of imaging in transient ischemic attacks and acute stroke. A report of the Stroke Council, American Heart Association. Stroke 28: 1480–1497
31. Vaughan CJ, Delanty N (2000) Hypertensive emergencies. Lancet 356: 411–417
32. Baethmann A, Maier-Hauff K, Kempski O, Unterberg A, Wahl M, Schurer L (1988) Mediators of brain edema and secondary brain damage. Crit Care Med 16: 972–978
33. Ferrara JL (2000) Pathogenesis of acute graft-versus-host disease: cytokines and cellular effectors. J Hematother Stem Cell Res 9: 299–306
34. Antin JH, Ferrara JL (1992) Cytokine dysregulation and acute graft-versus-host disease. Blood 80: 2964–2968
35. Holler E, Kolb HJ, Moller A, et al (1990) Increased serum levels of tumor necrosis factor alpha precede major complications of bone marrow transplantation. Blood 75: 1011–1016
36. Schots R, Kaufman L, Van Riet I, et al (2003) Proinflammatory cytokines and their role in the development of major transplant-related complications in the early phase after allogeneic bone marrow transplantation. Leukemia 17: 1150–1156
37. de Vries HE, Kuiper J, de Boer AG, Van Berkel TJ, Breimer DD (1997) The blood-brain barrier in neuroinflammatory diseases. Pharmacol Rev 49: 143–155
38. Stanimirovic D, Satoh K (2000) Inflammatory mediators of cerebral endothelium: a role in ischemic brain inflammation. Brain Pathol 10: 113–126
39. Narushima I, Kita T, Kubo K, et al (2003) Highly enhanced permeability of blood-brain barrier induced by repeated administration of endothelin-1 in dogs and rats. Pharmacol Toxicol 92: 21–26
40. Wijdicks EF (2001) Neurotoxicity of immunosuppressive drugs. Liver Transpl 7: 937–942
41. Bartynski WS, Boardman JF (2008) Catheter angiography, MR angiography, and MR perfusion in posterior reversible encephalopathy syndrome. AJNR Am J Neuroradiol 29: 447–455
42. Brubaker LM, Smith JK, Lee YZ, Lin W, Castillo M (2005) Hemodynamic and permeability changes in posterior reversible encephalopathy syndrome measured by dynamic susceptibility perfusion-weighted MR imaging. AJNR Am J Neuroradiol 26: 825–830
43. Engelter ST, Petrella JR, Alberts MJ, Provenzale JM (1999) Assessment of cerebral microcirculation in a patient with hypertensive encephalopathy using MR perfusion imaging. AJR Am J Roentgenol 173: 1491–1493

44. Wang X, Lo EH (2003) Triggers and mediators of hemorrhagic transformation in cerebral ischemia. Mol Neurobiol 28: 229–244
45. Szabo C (2005) Mechanisms of cell necrosis. Crit Care Med 33 (12 Suppl): S530–534
46. Allport JR, Ding H, Collins T, Gerritsen ME, Luscinskas FW (1997) Endothelial-dependent mechanisms regulate leukocyte transmigration: a process involving the proteasome and disruption of the vascular endothelial-cadherin complex at endothelial cell-to-cell junctions. J Exp Med 186: 517–527
47. Bartynski WS, Tan HP, Boardman JF, Shapiro R, Marsh JW (2008) Posterior reversible encephalopathy syndrome after solid organ transplantation. AJNR Am J Neuroradiol 29: 924–930
48. Kwon EJ, Kim SW, Kim KK, Seo HS, Kim do Y (2009) A case of gemcitabine and cisplatin associated posterior reversible encephalopathy syndrome. Cancer Res Treat 41: 53–55
49. Nagata Y, Omuro Y, Shimoyama T, et al (2009) [A case of colon cancer with reversible posterior leukoencephalopathy syndrome following 5-FU and oxaliplatin (FOLFOX regime)]. Gan To Kagaku Ryoho 36: 1163–1166
50. Vieillot S, Pouessel D, de Champfleur NM, Becht C, Culine S (2007) Reversible posterior leukoencephalopathy syndrome after carboplatin therapy. Ann Oncol 18: 608–609
51. Saito B, Nakamaki T, Nakashima H, et al (2007) Reversible posterior leukoencephalopathy syndrome after repeat intermediate-dose cytarabine chemotherapy in a patient with acute myeloid leukemia. Am J Hematol 82: 304–306
52. Dicuonzo F, Salvati A, Palma M, et al (2009) Posterior reversible encephalopathy syndrome associated with methotrexate neurotoxicity: conventional magnetic resonance and diffusion-weighted imaging findings. J Child Neurol 24: 1013–1018
53. Hualde Olascoaga J, Molins Castiella T, Souto Hernandez S, et al (2008) [Reversible posterior leukoencephalopathy: report of two cases after vincristine treatment]. An Pediatr (Barc) 68: 282–285
54. Allen JA, Adlakha A, Bergethon PR (2006) Reversible posterior leukoencephalopathy syndrome after bevacizumab/FOLFIRI regimen for metastatic colon cancer. Arch Neurol 63: 1475–1478
55. Cumurciuc R, Martinez-Almoyna L, Henry C, Husson H, de Broucker T (2008) Posterior reversible encephalopathy syndrome during sunitinib therapy. Rev Neurol (Paris) 164: 605–607
56. Govindarajan R, Adusumilli J, Baxter DL, El-Khoueiry A, Harik SI (2006) Reversible posterior leukoencephalopathy syndrome induced by RAF kinase inhibitor BAY 43–9006. J Clin Oncol 24: e48
57. Kamar N, Kany M, Bories P, et al (2001) Reversible posterior leukoencephalopathy syndrome in hepatitis C virus-positive long-term hemodialysis patients. Am J Kidney Dis 37: E29
58. Karp BI, Yang JC, Khorsand M, Wood R, Merigan TC (1996) Multiple cerebral lesions complicating therapy with interleukin-2. Neurology 47: 417–424
59. Zito JA, Lee CC, Johnson S, Singer A, Vacirca J (2010) Reversible posterior leukoencephalopathy syndrome after rituximab. Am J Emerg Med 28: 537
60. Zamvar V, Sugarman ID, Tawfik RF, Macmullen-Price J, Puntis JW (2009) Posterior reversible encephalopathy syndrome following infliximab infusion. J Pediatr Gastroenterol Nutr 48: 102–105
61. Belmouaz S, Desport E, Leroy F, et al (2008) Posterior reversible encephalopathy induced by intravenous immunoglobulin. Nephrol Dial Transplant 23: 417–419
62. Kastrup O, Diener HC (2008) TNF-antagonist etanercept induced reversible posterior leukoencephalopathy syndrome. J Neurol 255: 452–453
63. Greaves P, Oakervee H, Kon SS, Jones R, Farah N (2006) Posterior reversible encephalopathy syndrome following anti-lymphocyte globulin treatment for severe aplastic anaemia. Br J Haematol 134: 251
64. Bodkin CL, Eidelman BH (2007) Sirolimus-induced posterior reversible encephalopathy. Neurology 68: 2039–2040
65. Huang YC, Tsai PL, Yeh JH, Chen WH (2008) Reversible posterior leukoencephalopathy syndrome caused by blood transfusion: a case report. Acta Neurol Taiwan 17: 258–262
66. Leniger T, Kastrup O, Diener HC (2000) Reversible posterior leukencephalopathy syn-

drome induced by granulocyte stimulating factor filgrastim. J Neurol Neurosurg Psychiatry 69: 280–281
67. Ridolfo AL, Resta F, Milazzo L, et al (2008) Reversible posterior leukoencephalopathy syndrome in 2 HIV-infected patients receiving antiretroviral therapy. Clin Infect Dis 46:e19–22
68. Nagel S, Kohrmann M, Huttner HB, Storch-Hagenlocher B, Schwab S (2007) Linezolid-induced posterior reversible leukoencephalopathy syndrome. Arch Neurol 64: 746–748
69. Delanty N, Vaughan C, Frucht S, Stubgen P (1997) Erythropoietin-associated hypertensive posterior leukoencephalopathy. Neurology 49: 686–689
70. Moawad FJ, Hartzell JD, Biega TJ, Lettieri CJ (2006) Transient blindness due to posterior reversible encephalopathy syndrome following ephedra overdose. South Med J 99: 511–514
71. Furuta N, Fujita Y, Sekine A, Ikeda M, Okamoto K (2009) [Reversible posterior leukoencephalopathy syndrome associated with carbamazepine-induced hypertension]. Rinsho Shinkeigaku 49: 191–193
72. Ortiz GA, Bianchi NA, Tiede MP, Bhatia RG (2009) Posterior reversible encephalopathy syndrome after intravenous caffeine for post-lumbar puncture headaches. AJNR Am J Neuroradiol 30: 586–587
73. Fabbian F, Pala M, Fallica E, et al (2010) Posterior reversible encephalopathy syndrome in an 87-year-old woman with Escherichia coli bloodstream infection. Clin Exp Nephrol 14: 176–179
74. Servillo G, Apicella E, Striano P (2008) Posterior reversible encephalopathy syndrome (PRES) in the parturient with preeclampsia after inadvertent dural puncture. Int J Obstet Anesth 17: 88–89
75. Baizabal-Carvallo JF, Barragan-Campos HM, Padilla-Aranda HJ, et al (2009) Posterior reversible encephalopathy syndrome as a complication of acute lupus activity. Clin Neurol Neurosurg 111: 359–363
76. Yong PF, Hamour SM, Burns A (2003) Reversible posterior leukoencephalopathy in a patient with systemic sclerosis/systemic lupus erythematosus overlap syndrome. Nephrol Dial Transplant 18: 2660–2662
77. Stanzani L, Fusi L, Gomitoni A, Roncoroni M, Villa P, Grampa G (2008) A case of posterior reversible encephalopathy during polyarteritis nodosa vasculitis. Neurol Sci 29: 163–167
78. Nishio M, Yoshioka K, Yamagami K, et al (2008) Reversible posterior leukoencephalopathy syndrome: a possible manifestation of Wegener's granulomatosis-mediated endothelial injury. Mod Rheumatol 18: 309–314
79. Burrus TM, Mandrekar J, Wijdicks EF, Rabinstein AA (2010) Renal failure and posterior reversible encephalopathy syndrome in patients with thrombotic thrombocytopenic purpura. Arch Neurol 67: 831–834
80. Kamimura H, Hirose S, Tazaki K, Suzuki Y, Satou M (2007) [Reversible posterior leukoencephalopathy syndrome with microscopic polyangiitis]. Nippon Naika Gakkai Zasshi 96: 2532–2535
81. Fujita M, Komatsu K, Hatachi S, Yagita M (2008) Reversible posterior leukoencephalopathy syndrome in a patient with Takayasu arteritis. Mod Rheumatol 18: 623–629
82. Yildiz OK, Segmen H, Oztoprak I, Bolayir E, Topaktas S (2010) Posterior reversible encephalopathy and alexia without agraphia in a patient with Hashimoto's encephalopathy. Neurol Sci 31: 523–525
83. Zipper SG, Tischendorf M, Westphal K (2006) [Postoperative occurrence of reversible posterior encephalopathy in a patient with Crohn's disease]. Anaesthesist 55: 1064–1067
84. Fugate JE, Wijdicks EF, Kumar G, Rabinstein AA (2009) One Thing Leads to Another: GBS Complicated by PRES and Takotsubo Cardiomyopathy. Neurocrit Care 11: 395–397
85. Ma ES, Chiu EK, Fong GC, Li FK, Wong CL (2009) Burkitt lymphoma presenting as posterior reversible encephalopathy syndrome secondary to hypercalcaemia. Br J Haematol 146: 584
86. Greenwood MJ, Dodds AJ, Garricik R, Rodriguez M (2003) Posterior leukoencephalopathy in association with the tumour lysis syndrome in acute lymphoblastic leukaemia--a case with clinicopathological correlation. Leuk Lymphoma 44: 719–721

87. Kang SY, Kang JH, Choi JC, Lee JS (2010) Posterior reversible encephalopathy syndrome in a patient with acute intermittent porphyria. J Neurol 257: 663 – 664
88. Rodriguez-Uranga JJ, Franco-Macias E, Bernal Sanchez-Arjona M, Villalobos-Chavez F (2003) [Posterior reversible leukoencephalopathy syndrome, pheochromocytoma and von Hippel-Lindau disease]. Rev Neurol 37: 797 – 798
89. Lodish M, Patronas NJ, Stratakis CA (2010) Reversible posterior encephalopathy syndrome associated with micronodular adrenocortical disease and Cushing syndrome. Eur J Pediatr 169: 125 – 126
90. Narbone MC, Musolino R, Granata F, Mazzu I, Abbate M, Ferlazzo E (2006) PRES: posterior or potentially reversible encephalopathy syndrome? Neurol Sci 27: 187 – 189
91. Schiff D, Lopes MB (2005) Neuropathological correlates of reversible posterior leukoencephalopathy. Neurocrit Care 2: 303 – 305
92. Meierkord H, Boon P, Engelsen B, et al (2010) EFNS guideline on the management of status epilepticus in adults. Eur J Neurol 17: 348 – 355
93. Ramsay LE, Williams B, Johnston GD, et al (1999) British Hypertension Society guidelines for hypertension management 1999: summary. BMJ 319: 630 – 635
94. Varon J, Marik PE (2003) Clinical review: the management of hypertensive crises. Crit Care 7: 374 – 384
95. Buch J (2010) Urapidil, a dual-acting antihypertensive agent: Current usage considerations. Adv Ther 27: 426 – 443

Prediction of Neurological Outcome after Cardiac Arrest

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Introduction

The introduction of cardiopulmonary resuscitation (CPR) into clinical practice more than 50 years ago [1] has allowed many patients in cardiac arrest to achieve a recovery of spontaneous circulation (ROSC) and to be admitted to hospital alive. Unfortunately, most resuscitated patients die in the first day after cardiac arrest and in about one fourth of those who survive to hospital discharge, the postanoxic insult results in severe neurological impairment [2]. Accurate prognostication of poor neurological outcome, made as early as possible, is of paramount importance to avoid futile treatments for unrecoverable patients and unreasonable hopes of recovery in their relatives.

Definition of Neurological Outcome

Good neurological outcome after cardiac arrest is generally interpreted as recovery of consciousness, which implies an awake state, self-awareness and the ability to interact with the environment. However, even those patients who recover consciousness after cardiac arrest may still show a variable degree of neurological impairment ranging from mild memory deficits to severe loss of motor and upper mental functions, leading to complete dependence. To avoid inconsistency in outcome description, the use of standardized outcome scales is recommended. The Cerebral Performance Categories (CPC) (**Box 1**) [3], partly derived from the Glasgow Outcome Scale (GOS), [4] are currently recommended as a core component of cardiac arrest reports [5] and are widely used, although their correlation with long-term measures of disability and quality of life (QOL) is only moderate [6].

In general, in order to assess the accuracy of predictors of neurological outcome after cardiac arrest, clinical investigators dichotomize the outcome as good or poor. Unfortunately, while there is no doubt that persistent vegetative state or death (CPC 4-5) represent an undesirable outcome, there is no universal consensus on how to classify severe neurological disability (CPC 3). This category encompasses a wide range of cerebral abnormalities, from important memory loss to dementia and minimally conscious states which generally preclude an independent existence outside specialized institutions. The majority of clinical studies describing neurological outcome after CPR includes CPC 3 among good outcomes, so the outcome is dichotomized as CPC 1 – 3 vs. 4 – 5, but others [7 – 9] do not, so the outcome is dichotomized as CPC 1 – 2 vs. 3 – 5. The reader should

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Box 1. Cerebral Performance Categories (from [2, 3])

1. Good Cerebral Performance
Conscious. Alert, able to work and lead a normal life. May have minor psychological or neurological deficits (mild dysphasia, non-incapacitating hemiparesis, or minor cranial nerve abnormalities).

2. Moderate Cerebral Disability
Conscious. Sufficient cerebral function for part-time work in sheltered environment or independent activities of daily life (dressing, traveling by public transportation, and preparing food). May have hemiplegia, seizures, ataxia, dysarthria, dysphasia, or permanent memory or mental changes.

3. Severe Cerebral Disability
Conscious. Dependent on others for daily support because of impaired brain function (in an institution or at home with exceptional family effort). At least limited cognition. Includes a wide range of cerebral abnormalities from ambulatory with severe memory disturbance or dementia precluding independent existence to paralytic and able to communicate only with eyes, as in the locked-in syndrome.

4. Coma, Vegetative State
Not conscious. Unaware of surroundings, no cognition. No verbal or psychological interactions with environment.

5. Death
Certified brain dead or dead by traditional criteria.

keep this in mind in order to correctly interpret the results reported in the literature.

In some cases, death due to non-neurological causes, such as cardiac arrhythmia, may occur during the clinical course of cardiac arrest survivors, so that even patients who had showed a variable degree of recovery are assigned to a CPC category of 5. To avoid confusion, the updated guidelines for reviewing, reporting, and conducting research on post-resuscitation care [10] recommend documenting both the best CPC achieved during the patient's hospital stay and the CPC at hospital discharge. The cause of death – cardiac, neurological or other – should be reported separately.

The perceived need to limit high-intensity care for patients with an invariably poor long-term prognosis has focused research on predictors of poor neurological outcome. Ideally, such a predictor should have a 0 % false positive rate, or 100 % specificity (i.e., no patient who will recover should be mistakenly predicted as having a poor prognosis), with the narrowest possible confidence intervals (CIs). We will describe here indexes with these characteristics, whenever available.

Prognostication in Normothermic Patients

In 2003, the International Liaison Committee on Resuscitation (ILCOR) guidelines recommended the use of therapeutic hypothermia for comatose survivors of cardiac arrest [11]. However, only very recently has therapeutic hypothermia achieved widespread implementation in clinical practice; as an example, in 2010 a national survey [12] showed that the majority of intensive care units (ICUs) in the United Kingdom started to use therapeutic hypothermia only in 2007 or 2008. For this reason, most of the evidence available on prognostication after cardiac arrest presently regards normothermic patients.

Clinical Examination

Clinical examination represents an immediate and inexpensive way to obtain useful information for prognostication in comatose patients. Prognostic indexes obtained from clinical examination include absence of brainstem reflexes (such as pupillary response to light, corneal and oculocephalic reflexes); presence of myoclonus status, defined as spontaneous, repetitive, unrelenting, generalized multifocal twitching involving the face, limbs, and axial musculature [13], and the score from combined neurological scales, such as the Glasgow Coma Scale (GCS).

Presence of myoclonus is one of the earliest predictors of poor neurological outcome after CPR. An observational study by Wijdicks et al. [14] reported the occurrence of myoclonus status on admission in 40/107 (37 %) comatose cardiac arrest survivors. All of them died (false positive rate 0 %; 95 % CI: 0 – 17). In two other observational studies [15, 16] including a total of 521 patients, the occurrence of myoclonus status within 24 and 36 hours, respectively, after cardiac arrest was associated with death or vegetative state in 100 % of cases (false positive rate 0 %; 95 %CI: 0 – 7 and 0 – 16). Finally, in a series of 50 comatose patients presenting myoclonus status within 24 hours after cardiac arrest, 45 died and 5 were in persistent vegetative state 48 months later [17]. In 42 of those patients (84 %), the electroencephalogram (EEG) documented burst-suppression, a pattern typically associated with poor outcome. In all good-quality cohort studies made on normothermic patients, presence of myoclonus has been consistently associated with poor prognosis; however, isolated case reports of good recovery have been documented, mainly in patients whose cardiac arrest was due to respiratory failure [18 – 20]. At least some of these cases have been later reinterpreted as a misdiagnosed form of benign action myoclonus (Lance-Adams syndrome) [13, 17].

With regards the GCS, in a study from Bassetti et al. [21], a GCS < 5 recorded at 48 hours in 20/60 patients resuscitated from cardiac arrest predicted death or persistent vegetative state (CPC 4 – 5) with a 0 % false positive rate (95 % CI 0 – 23). Similarly, in another study from Edgren et al. [8], a GCS < 5 recorded at 72 hours in 45/109 patients predicted poor outcome (CPC 3 – 5) with a 0 % false positive rate (95 % CI 0 – 24). A major limitation of the GCS is that it is a summary score, so the same value may result from different combinations of its single components. For example, in 2006 a paper from Zandbergen et al. [15] documented that the absence of motor response to pain at 72 hours (M = 1) was still compatible with neurological recovery (false positive rate 19 %; 95 % CI: 6 – 37). In intubated patients (V = 1) with no eye opening to verbal stimuli (E = 1 – 2) this would correspond to a GCS < 5. To avoid confusion, clinicians should avoid referring only to summary scores and report the scores of single GCS components separately as well.

The absence of brainstem reflexes immediately after resuscitation may still be compatible with neurological recovery. In a paper from Young et al. [22], 2/18 patients with no pupillary reflex and 2/32 patients with no corneal reflex 24 hours after cardiac arrest survived with good outcome. In a multicenter study [15] including 407 comatose patients, the combined absence of both pupillary and corneal reflexes was still compatible with neurological recovery at 24 and 48 hours from cardiac arrest (false positive rate 4 %). However, after 72 hours this sign became 100 % predictive of poor outcome (38/289 patients; 0 % false positive rate). It should be noted that the absence of three or more brainstem reflexes in ventilated comatose patients (GCS 3) has been recently identified as a sign of imminent brainstem death [23].

In summary, in comatose resuscitated patients who have not been treated with therapeutic hypothermia, clinical examination allows accurate prediction of poor outcome as early as 24 hours from cardiac arrest. Status myoclonus and pupillary and corneal reflexes appear more reliable, having the narrowest confidence intervals. The major limitation of clinical examination is that its findings may be influenced by pathological factors, such as circulatory or metabolic derangements, and by the effects of treatments, e.g., sedatives and muscle relaxants. Patient stabilization and removal of any possible interference are necessary to avoid incorrect prognostication.

Biochemical Markers

In the last 20 years, a series of biochemical markers of brain damage obtained from peripheral blood and cerebrospinal fluid (CSF) have been investigated as predictors of functional outcome after CPR. Since blood samples are much easier and less dangerous to obtain than CSF, serum markers have been more extensively investigated and are considered more suitable for routine clinical practice.

The serum marker which has so far demonstrated the best accuracy to predict poor outcome is neuron-specific enolase (NSE). NSE is the neuronal form of the cytoplasmic glycolytic enzyme enolase and it is found in neurons and neuroendocrine cells. NSE is released in blood and in CSF after neuronal ischemia and its serum concentrations correlate with the extent of brain damage [24]. Several studies showed that serum NSE in the first days after cardiac arrest could predict poor outcome with a 0 % false positive rate and narrow 95 % CIs, but the cut-off levels varied greatly. The largest study [15] which included 407 comatose patients, showed that serum NSE concentrations > 33 μg/l drawn between 24 and 72 h after CPR predicted persistent vegetative state or death with a false positive rate of 0 % (95 % CI 0 – 3). However, in two other studies [25, 26], serum concentrations as high as 60 μg/l and 90.9 μg/l in the first 36 and 72 hours, respectively, were needed to achieve a 0 % false positive rate. Finally, in a study from Pfeifer et al. [27] NSE levels higher than 65 μg/l at 72 hours were still compatible with neurological recovery (false positive rate 4 %). Sensitivity for the above cited studies ranged from 33 to 77 %.

Protein S100B is a calcium-binding protein secreted from glial and Schwann cells and released after cerebral ischemia. In the largest study conducted so far [15], 72/207 patients had serum levels of S100B greater than 0.7 μg/l at 72 hours from cardiac arrest. All of these patients died or survived in a persistent vegetative state (false positive rate 0 %; 95 % CI 0 – 5). Smaller studies confirmed a 0 % false positive rate at 72 h for serum S100B with cut-offs ranging from 0.20 to 2.76 μg/l [9, 26, 28, 29]. However, in another study [27], among 25 patients with serum levels above a threshold of 1.5 μg/l one survived with good neurological outcome (false positive rate 4 %). The sensitivity of S100B in the above studies ranged from 40 to 75 %.

In summary, in most studies, measurement of serum levels of NSE and S100B allowed prediction of poor neurological outcome with a zero false positive rate, but cut-offs varied considerably. Moreover, in at least one study, high levels of both these biomarkers were still compatible with a good outcome. At present, there is still insufficient evidence to recommend a specific serum level of NSE or S100B for a 100 % accurate prediction of poor outcome.

Electrophysiological Testing

The EEG is the simplest and most widely available electrophysiological investigation for outcome prediction after cardiac arrest. Some 'malignant' EEG patterns associated with poor outcome have been recognized [2]. These include isoelectric tracing, generalized suppression to < 20 μV, burst-suppression pattern with or without a generalized epileptiform activity or generalized periodic complexes on a flat background [22, 30–32]. In a meta-analysis by Wijdicks et al. [13], the presence of a malignant EEG pattern within the first 3 days post CPR predicted poor outcome with a pooled false positive rate of 3 % (95 % CI 0.9–11). In a large prospective study [15], an EEG amplitude < 20 μV or burst suppression in the first 3 days after CPR had a false positive rate of 0 (95 % CI: 0–5) for prognostication of poor outcome.

Evidence on prognostication using EEG is confounded by the presence of different classification systems and variable recording intervals after resuscitation. Moreover, the EEG is affected by various factors, including body temperature, metabolic status and interference from sedative drugs. For this reason, predicting outcome of post-anoxic coma exclusively on the basis of the EEG results is not recommended [13].

Evoked potentials (EPs) are based on modifications of the EEG induced by a repetitive sensory stimulus. Recording of EPs requires specific know-how and equipment, so that EPs are not as widely available as the EEG, but they are less influenced by sedatives, metabolic disorders and body temperature. Somatosensory evoked potentials (SSEP) explore the thalamo-cortical pathway using electric stimulation of a peripheral nerve. The earliest cortical component of the median nerve SSEP is the N20 peak, a negative wave occurring about 20 milliseconds after the electrical stimulus, which corresponds to the signal reaching the somatosensory cortex (postcentral gyrus), whereas longer-latency responses (such as N35 and N70) come from associative cortical areas and explore cortico-cortical interactions. In several studies [21, 33, 34], the bilateral absence of the N20 wave in the first week after CPR predicted no recovery of consciousness with a 0 % false positive rate. In a pooled analysis [35], among 187 patients with bilaterally absent N20, none had a good outcome, defined as CPC 1–3 (false positive rate 0 % [95 % CI 0–2]). However, one out of 801 patients included in a meta-analysis by Wijdicks et al. [13] awakened despite a bilaterally absent N20 (false positive rate 0.7 % [95 % CI 0.1–3.7]). In another large observational study [15], five of 256 patients had an initially absent N20 at 24 h after resuscitation but the response reappeared later. However, the prognosis of all these patients was equally poor.

Reported sensitivity of N20 SSEP is relatively low (range 28–73 [35], pooled value 46 % [13]), however, at least one study indicated that SSEP sensitivity may be improved by assessing the absence of its later components, such as the N70 wave [33].

Brainstem (BAEPs) and middle-latency (MLAEPs) auditory evoked potentials explore the acoustic pathway at brainstem and supratentorial level respectively. Likewise, bilateral absence of acoustic responses predicts no awakening [36, 37]. However, the predictive role of these components has not been widely investigated or consistently replicated.

Neuroimaging Studies

Evidence supporting the use of brain neuroimaging for outcome prediction in postanoxic coma is still limited. Moreover, most studies have been conducted in a chronic rather than in an acute setting of neurological impairment after cardiac arrest. Magnetic resonance imaging (MRI) is the neuroimaging technique with the largest supportive evidence, the most documented modalities being diffusion-weighted imaging (DWI) and fluid-attenuated inversion recovery (FLAIR). In a paper by Wu et al. [38], the whole median apparent diffusion coefficient (ADC) of the brain was the main predictor of poor outcome as measured by a 6-month modified Rankin scale score (sensitivity 41 % [95 % CI 29 – 54]; specificity 100 % [95 % CI 73 – 100]). In a paper by Wijman et al. [39], on 51 comatose resuscitated patients, when results of 72-hour clinical examination were combined with those of an MRI-derived index recorded between 49 and 108 hours after the arrest, the sensitivity for prediction of poor outcome improved by 38 % while maintaining 100 % specificity. Finally, in a recent paper from Topcuoglu et al. [40] on 22 resuscitated comatose normothermic patients, both the presence of an extensive cortical lesion pattern on MRI and a GCS motor score ≤ 3 at 72 hours predicted a poor outcome (CPC 4 – 5) with 87.5 % sensitivity (95 %CI 62 – 93) and 100 % specificity. Combining the results of these two indexes increased sensitivity to 100 % (95 %CI 79 – 100). Area under the receiver-operating characteristics (ROC) curve for this combination was 1.00 (95 %CI 0.84 – 1.00). The main limitation of this study is that recording times for MRI were heterogeneous, being 4.1 ± 2.9 days in patients with poor outcome and 9.8 ± 5.7 days in those with favorable outcome.

In conclusion, MRI may improve the accuracy of prognostication obtained using clinical examination, but results of clinical studies are preliminary and need confirmation from well-designed prospective trials. Furthermore, acquiring MRI studies in critically ill resuscitated patients connected to many monitoring and life support devices may be technically difficult. The availability of portable equipment and improvements in functional imaging techniques may promote more widespread use of neuroimaging for the investigation of post-cardiac arrest patients in the near future.

Prognostication in Patients Treated with Therapeutic Hypothermia

The use of therapeutic hypothermia [41, 42] significantly improves neurological outcome after cardiac arrest, so that patients previously predicted as having a poor prognosis now may recover an acceptable neurological function. For this reason, prediction of poor outcome based on indexes developed in normothermic conditions may not always be valid after therapeutic hypothermia. Moreover, both therapeutic hypothermia itself and sedative or muscle relaxant agents administered to maintain it may depress the central nervous system (CNS), making results of predictive indexes possibly appear worse than they are, especially those based on clinical neurological examination or on EEG. In both cases, the result could be an increase in the index false positive rate.

As regards clinical signs, a recent study from Rossetti et al. [7], in 109 patients treated with therapeutic hypothermia, showed that the absence of more than one among pupillary, corneal and occulocephalic reflexes at 72 hours from cessation of therapeutic hypothermia was associated with neurological recovery in 8 % of

cases (95 % CI 2–25). Unfortunately, the authors did not separate the results of the individual brainstem reflexes in their database, so that we cannot compare this sign with the absence of pupillary and corneal reflexes which has previously been described [15] as being 100 % predictive of poor outcome in normothermic patients at 72 hours from cardiac arrest. The same paper also documented a 4 % rate of good recovery (CPC 1 or 2) in patients with myoclonus status at 24 hours from CPR. These data contrast with absence of recovery in normothermic patients with post-arrest myoclonus documented in previous observational studies [14–16] in normothermic patients.

As regards biochemical markers, a very early study [43] showed that both the NSE and the S100 thresholds for prediction of poor outcome with a 0 % false positive rate were 2 to 3 times higher in patients treated with therapeutic hypothermia than in those treated in normothermic conditions (NSE > 25 vs. 8.8 μg/l; S100 > 0.23 vs. 0.12 μg/l). More recent studies [44, 45], however, showed that the thresholds for outcome prediction with a 0 % false positive rate at 24 and 72 hours in patients treated with therapeutic hypothermia were equal to or higher than those previously documented in normothermic conditions. The comparison is complicated by the lack of standardization in both study design and measuring techniques, so the real impact of therpautic hypothermia on outcome prediction using biochemical markers is difficult to assess.

As regards neurophysiological investigations, in a study from Rossetti et al. [46], the EEG diagnosis of post-arrest status epilepticus was associated with a 0 % false positive rate (95 % CI 0–40 %) in normothermic patients but with a false positive rate of 11.5 % (95 % CI 4–29 %) in hypothermic patients. SSEP seem to be influenced less by therapeutic hypothermia: one study [43] demonstrated that the bilateral absence of N20 wave on median nerve SSEPs still predicted poor outcome with a false positive rate of 0 %. However, only 3 patients had this finding, so the 95 % CI were very large (0–60 %).

The Bispectral Index Monitor (BIS; Aspect Medical Systems) processes EEG signals recorded on a frontal electrode to calculate a dimensionless number that provides a measure of the patient's level of consciousness [47]. Recent investigations have been made to assess the role of BIS in the prediction of functional outcome in resuscitated patients treated with therapeutic hypothermia. One-single center prospective study [48] measured BIS and suppression ratio during the first 5–10 minutes after the first dose of neuromuscular blockade for therapeutic hypothermia. Results showed that a BIS ≤ 22 had a false positive rate of 6 % (95 % CI 0–28 %) and a suppression ratio ≥ 48 had a 7 % false positive rate (95 % CI 1–26 %) for predicting poor outcome (CPC 3–5). However, another single-center prospective study [49] in whom continuous BIS monitoring was performed for the first 72 hours after resuscitation showed that a BIS value of 0 at any time predicted poor outcome (CPC 3–5) with a false positive rate of 0 % [95 % CI 0–27 %].

Conclusion

Prediction of poor neurological outcome after cardiac arrest should be made with the lowest possible false positive rate and the narrowest possible confidence intervals. In normothermic patients, the most accurate predictive indexes (0 % false positive rate with narrow CIs) based on clinical examination are the presence of

myoclonus status within 24 hours from CPR and the absence of both pupillary and corneal reflexes at 72 hours. Measurement of serum NSE and S100B also allows prediction of poor outcome with 0 % false positive rate within 72 hours from cardiac arrest but their cut-offs vary greatly. Among neurophysiological studies, SSEP showed the most consistent accuracy. Moreover, different from both clinical examination and EEG, they are relatively unaffected by sedative drugs, metabolic derangements and body temperature. As regards neuroimaging studies, MRI evidence of an extensive cortical lesion pattern can increase sensitivity of prediction based on clinical examination only but the role of MRI for outcome prediction after cardiac arrest is still to be defined.

During therapeutic hypothermia, clinical examination may be unreliable and clinical signs that invariably predict poor outcome in normothermic conditions may still be compatible with recovery when recorded after therapeutic hypothermia. In these conditions, neurophysiologic studies, such as SSEP and BIS, may provide more reliable prediction, but evidence is still limited and this needs to be confirmed in larger studies.

References

1. Kouwenhoven WB, Jude JR, Knickerbocker GG (1960) Closed-chest cardiac massage. JAMA 173: 1064 – 1067
2. Nolan JP, Neumar RW, Adrie C, et al (2008) Post-cardiac arrest syndrome: epidemiology, pathophysiology, treatment, and prognostication. A Scientific Statement from the International Liaison Committee on Resuscitation; the American Heart Association Emergency Cardiovascular Care Committee; the Council on Cardiovascular Surgery and Anesthesia; the Council on Cardiopulmonary, Perioperative, and Critical Care; the Council on Clinical Cardiology; the Council on Stroke. Resuscitation 79: 350 – 379
3. Brain Resuscitation Clinical Trial Study Group (1986) Randomized clinical study of thiopental loading in comatose survivors of cardiac arrest. Brain Resuscitation Clinical Trial I Study Group. N Engl J Med 314: 397 – 403
4. Jennett B, Bond M (1975) Assessment of outcome after severe brain damage. Lancet 1: 480 – 484
5. Cummins RO, Chamberlain DA, Abramson NS, et al (1991) Recommended guidelines for uniform reporting of data from out-of-hospital cardiac arrest: the Utstein Style. A statement for health professionals from a task force of the American Heart Association, the European Resuscitation Council, the Heart and Stroke Foundation of Canada, and the Australian Resuscitation Council. Circulation 84: 960 – 975
6. Raina K, Callaway C, Rittenberger J, Holm M (2008) Neurological and functional status following cardiac arrest: Method and tool utility. Resuscitation 79: 249 – 256
7. Rossetti AO, Oddo M, Logroscino G, Kaplan PW (2010) Prognostication after cardiac arrest and hypothermia: a prospective study. Ann Neurol 67: 301 – 307
8. Edgren E, Hedstrand U, Kelsey S, Sutton-Tyrrell K, Safar P (1994) Assessment of neurological prognosis in comatose survivors of cardiac arrest. BRCT I Study Group. Lancet 343: 1055 – 1059
9. Rosen H, Sunnerhagen KS, Herlitz J, Blomstrand C, Rosengren L (2001) Serum levels of the brain-derived proteins S-100 and NSE predict long-term outcome after cardiac arrest. Resuscitation 49: 183 – 191
10. Langhelle A, Nolan J, Herlitz J, et al (2005) Recommended guidelines for reviewing, reporting, and conducting research on post-resuscitation care: the Utstein style. Resuscitation 66: 271 – 283
11. Nolan JP, Morley PT, Vanden Hoek TL, et al (2003) Therapeutic hypothermia after cardiac arrest: an advisory statement by the advanced life support task force of the International Liaison Committee on Resuscitation. Circulation 108: 118 – 121
12. Binks AC, Murphy RE, Prout RE, et al (2010) Therapeutic hypothermia after cardiac arrest – implementation in UK intensive care units. Anaesthesia 65: 260 – 265

13. Wijdicks EF, Hijdra A, Young GB, Bassetti CL, Wiebe S (2006) Practice parameter: prediction of outcome in comatose survivors after cardiopulmonary resuscitation (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 67: 203–210
14. Wijdicks EF, Parisi JE, Sharbrough FW (1994) Prognostic value of myoclonus status in comatose survivors of cardiac arrest. Ann Neurol 35: 239–243
15. Zandbergen EG, Hijdra A, Koelman JH, et al (2006) Prediction of poor outcome within the first 3 days of postanoxic coma. Neurology 66: 62–68
16. Krumholz A, Stern BJ, Weiss HD (1988) Outcome from coma after cardiopulmonary resuscitation: relation to seizures and myoclonus. Neurology 38: 401–405
17. Thomke F, Marx JJ, Sauer O, et al (2005) Observations on comatose survivors of cardiopulmonary resuscitation with generalized myoclonus. BMC Neurol 5:14
18. Datta S, Hart GK, Opdam H, Gutteridge G, Archer J (2009) Post-hypoxic myoclonic status: the prognosis is not always hopeless. Crit Care Resusc 11: 39–41
19. English WA, Giffin NJ, Nolan JP (2009) Myoclonus after cardiac arrest: pitfalls in diagnosis and prognosis. Anaesthesia 64: 908–911
20. Morris H, Howard R, Brown P (1998) Early myoclonic status and outcome after cardiorespiratory arrest. J Neurol Neurosurg Psychiatry 64: 267–268
21. Bassetti C, Bomio F, Mathis J, Hess CW (1996) Early prognosis in coma after cardiac arrest: a prospective clinical, electrophysiological, and biochemical study of 60 patients. J Neurol Neurosurg Psychiatry 61: 610–615
22. Young GB, Doig G, Ragazzoni A (2005) Anoxic-ischemic encephalopathy: clinical and electrophysiological associations with outcome. Neurocrit Care 2: 159–164
23. de Groot YJ, Jansen NE, Bakker J, et al (2010) Imminent brain death: point of departure for potential heart-beating organ donor recognition. Intensive Care Med 36: 1488–1494
24. Fogel W, Krieger D, Veith M, et al (1997) Serum neuron-specific enolase as early predictor of outcome after cardiac arrest. Crit Care Med 25: 1133–1138
25. Rech TH, Vieira SR, Nagel F, Brauner JS, Scalco R (2006) Serum neuron-specific enolase as early predictor of outcome after in-hospital cardiac arrest: a cohort study. Crit Care 10: R133
26. Zingler VC, Krumm B, Bertsch T, Fassbender K, Pohlmann-Eden B (2003) Early prediction of neurological outcome after cardiopulmonary resuscitation: a multimodal approach combining neurobiochemical and electrophysiological investigations may provide high prognostic certainty in patients after cardiac arrest. Eur Neurol 49: 79–84
27. Pfeifer R, Borner A, Krack A, Sigusch HH, Surber R, Figulla HR (2005) Outcome after cardiac arrest: predictive values and limitations of the neuroproteins neuron-specific enolase and protein S-100 and the Glasgow Coma Scale. Resuscitation 65: 49–55
28. Fries M, Kunz D, Gressner AM, Rossaint R, Kuhlen R (2003) Procalcitonin serum levels after out-of-hospital cardiac arrest. Resuscitation 59: 105–109
29. Prohl J, Rother J, Kluge S, et al (2007) Prediction of short-term and long-term outcomes after cardiac arrest: a prospective multivariate approach combining biochemical, clinical, electrophysiological, and neuropsychological investigations. Crit Care Med 35: 1230–1237
30. Scollo-Lavizzari G, Bassetti C (1987) Prognostic value of EEG in post-anoxic coma after cardiac arrest. Eur Neurol 26: 161–170
31. Synek VM (1990) Value of a revised EEG coma scale for prognosis after cerebral anoxia and diffuse head injury. Clin Electroencephalogr 21: 25–30
32. Young GB (2000) The EEG in coma. J Clin Neurophysiol 17: 473–485
33. Madl C, Kramer L, Domanovits H, et al (2000) Improved outcome prediction in unconscious cardiac arrest survivors with sensory evoked potentials compared with clinical assessment. Crit Care Med 28: 721–726
34. Logi F, Fischer C, Murri L, Mauguiere F (2003) The prognostic value of evoked responses from primary somatosensory and auditory cortex in comatose patients. Clin Neurophysiol 114: 1615–1627
35. Zandbergen EG, de Haan RJ, Stoutenbeek CP, Koelman JH, Hijdra A (1998) Systematic review of early prediction of poor outcome in anoxic-ischaemic coma. Lancet 352: 1808–1812
36. Fischer C, Luaute J, Nemoz C, Morlet D, Kirkorian G, Mauguiere F (2006) Improved pre-

diction of awakening or nonawakening from severe anoxic coma using tree-based classification analysis. Crit Care Med 34: 1520 – 1524
37. Sakurai A, Kinoshita K, Moriya T, et al (2006) Reduced effectiveness of hypothermia in patients lacking the wave V in auditory brainstem responses immediately following resuscitation from cardiac arrest. Resuscitation 70: 52 – 58
38. Wu ET, Li MJ, Huang SC, et al (2009) Survey of outcome of CPR in pediatric in-hospital cardiac arrest in a medical center in Taiwan. Resuscitation 80: 443 – 448
39. Wijman CA, Mlynash M, Caulfield AF, et al (2009) Prognostic value of brain diffusion-weighted imaging after cardiac arrest. Ann Neurol 65: 394 – 402
40. Topcuoglu M (2009) Prognostic value of magnetic resonance imaging in postresuscitation encephalopathy. Intern Med 48: 1635 – 1645
41. Bernard SA, Gray TW, Buist MD, et al (2002) Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. N Engl J Med 346: 557 – 563
42. Hypothermia after Cardiac Arrest Study Group (2002) Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. N Engl J Med 346: 549 – 556
43. Tiainen M, Kovala TT, Takkunen OS, Roine RO (2005) Somatosensory and brainstem auditory evoked potentials in cardiac arrest patients treated with hypothermia. Crit Care Med 33: 1736 – 1740
44. Rundgren M, Karlsson T, Nielsen N, Cronberg T, Johnsson P, Friberg H (2009) Neuron specific enolase and S-100B as predictors of outcome after cardiac arrest and induced hypothermia. Resuscitation 80: 784 – 789
45. Shinozaki K, Oda S, Sadahiro T, et al (2009) Serum S-100B is superior to neuron-specific enolase as an early prognostic biomarker for neurological outcome following cardiopulmonary resuscitation. Resuscitation 80: 870 – 875
46. Rossetti AO, Logroscino G, Liaudet L, et al (2007) Status epilepticus: an independent outcome predictor after cerebral anoxia. Neurology 69: 255 – 260
47. Avidan MS, Zhang L, Burnside BA, et al (2008) Anesthesia awareness and the bispectral index. N Engl J Med 358: 1097 – 1108
48. Seder DB, Fraser GL, Robbins T, Libby L, Riker RR (2009) The bispectral index and suppression ratio are very early predictors of neurological outcome during therapeutic hypothermia after cardiac arrest. Intensive Care Med 36: 281 – 288
49. Stammet P, Werer C, Mertens L, Lorang C, Hemmer M (2009) Bispectral index (BIS) helps predicting bad neurological outcome in comatose survivors after cardiac arrest and induced therapeutic hypothermia. Resuscitation 80: 437 – 442

Neuroprotection in Sepsis by Complement Inhibition and Immunoglobulin Therapy

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Introduction

Understanding of the importance of inflammation's role in many neurologic disease pathogenesis has increased rapidly in recent years. Neuroinflammation has been viewed as the most common phenomenon observed in disorders of the central nervous system (CNS), either in the acute insult, like infection, trauma, and stroke, or in chronic neurodegenerative states like Alzheimer's disease, Parkinson's disease and multiple sclerosis [1]. This 'neuroinflammation hypothesis' further challenged attempts to expand our understanding of neuronal injury and neurodegeneration because of the activation of brain cells to stress and insult, and targeting neuroinflammation and the major elements of the inflammatory response has become the most effective neuroprotective strategy [2].

Activation of the complement system, which is a component of the innate immune response, has been shown to play a critical role in tissue damage caused by neuroinflammation. Studies have demonstrated that all of the activation components and receptors of the complement system are produced by brain cells [3]. There is also evidence to indicate an active role of the complement system in cerebral ischemic injury [4], and the pathogenesis of several neurodegenerative diseases [5, 6]. The role of the complement cascade in endotoxin-induced septic encephalopathy has been studied recently, with the results suggesting that targeting activation of the complement system may be a viable therapeutic avenue in septic encephalopathy [7].

Complement inhibition strategies have been shown to be effective in animal models of cerebral ischemia/reperfusion injury [8], traumatic brain injury (TBI) [9] and cerebral injury due to sepsis [10]. Experimental studies have demonstrated that the use of specific inhibitors to block complement activation or their mediators, such as C5a, can reduce local tissue injury after ischemia/reperfusion [8] and attenuate brain damage in sepsis [10]. One new form of therapy against neuroinflammation is the use of intravenous immunoglobulins, which are less specific in targeting complement activation than the monodrug complement inhibitors. Intravenous immunoglobulin (IVIG) has the potential to regulate many components of the inflammatory response, including complement activation, cytokine production, and cell adhesion [11]. Thus, IVIG may directly protect neurons by reducing the activation of the brain cells, and by inhibiting infiltration of leukocytes into the brain parenchyma [12]. Neuroprotective actions of IVIG have been demonstrated recently in animal models of ischemic stroke [8]. We recently showed that administration of IVIG to septic rats reduced the amount of brain damage by protecting the integrity of the blood brain barrier

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[13]. This chapter will address our current understanding of neuroprotection by complement inhibition and immunoglobin therapy in sepsis-induced brain damage.

'The Neuroinflammatory Hypothesis' and Brain Injury in Sepsis

The brain was once considered as an immune-privileged organ; however, research has showed that brain cells (microglia, astrocytes and oligodendrocytes) are involved in neuroinflammation and neuroimmune activation [14]. These cells not only serve supportive and nutritive roles for neurons, but in healthy brain they respond to any type of stress and insult by upregulating inflammatory processes. This response is usually kept in balance with other endogeneous anti-inflammatory and neuroprotective responses that return the brain to homeostasis. When this homeostasis is disturbed in disease states, like trauma, ischemia or sepsis, uncontrolled glial activation causes release of cytokines, chemokines and other neurotoxic substances, which enter the brain by volume diffusion and gain access to neural structures in the deeper areas causing cellular dysfunction and neuronal cell loss [2]. As a consequence, the clinical picture includes functional disturbances, behavioral disorders and even neurodegeneration causing permanent loss.

In sepsis, the exact mechanism of brain injury remains elusive. The association between inflammation and the brain is complex and reciprocal. Brain involvement in sepsis is both a direct consequence of sepsis and secondary to various associated complications. In normal conditions, the brain plays an important role in response to infection and inflammation. The brain senses the presence of infection and inflammation and then mounts a strong modulatory response through three efferent pathways: The hypothalamic-pituitary-adrenal (HPA) axis, the sympathetic nervous system, and the cholinergic anti-inflammatory pathway [15]. In this way, the brain orchestrates the host response in a coordinated manner at behavioral, neuroendocrine and autonomic levels. When this normal response is disrupted, like in severe sepsis, these disturbances alter the homeostasis and influence the course of septic shock which then will cause various complications leading to organ dysfunction, including the brain itself. Hence, the associated complications of organ failure, e.g., hemodynamic and metabolic alterations, liver failure, hypoxemia, contribute to brain dysfunction as a secondary consequence of sepsis. But, most importantly, this activation pathway sensed by the target brain structures may in fact become directly harmful for brain cells, for the endothelium and for the blood brain barrier [16].

The breakdown of the blood brain barrier is considered as the major pathophysiologic mechanism of brain involvement in sepsis [17]. Lipopolysaccharide (LPS) and pro-inflammatory cytokines activate cerebral endothelial cells, which disrupts the integrity of the blood brain barrier and facilitates passage of neurotoxic factors and cytokines, which further activate target brain cells and cause cellular dysfunction, oxidative stress and apoptosis [17, 18]. Dysfunction of the blood brain barrier has been shown to be induced by various inflammatory mediators, such as interleukin (IL)-1, tumor necrosis factor (TNF)-α, in the absence of a bacterial pathogen [19]. Complement activation has been linked to sepsis-induced breakdown of the blood brain barrier; moreover, the permeability defect has been shown to cause further complement activation inside the CNS

leading to further neuronal damage [20]. Manipulating this immune activation and its effects on the blood brain barrier has been investigated as a therapeutic target in sepsis-induced brain injury. A different pharmacological approach to LPS-induced changes in blood brain barrier permeability was investigated *in vitro* [21]. Dexamethasone-pretreated endothelial cells were shown to be more resistant to LPS-induced disruption of the blood brain barrier. LPS has been targeted as a therapy option and binding circulating LPS by serum amyloid P component showed protective effects on mice [22]. Recently, targeting activation of the complement system has been suggested as a viable therapeutic avenue in septic encephalopathy [7]. Since IVIG has the potential to inhibit many components of inflammation, we tested the effect of IVIG in an experimental model of cecal ligation and puncture (CLP)-induced septic encephalopathy [13]. IVIG treatment in acute and chronic neuroinflamatory disorders is a relatively new area of research. Both bench and bedside research have demonstrated the beneficial effects of IVIG not only in chronic insults due to neuroinflammation but also in acute injury states, like ischemia and stroke [23]. The mechanisms by which IVIG exerts these therapeutic effects involve multiple immunomodulatory processes.

Brain Injury Pathways Targeted by IVIG Treatment

Targeting complex immune activation in neuroinflammation by immunoglobulin therapy for immunomodulation is not a new event. IVIG treatment has been used to treat various inflammatory and autoimmune diseases and has become an established treatment for many neurological disorders, such as chronic inflammatory demyelinating polyneuropathy [24], multifocal motor neuropathy [25] and Guillain–Barré syndrome [26]. The effect of IVIG has also been tested in patients with Alzheimer's disease [27]. There are also experimental studies on acute injury like traumatic spinal cord injury [28], and ischemic brain injury [29].

Although the mechanisms by which IVIG exerts a therapeutic effect in numerous diseases are not well understood, many groups have suggested immunoregulatory mechanisms of action for IVIG [30]. Specifically the mode of action of IVIGs on neuronal tissue injury seems complex; however *in vivo* and *in vitro* trials on different brain injury models due to inflammation have recently thrown light on how IVIG might work for neuroprotection. The demonstrated mechanisms include neutralization of pathogenic antidodies by crystallizable fragment (Fc) receptor blockade [31], effects on the Fas apoptotic pathway [32], regulation of complement components [33], modulation of cytokine secretion [34], decrease in leukocyte recruitment [35], attenuation of T cell stimulation, and direct effects on brain cells [36].

Efficacy of IVIG therapy during inflammatory diseases depends on two major mechanisms. The first is the antigen binding and modification of various effector functions that is mediated by the antigen binding fragment (Fab) of IVIG. With this function IVIG eliminates bacteria, toxins andother pathogens. The second function involves IVIG binding to various Fc receptors resulting in modulation of expression and function of these receptors. This is critical for immunomodulatory actions such as modulation of complement activation, interference with cytokine production and modulation of T and B cell activation [33–36]. These functions are critical for IVIG to play important roles in various features of inflammation causing brain injury in different disease states.

Using intravital microscopy, the effects of IVIG on leukocyte recruitment in superficial brain vessels were visualized. IVIG reduced leukocyte rolling and adhesion in experimental autoimmune encephalomyelitis (EAE) and treatment with IVIG decreased the EAE score, an indicator of disease severity [12]. It has been suggested that IVIG exerts these actions either through its effects on cytokine production, or direct effects by reducing cell adhesion molecule production. The possibility that this kind of inflammatory reaction contributes to brain injury is supported by experimental data that describe a reduction in stroke-induced infarct size and brain edema formation in animals treated with antibodies against specific cell adhesion molecules [8]. There is evidence to indicate that IVIG prevents cell adhesion by downregulating endothelial cell intercellular adhesion molecule (ICAM)-1 and targeting E-selectin and P-selectin interactions [35].

Modulation of the production of cytokines and cytokine antagonists is another major mechanism by which IVIG exerts its anti-inflammatory effects in various neurologic disorders. Studies have demonstrated that IVIG contains high affinity neutralizing antibodies against IL-1, IL-6, and TNF-α that are sufficient to inhibit circulating pro-inflammatory pathogenic cytokines downregulating their synthesis by their effects on T cells. IVIG was shown to selectively trigger the production of IL-1 receptor antagonist (IL-1ra), the natural antagonist of IL-1 [34].

With its receptor binding effect, IVIG also modulates apoptosis. Studies demonstrated that IVIG contains natural anti-Fas receptor autoantibodies that block Fas ligand/anti-Fas receptor interactions and prevent apoptosis and directly protect neurons against ischemia [32]. In contrast, IVIG was shown to induce apoptosis in lymphocytes and monocytes as well as normal B cells. By promoting apoptosis of activated immune cells, IVIG attenuates the severity of the pro-inflammatory reaction.

Finally, the striking neuroprotective actions of IVIG have been attributed to its complement regulatory effects, since the involvement of the complement system in promoting acute brain injury following infection, trauma, and stroke seems assured. It has been shown that interaction of IVIG with the complement system prevents the generation of harmful complement fragments and subsequent tissue damage by scavenging active complement components and diverting complement attack from cellular targets [37]. IVIG binds the activated components and prevents the deposition of these fragments on target cell surfaces. These effects of immunoglobulins on the complement system imply their role in diseases mediated by inappropriate complement activation.

The Role of the Complement Cascade In Brain Injury

The complement cascade is the major element of the inflammatory response. Complement proteins are the first line of defense against invading microorganisms. Complement also acts as an effector arm of the acquired immune system. Through its action of complementing specific antibodies, the complement system helps to eliminate the intruding pathogens. This kind of complement activation, either local or from the periphery, is necessary and works for good; however, it may also promote tissue damage. This latter effect plays an important role in the pathogenesis of numerous disease states in humans [38, 39]. Complement activation has been shown to occur after trauma, hemorrhage, and ischemia/reperfusion injury [40], and changes in host cells leading to antigen-antibody complexes

can activate complement and result in cell lysis and tissue damage. Activation of the complement system also occurs in a variety of neuroinflammatory diseases and neurodegenerative procedures of the CNS. Complement activation within the CNS is a double edge sword as it is necessary to maintain health, yet can have deleterious effects when activated [19]. Complement proteins have been shown to be induced in brains of patients with Alzheimer's disease [5]. Complement activation products have also been observed in patients with motor neuron degenerative disease [6]. The role of complement in TBI is also well reported [9].

Experimental studies suggest a pathophysiologic role for intracerebral complement activation contributing to inflammation, leukocyte recruitment, neuronal cell death and blood brain barrier dysfunction in ischemia/reperfusion injury, and also in a stroke model [40]. Regional brain ischemia induced an inflammatory response initiated by complement activation and generation of active fragments such as C3a and C5a anaphylatoxins [41, 42]. In addition to their direct biological effects, these fragments stimulate the expression of pro-inflammatory cytokines in leukocytes which further augment the severity of the inflammatory response. In these trials, the complement anaphylatoxin, C5a, seemed to be a key initiator leading to neuronal damage and loss. C5a has been characterized as a mediator of blood brain barrier dysfunction in a variety of CNS disorders, including TBI and meningitis [43, 44]. C5Ra, a C5a receptor antagonist, has been tested in these models and tissue damage was reduced by antagonizing the complement.

The activation of the complement cascade has been associated with organ failures and fatal outcomes in sepsis. Excessive production of the complement activation product, C5a, has been reported during the development of sepsis in rodents [45]. The role of the complement cascade has been recently implicated in the pathophysiology of septic encephalopathy [7]. In this experimental trial, LPS treatment induced complement activation leading to upregulation of brain expression of CD45, TNF-α and Toll-like receptor (TLR)4. These alterations were shown to be complement-dependent and were prevented by complement inhibition. Consistent with the capacity of these inflammatory mediators, there was increased apoptosis as determined by DNA fragmentation and TUNEL staining on LPS treatment. In addition, there was increased water content in the brain, similar to the cerebral edema observed in sepsis [7]. These results suggested that targeting activation of the complement system may be a viable therapeutic avenue in septic encephalopathy.

Blocking complement has been shown to markedly reduce brain inflammation and tissue damage [10]. Inhibition of complement showed neuroprotective effects in CLP-induced septic animals. Complement anaphylatoxin, C5a, characterized as a mediator of blood brain barrier dysfunction was blocked and permeability and pituitary function were assessed. Results showed blockage prevented the blood brain barrier breakdown and ameliorated the sepsis-induced pituitary dysfunction. These results were challenged by the discussion on the total blockage of complement fragments, since many actions of the complement system appear to promote beneficial effects, like neuronal survival and tissue remodeling [46]. Directing activation of the complement system or regulating the activation and scavenging the fragments has been suggested to provide a better therapeutic rationale than inhibiting it. The use of IVIG is a new form of therapy which is less specific in targeting complement than complement blocking monodrug administration. Studies demonstrated that IVIG is a perfect complement cascade regulator and complement fragment scavenger [37].

Immunoglobulins play an interesting role in complement activation and regulation. They have the ability to trigger generation of active complement fragments for good, e.g., to eliminate pathogens, and they also have the capacity to attenuate the damaging effects of activated complement fragments. By scavenging complement fragments, they prevent the effects of these fragments on target cells and subsequent immune damage. This switch between activation and suppression seems to depend on the specificity of the antibody. When a single clone of plasma cells start producing specific antibodies against a pathogen or auto-antigen, the rest of the plasma cells contribute to the normal circulating immunoglobulin pool which serve as a buffer against the harmful effects of excessive production of complement fragments. In case of overproduction of pathogenic antibodies, the capacity of normal 'non-specific' immunoglobulins to attenuate complement activation by scavenging harmful fragments reaches saturation. At that point it becomes necessary to infuse exogenous immunoglobulins in the form of IVIG [37]. Among IVIG classes, IgM containing IVIG preparations appeared to be more efficient complement suppressors than standard IgG. The complement inhibitory activity of different types of IgG was assessed *in vitro* by measurement of C1, C4 and C3 deposition [47]. Complement inhibition was best for IgM followed by IgGAM, whereas an IgA preparation did not show any inhibitory effect. Among immunoglobulin types, pure IgM was shown to be most effective in preventing complement deposition followed by IgG. As in various types of autoimmune and systemic inflammatory diseases, targeting complement activation in neuroiflammation with immunoglobulins has recently been shown to be beneficial in many neurological diseases [23–29].

Neuroprotection by IVIG in Sepsis

The effect of immunoglobulins on the complement system explains their role in homeostasis as well as the expansion of the use of IVIGs in diseases mediated by inappropriate complement activation [37]. The role of IVIG as an adjunctive treatment in sepsis has been a subject of debate for years. However, there is evidence that the use of hyperimmune serum, containing an enriched fraction of IVIGs may be of benefit in sepsis, the pathology of which is also thought to include activation of the complement system [48].

The neuroprotective effects of IVIGs were first mentioned in a retrospective study evaluating the incidence of critical illness polyneuropathy (CIP) [49] in patients with Gram-negative sepsis and organ dysfunction. Here the investigators found that those patients who had been treated with IVIG enriched with IgM, showed no signs of CIP during electrophysiological examination. Similar results were also demonstrated in a large randomized control trial, the SBITS trial [50], in which a shorter duration of mechanical ventilation was correlated with IVIG treatment. Amelioration in the motor response accounted for the effect on critical illness neuropathy, which might explain the shorter duration of mechanical ventilation in the treatment arm.

Other than neurodegenerative diseases, the protective effect of IVIG on brain dysfunction due to inflammatory response has also been studied in different diseases like stroke, ischemia/reperfusion and trauma. However, use of IVIG in sepsis-induced encephalopathy has not yet been reported, although there seems potential for the exploratory use of IVIG in encephalopathy due to sepsis. We

tested the neuroprotective effect of two different kinds of IVIG preparations in an experimental model of sepsis [13].

In CLP-induced septic rats, we investigated the effects of commercially available IVIGs on blood-brain barrier integrity and survival rate. Since the superior activity of IgM on the complement system has been demonstrated in experimental trials, we also tested the effects of IgM-enriched immunoglobulins (IgGAM-Pentaglobin) as well as standard IVIG. A high mortality rate (34 %) was noted in septic animals and the mortality rate was decreased to 15 % and 3 % by IgG and IgGAM, respectively. Both IgG and IgGAM alleviated the sickness behavior in septic rats and the animals were observed to be healthy and active.

Using Evans blue (EB) dye to color the brain revealed both visual (**Fig. 1**) and quantitative (**Fig. 2**) blood brain barrier breakdown after sepsis induction. This extravasation of EB dye into the brain tissue of septic animals was markedly decreased by both IgG and IgGAM. We also measured occludin immunoreactivity, which remained essentially unchanged in all groups including CLP. In addition, strong staining for horseradish peroxidase (HRP) was seen around vessels located in the cerebral cortex and the hippocampus in septic animals. Increased luminal and abluminal vesicles containing electron-dense HRP reaction product were noted in the cytoplasm of endothelial cells in the cerebral cortex and hippocampus of septic rats emphasizing increased blood brain barrier permeability predominantly by the transendothelial route. In these animals, tight junctions were ultrastructurally intact suggesting that the paracellular pathway of the blood brain barrier is not responsible for the blood brain barrier breakdown in sepsis. Following IgG or IgGAM treatment, no ultrastructural evidence of leaky capillaries was observed in the brain in septic animals indicating blockade of the transcellular pathway. Electronmicroscopy findings also supported sepsis-induced transcellular dysfunction of the blood brain barrier, which was reversed with the administration of IgG and IgGAM preparations. To our knowledge, our data are

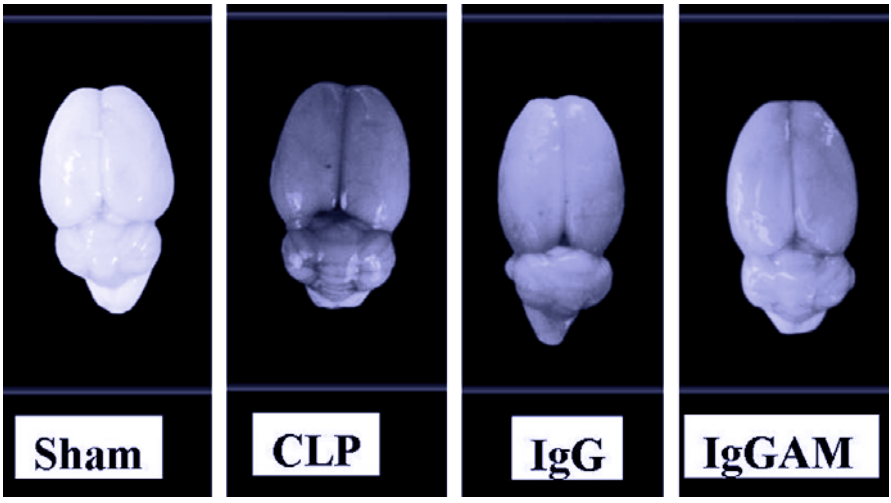

Fig. 1. Gross view of rat brains showing Evans blue (EB) extravasation into the brain in sham rats, and rats that underwent cecal ligation and puncture (CLP) with/without IgG and IgGAM. Note reduced EB dye leakage in IgG and IgGAM-treated rats at 24 h after CLP.

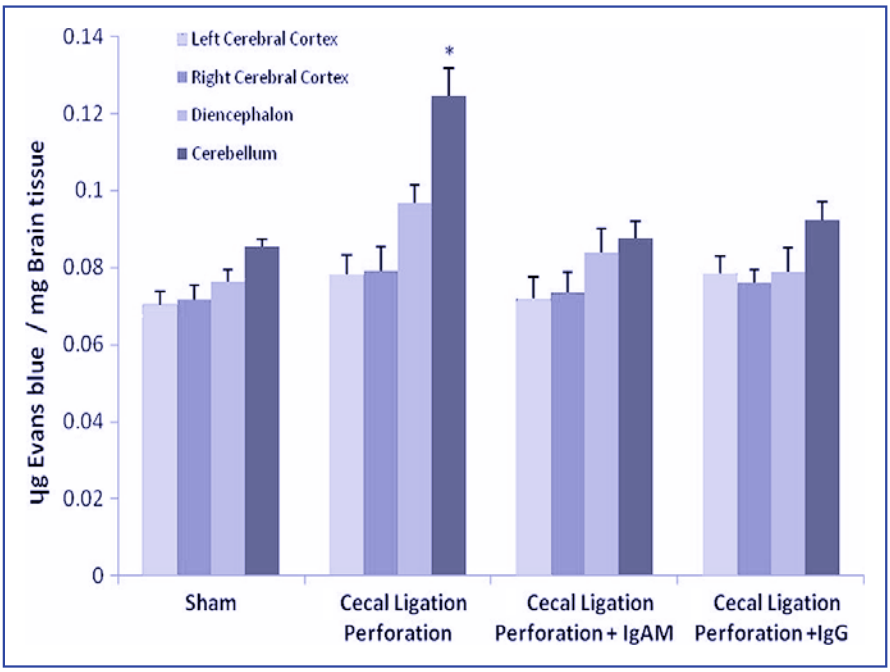

Fig. 2. Evans blue (EB) dye content in the brain regions of animals. Data are shown as means ± S.E.M. *$p < 0.01$ versus other groups.

the first to show neuroprotection with immunoglobulins in sepsis-induced brain injury. This is not surprising since IVIG involve multiple immunomodulatory pathways. We think that the major effect is most probably through action on the complement activation pathway, since this pathway has been demonstrated in many different animal models of brain injury due to inflammation. It remains to be determined whether our findings can be extrapolated to humans, since this neuroprotective action of IVIG in animal models of different neuroinflammatory injuries, like stroke, trauma and sepsis, suggests a therapeutic potential that merits consideration for clinical trials in patients.

Conclusion

Initially introduced as a replacement therapy, IVIG is now widely used for the treatment of a number of autoimmune and systemic inflammatory diseases. Besides these medical conditions, evidence suggests that many other conditions, such as inflammatory disorders with an imbalance in the cytokine network, could benefit from IVIG treatment. Targeting complex immune activation in neuroinflammation by immunoglobulin therapy for immunomodulation is not new. IVIG treatment has been used to treat many neurological disorders such as chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy and Guillain–Barré syndrome. The effects of IVIG have also been tested in patients with Alzheimer's disease. There are also experimental studies on acute injury like TBI and ischemia/reperfusion injury.

In sepsis, the use of IVIG represents a therapeutic effort to positively modulate the immune response, thereby preventing organ dysfunction. Brain dysfunction is a serious and common complication of sepsis. Although the exact pathophysiology of brain injury in sepsis is far from fully understood, activation of the complement cascade, a potent arm of the innate immune response, has been suggested to play a critical role. Inhibition of complement anaphylatoxin C5a showed neuroprotective effects in CLP-induced septic animals. However, total blockage of complement fragments was discussed, since many effects of the complement system appear to promote beneficial effects on neurons. IVIG is a new form of therapy which is less specific in its targeting of complement than monodrug administration. We recently demonstrated that administration of IVIG to septic rats reduced the amount of blood brain barrier damage and eliminated mortality. Our results suggest another rationale for the use of IVIG in sepsis. We think that the neuroprotective actions of IVIG in animal models of different neuroinflammatory injuries, like stroke, trauma and sepsis, suggest a therapeutic potential that merits consideration for clinical trials in patients.

References

1. GriffinWS, Sheng JG, Royston MC, et al (1998) Glial-neuronal interactions in Alzheimer's disease : the potential role of a "cytokine cycle" in disease progression. Brain Pathol 8: 65 – 72
2. Craft JM, Watterson DM, Van Eldik LJ (2005) Neuroinflammation : a potential therapeutic target. Expert Opin Ther Targets 9: 887 – 900
3. Gasque P, Pontaine M, Morgan BP (1995) Complement expression in human brain. J Immunol. 154: 4726 – 4733
4. Arumugam TV, Shiels IA, Woodruff TM, Granger DN, Taylor SM (2004) The role of the complement system in ischemia-reperfusion injury. Shock 5: 401 – 409
5. Bradt BM, Kolb WP, Cooper NR (1998) Complement dependent proinflammatory proteins of Alzheimer's disease beta-peptide. J Exp Med 188: 431 – 438
6. Kulkarni AP, Kellaway LA, Lahiri DK, Kotwal GJ (2004) Neuroprotection from complement-mediated inflammatory damage. Ann NY Acad Sci 1035: 147 – 164
7. Jacob A, Hensley LK, Safratowich BD, Quigg RJ, Alexander JJ (2007) The role of complement cascade in endotoxin-induced septic encephalopathy. Lab Invest 87: 1186 – 1194
8. Arumugam TV, Tang SC, Lathia JD, et al (2007) Intravenous immunoglobulin (IVIG) protects the brain against experimental stroke by preventing complement-mediated neuronal cell death. Proc Natl Acad Sci USA 104: 14104 – 14109
9. Sewell DL, Nacewicz B, Liu F, et al (2004) Complement C3 and C5 play critical roles in traumatic brain cryoinjury: blocking effects on neutrophil extravasation by C5a receptor antagonist. J Neuroimmunol 155: 55 – 63
10. Flierl MA, Stahel PF, Rittirsch D, et al (2009) Inhibition of complement C5a prevents breakdown of the blood-brain barrier and pituitary dysfunction in experimental sepsis. Crit Care 13: R12
11. Sapir T, Shoenfeld Y (2005) Facing the enigma of immunomodulatory effects of intravenous immunoglobulin. Clin Rev Allergy Immunol 180: 9 – 16
12. Lapointe BM, Herx LM, Gill V, Metz LM, Kubes P (2004) IVIg therapy in brain inflammation: etiology dependent differential effects on leukocyte recruitment. Brain 127: 2649 – 2656
13. Esen F, Senturk E, Ergin Ozcan P, et al. (2010) Intravenous immunoglobulins prevent breakdown of the blood-brain barrier in experimental sepsis. Crit Care 14 (Suppl 1): P24(abst)
14. Skaper SD (2007) The brain as a target for inflammatory processes and neuroprotective strategies. Ann NY Acad Sci 1122: 23 – 34
15. Tracy KJ (2002) The inflammatory reflex. Nature 420: 853 – 859
16. Sharshar T, Hopkinson NS, Orlikowski D, Annane D (2005) Science review: The brain in sepsis – culprit and victim. Crit Care 9: 37 – 44

17. Papadopoulos MC, Davies DC, Moss RF, Tighe D, Bennett ED (2000) Pathophysiology of septic encephalopathy: a review. Crit Care Med 28: 3019 – 3024
18. Papadopoulos MC, Lamb FJ, Moss RF, Davies DC, Tighe D, Bennett ED (1999) Faecal peritonitis causes edema and neuronal injury in pig cerebral cortex Clin Sci 96: 461 – 466
19. Alexander JJ, Anderson AJ, Barnum SR, Stevens B, Tenner AJ (2008) The complement cascade: Yin-Yang in neuroinflammation – neuro-protection and –degeneration. J Neurochem 107: 1169 – 1187
20. Lossinsky AS, Shivers RR (2004) Structural pathways for macromolecular and cellular transport across the blood-brain barrier during inflammatory conditions Review Histol Histopathol 19: 535 – 564
21. Gaillard PJ, de Boer AB, Breimer DD (2003) Pharmacological investigations on LPS-induced permeability changes in the blood– brain barrier invitro. Microvasc Res 65: 24 – 31
22. Vaszelka S, Urbanyi Z, Pazmany T, et al (2005) Human serum amyloid P component attenuates the bacterial lipopolysaccaride-induced increase in blood brain barrier permeability in mice. Neurosci Lett 352: 57 – 60
23. Arumugam TV, Woodruff TM, Lathia JD, Selvaraj PK, Mattson MP, Taylor SM (2009) Neuroprotection in stroke by complement inhibition and immunoglobulin therapy. Neuroscience 158: 1074 – 1089
24. Misra N, Bayry J, Ephrem A, et al (2005)Intravenous immunoglobulin in neurological disorders: a mechanistic perspective. J Neurol 252: 11 – 16
25. Antel J, Bar-Or A (2006) Roles of immunoglobulins and B cells in multiple sclerosis: from pathogenesis to treatment. J Neuroimmunol 180: 3 – 8
26. Hughes RA, Comblath DR (2005) Guillain-Barre syndrome. Lancet 366: 1653 – 1666
27. Dodel RC, Du Y, Depboylu C, et al (2004) Intravenous immunoglobulins containing antibodies against beta-amyloid for the treatment of Alzheimer's disease. J Neurol Neurosurg Psychiatry 75: 1472 – 1474
28. Gok B, Sciubba DM, Okutan O, et al (2009) Immunomodulation of acute experimental spinal cord injury with human immunoglobulin. J Clin Neurosci 16: 549 – 553
29. Arumugam TV, Selvaraj PK, Woodruff TM, Mattson MP (2008) Targeting ischemic brain injury with intravenous immunoglobulin. Expert Opin Ther Targets 12: 19 – 29
30. Negi VS, Elluru S, Sibéril S, et al (2007) Intravenous immunoglobulin: an update on the clinical use and mechanisms of action. J Clin Immunol 27: 233 – 245
31. Stangel M, Compston A (2001) Polyclonal immunoglobulins (IVIg) modulate nitric oxide production and microglial functions invitro via Fc receptors. J Neuroimmunol 112: 63 – 71
32. Prasad NK, Papoff G, Zeuner A, et al (1998) Therapeutic preparations of normal polyspecific IgG (IVIg) induce apoptosis in human lymphocytesa nd monocytes: a novel mechanism of action od IVIg involving the Fas apoptotic pathway. J Immunol 161: 3781 – 3790
33. Basta M, Van Goor F, Luccioli S, et al (2003) F(ab)-mediated neutralization of C3a and C5a anaphylatoxins: a novel effector function of immunoglobulins. Nature Med 4: 431 – 438
34. Crow AR, Song S, Semple JW, Freedman J, Lazarus AH (2007) A role for IL-1 Receptor antagonist or other cytokines in the acute therapeutic effects of IVIg? Blood 109: 155 – 158
35. Jonas E, Dwenger A, Jonas M. (1995) Chemiluminescence response and adherence of neutrophils to cultured endothelial cells – influence of immunoglobulin G. J Biolumin Chemilumin 10: 169 – 173
36. Toungouz M, Denys CH, De Groote D, Dupont E (1995) In vitro inhibition of tumor necrosis factor–alpha and interleukin – 6 production by intravenous immunoglobulins. Br J Haematol 89: 698 – 703
37. Basta M (2008) Ambivalent effects of immunoglobulins on the complement system: Activation versus inhibition. Mol Immunol 45: 4073 – 4079
38. Ballander BM, Singhrao SK, Ohlsson M, Mattsson P, Svensson M (2001) Complement activation in the human brain after traumatic brain injury. J Neurotrauma 18: 1295 – 1311
39. Kaczorowski SL, Schiding JK, Toth CA, Kochanek PM (1995) Effect of soluble complement receptor-1 on neutrophil accumulation after traumatic brain injury in rats. J Cereb Blood Flow Metab 15: 860 – 864
40. Arumugam TV, Magnus T, Woodruff TM, Proctor LM, Shiels IA, Taylor SM (2006) Complement mediators in ischemia-reperfusion injury. Clin Chim Acta 374: 33 – 45

41. Mocco J, Mack WJ, Ducruet AF, et al (2006) Complement component C3 mediates inflammatory injury following focal cerebral ischemia. Circ Res 99: 209 – 217
42. O'Barr SA, Caguioa J, Gruol D, et al (2001) Neuronal expression of a functional receptor for the C5a complement activation fragment. J Immunol 166: 4154 – 4162
43. Persson M, Pekna M, Hansson E, Rönback L (2009) The complement derived anaphylatoxin C5a increases microglial GLT-1 expession and glutamate uptake in a TNF-a independent manner. Eur J Neurosci 29: 267 – 274
44. Faustmann PM, Krause D, Dux R, Dermietzel R (1995) Morphological study in the early stages of complement C5a fragment-induced experimental meningitis: activation of macrophages and astrocytes. Acta Neuropathol 89: 239 – 247
45. Riedemann NC, Guo RF, Neff TA, et al (2002) Increased C5a receptor expression in sepsis. J Clin Invest 110: 101 – 108
46. Annane D (2009) Sepsis associated delirium: the pro and con of C5a blockade. Crit Care 13: 135
47. Rieben R, Roos A, Mulzert Y, Tinguely C, Gerritsen AF, Daha MR (1999) Immunoglobulin M-enriched human intravenous immunoglobulin prevents complement activation in-vitro and in-vivo in a rat model of acute inflammation. Blood 93: 942 – 951
48. Laupland KB, Kirkpatrick AW, Delaney A (2007) Polyclonal intravenous immunoglobulin for the treatment of severe sepsis and septic shock in critically ill adults: a systematic review and metaanalysis. Crit Care Med 35: 2689 – 2692
49. Mohr M, Englisch L, Roth A, Burchardi H, Zielmann S (1997) Effects of early treatment with immunoglobulin on critical illness polyneuropathy following multiple organ failure and gram-negative sepsis. Intensive Care Med 23: 1144 – 1149
50. Werdan K, Pilz G, Bujdoso O, et al (2007) Score-based immunoglobulin G therapy of patients with sepsis: the SBITS study. Crit Care Med 35: 2693 – 2701

Ethics in Disorders of Consciousness

A. Demertzi, S. Laureys, and M.-A. Bruno

Introduction

The introduction of the mechanical ventilator in the 1950s and the development of intensive care in the 1960s permitted many patients to sustain their vegetative functions and survive severe injuries. Despite such advances, in many cases patients were found to suffer from altered states of consciousness which had never been encountered before as these patients would normally have died from apnea [1]. The imminent ethical impact of these profound states of unconsciousness was reflected in the composition of the first bioethical committees discussing the redefinition of life and the concept of therapeutic obstinacy. In 1968, the Ad Hoc Committee of Harvard Medical School published a milestone paper for the redefinition of death as irreversible coma and brain failure [2]. The committee was comprised of ten physicians, a theologian, a lawyer and a historian of science, betokening the medical, legal and societal debates that were to follow. We will here give a brief overview of some ethical issues related to the concept of consciousness and the medical management of patients with disorders of consciousness, such as comatose, vegetative and minimally conscious states that may be encountered in the intensive care setting. We will emphasize the problem of pain management and end-of life decision-making.

Ethical Issues in Clinical Management

Confusions and controversies are often related to the way we define things. One such multifaceted term is consciousness, which has many divergent connotations [3]. The way we define consciousness is crucial, as it may govern our attitudes towards medical management of disorders of consciousness. For example, in a survey among medical and paramedical professionals (n = 1858), compared to a student population (n = 250), we recently found that although the majority of health-care workers denied a distinction between consciousness and the brain, more than one-third of medical and paramedical professionals still regarded the mind and brain as separate entities (**Fig. 1**). Such dualistic opinions may have implications in the formulation of scientific questions about the nature of consciousness, in the clinical management of disorders of consciousness, and in the reception of both by the general public [4]. We here adopt a perspective where consciousness is clinically defined as having two components, wakefulness and awareness [5]. Under this definition, many variant altered states of consciousness may be hosted. The most transient and most familiar to us all is the transition

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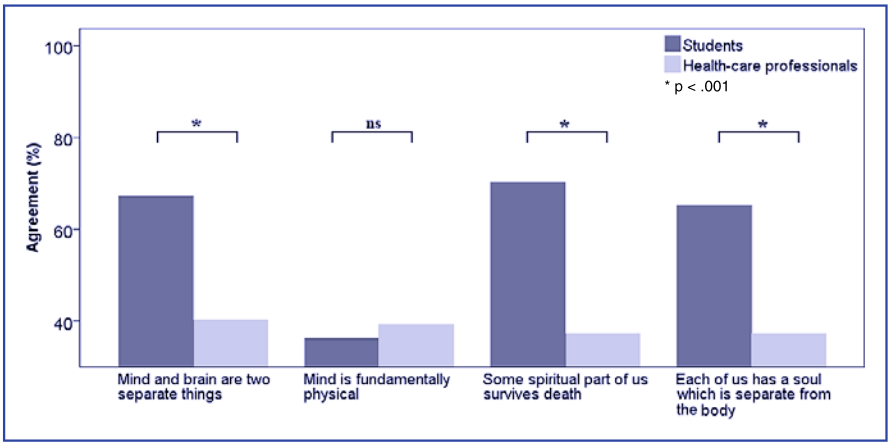

Fig. 1. Dualistic attitudes towards the mind-brain relationship among students (Edinburgh survey, n = 250) and health-care professionals (Liège survey, n = 1858). Adapted from [4] with permission.

from conscious wakefulness to deep sleep; the drowsier we become, the less aware we get of our surroundings and of ourselves. This implies that patients in coma and under anesthesia (i.e., pharmacological coma) are unaware because they cannot be awakened, even after noxious stimulation. The vegetative state is defined as 'wakefulness without awareness', in which patients may open their eyes but will never exhibit non-reflex voluntary movements [6]. A patient in a minimally conscious state may show some signs declaring awareness (e.g., visual pursuit, orientation to pain or non-systematic command following) but is unable to communicate his or her thoughts or feelings [7]. Because these behavioral signs of consciousness are often small and fluctuating in time, this condition may be challenging to diagnose and differentiate from vegetative state [8]. It has been suggested that once conscious awareness has been identified and its quality is estimated in a non-communicating patient (e.g., see [9, 10]), this may well be a good reason to preserve life-sustaining aids [11]. However, the moral significance of preserved consciousness has been questioned on the grounds that it may not always be in a patient's best interest to continue a severely handicapped life [12].

One challenging issue in this debate is the conscious perception of pain in these patients. As defined by the Multi-Society Task Force on persistent vegetative state (PVS), 'pain and suffering refer to the unpleasant experiences that occur in response to stimulation of peripheral nociceptive receptors and their peripheral and central afferent pathways or that may emanate endogenously from the depths of human self-perception' [13]. Thus, pain constitutes a conscious experience with a physical (nociception) and a psychological counterpart (suffering), suggesting that nociception by itself is not sufficient to cause suffering. The management of pain in patients with disorders of consciousness is challenging because patients in a vegetative or minimally conscious state cannot verbally or non-verbally communicate their feelings or experiences [1]. This is reflected in how clinicians perceive pain in these patients. According to recently surveyed attitudes among health-care professionals, there was unanimous support that patients in a minimally conscious state (96 %) perceived pain whereas opinions were less clear for the patients in a vegetative state (56 %) [14]. Considering these results on

varying beliefs about pain perception in disorders of consciousness, physicians and health-care workers' views on analgesia and symptom management may also be affected. Since nearly half of the surveyed doctors stated that vegetative state patients do not feel pain, these physicians could be expected to act accordingly, for instance, by not providing analgesic medication to these patients during care or during the dying process after withdrawal of artificial hydration and nutrition [15], the latter on the grounds that these patients do not experience suffering from hunger or thirst [16].

How are clinicians supposed to determine whether patients in a vegetative or minimally conscious state feel pain or suffering? At the patient's bedside, we are limited to evaluating the behavioral responsiveness to pain: If patients show no signs of voluntary movement (i.e., localizing the source of pain) in response to a noxious stimulus, it can be concluded that they do not experience pain. Conscious but paralyzed 'locked-in syndrome' patients, who classically show absent or 'decerebration' (i.e., stereotyped extension) or 'decortication' (i.e., stereotyped flexion) movements, teach that this need not necessarily be the case. In response to noxious stimulation, patients with disorders of consciousness will frequently show increased arousal levels (evidenced by opening or widening of the eyes), quickening of breathing, increased heart rate and blood pressure, or grimace-like or crying-like behavior. As all these abilities are also seen in infants with anencephaly [17], they are considered to be of subcortical origin and not necessarily reflecting conscious perception of pain. However, the absence of a behavioral response cannot be taken as proof of the absence of conscious perception [18] and the inference of pain and suffering merely by observing behavioral responses may be misleading. Repeated clinical examinations by experienced examiners with standardized tools such as the recently proposed 'coma nociception scale' (e.g., [19]) are paramount for the behavioral assessment of pain. Additional information coming from functional neuroimaging studies may assist in the formulation of a clearer clinical picture. For example, in a positron emission tomography (PET) study, it was shown that patients in a vegetative state may show cerebral processing of the incoming noxious stimulus (activation of primary somatosensory areas), but the observed neural activity was isolated and disconnected from higher-order associative brain areas which are considered necessary for conscious perception of pain [20]. It is important to stress that very different results were obtained in patients in a minimally conscious state in whom functional neuroimaging studies have shown more widespread activation in the cerebral network compared to patients in vegetative state, but similar to healthy controls, suggesting potential pain perception these patients [21]. In light of the incomplete picture of pain perception in patients in vegetative state, the existing risk for misdiagnosis [8], the inconclusive drug-related effects in disorders of consciousness [22], and the limitations of interpreting neuroimaging results [23], pain prophylaxis and drug treatment have been proposed for all patients suffering from disorders of consciousness [24].

In intensive care settings, medical doctors and assisting staff are confronted daily with situations where clinical decisions are still more critical, such as continuing or withdrawing life sustaining treatment. Treatment limitations can be viewed as having two directions depending on whether the decision is made preoperatively or after an intervention [25]. In the former case, it may come as a refusal of cardiopulmonary resuscitation (CPR) in case of cardiopulmonary arrest; in the latter case, it most usually comes as a decision to withdraw treat-

ment, such as the artificial respirator or artificial nutrition and hydration. CPR is almost automatically performed as an emergency therapy in order to restore heartbeat and ceased breathing, unless the patient or the legal representative have refused it in advance in a form of a do-not-resuscitate order (DNR). Nevertheless, it should be noted that DNR orders do not necessarily prohibit other therapies; they rather authorize the physician to act on this specific manner of therapy [26]. When the clinical condition of a patient has been stabilized and denoted as irreversible, decisions about artificial nutrition and hydration limitation may come into play. From a bioethical standpoint, withdrawing artificial nutrition and hydration is comparable to withdrawing mechanical ventilation, even if emotionally these two actions may be perceived differently. In the intensive care unit (ICU) setting, the majority of deaths are the result of a medical decision to withhold or withdraw treatment [27]. Such decisions are evidence-based and rely on validated clinical or paraclinical markers of bad outcome ([e.g., for anoxic coma see [28]). Despite the controversy as to whether artificial nutrition and hydration constitutes a medical treatment [29] and thus should never be withdrawn from patients [30], most of the medical community (especially Anglo-Saxon) would agree with its being a medical therapy which can be refused by patients and surrogate decision makers [31]. Such decisions in vegetative state patients are only justified when a case is denoted as irreversible [32]. Guidelines with regard to temporal determination of a definitive outcome in vegetative state currently state that if no recovery is observed within 3 months after a non-traumatic or 12 months after a traumatic accident, the condition of the patient can be denoted as permanent [13].

The controversies around the clinical management at the end-of-life in patients with disorders of consciousness were reflected in a recent European survey (n = 2475), where the majority of health-care professionals (66 %) agreed to withdraw treatment from chronic vegetative state patients whereas only 28 % agreed to do so for chronic minimally conscious state patients; additionally, most clinicians wished not to be kept alive if they imagined themselves in a chronic vegetative state (82 %) and a similar proportion (67 %) agreed if they imagined themselves in a chronic minimally conscious state [33]. Geographical region and religion were among the factors that explained most of the variance in the responses and these results are in line with previous surveys in which physicians' characteristics (i.e., age, religion and geographic region) seem to play a critical role in governing such options [34]. The detected differences between the two states could be due to the existing legal ambiguity around minimally conscious state which may have influenced the surveyed participants to differentiate between expressing preferences for self versus others, by implicitly recognizing that the latter could be a step on the slippery slope to euthanasia.

Clinicians' opinions appear much more uniform with regard to brain death [35]. As mentioned earlier, the Ad Hoc Committee of the Harvard Medical School went on to the redefinition of death as a consequence of the technological advancements in intensive care, where patients could sustain severe injuries but maintain the function of vital organs [2]. It was, therefore, possible to dissociate between cardiac, respiratory and brain functions which in turn required an alternative definition of death, moving from a cardiorespiratory towards a neurocentric formulation (i.e., irreversible coma). According to the latter, death can be viewed either as death of the whole brain or of the brainstem [36] or as neocortical [37]. The first two are defined as the irreversible cessation of the organism as

a whole, differing in their anatomical interpretation [38], whereas the last solely requires the irreversible loss of the capacity of consciousness and social interaction but has never convinced medical or legal scholars. The main utility of the introduction of brain death is that it permitted vital organ procurement for transplantation with the application of ethical restrictions, such as the dead donor rule (i.e., a patient has to be declared dead before the removal of life-sustaining organs). Based on the neocortical definition of death, however, both vegetative and minimally conscious state patients can be declared dead. It has been argued that the neocortical definition is conceptually inadequate and practically unfeasible, especially with the lack of a complete understanding of higher-order conscious functioning; hence, patients with disorders of consciousness are not dead [27] and organ donation options in these patients should be excluded since they violate the dead donor rule [39] – despite opposing opinions to abandon this ethical axiom [40].

Legal Issues in Disorders of Consciousness

Disorders of consciousness have posed not only medical challenges but in many cases they required the mediation of legal authorities in order to regulate ambiguous and controversial issues, such as end-of-life decisions. When end-of-life wishes have not been earlier formulated in the form of an advanced directive (i.e., written statement completed by a competent person in anticipation of her/his future incompetence, expressing personal treatment preferences and formal surrogacy appointment), then a surrogate decision maker is eligible to take responsibility for the patient's clinical management. The way the legal representative should act on behalf of the patient is a progressive one. The surrogate should first attempt to follow the wishes of the patient as closely as possible, in the way in which they were expressed before the accident, either orally or in the form of advance directives. When the wishes are unknown and an advance directive is not available, the surrogate decision maker should try to reproduce the patient's preferences based on their history and personal values. When this is not possible, decisions should rely on more objective markers that determine the patient's best interest (e.g., likelihood of recovery, pain management, impact on family) [25, 41]. The proxy decision maker should mediate trying to maximize the patient's self-determination and protect their interests using the principles of beneficence and non-maleficence [42].

The use of advance directives could also be considered as a means to regulate cost savings in the end-of-life; once the wishes of a terminal patient are known, care can be taken to constrain extraordinary means and spare the available resources for other urgent cases. However, no such rationale corresponds to the reality and advance directives, together with hospice care and the elimination of futile care, have not contributed to the effective regulation of the economics of dying [43]. Treatment resources are not unlimited and despite care for a good death sometimes physicians need to make do with the means they have available. The allocation of resources and the economics at the end-of-life have not yet been fully determined for patients with disorders of consciousness. In intensive care medicine, some unwritten rules can facilitate decisions as to who is to be treated, like the 'first come' principle or 'who will most likely benefit from intensive care' [44]. However, for chronic disorder of consciousness cases, information on

resource allocation is often lacking. This may be due to the nature of patients with chronic vegetative or minimally conscious state. These are severely brain-damaged patients for whom the dilemma on treating becomes crucial either because treatments are not guaranteed as successful (i.e., the condition is too bad to be treated) or unkind (i.e., the quality of life of those surviving is not acceptable) which may lead to an unwise way to allocate available resources [44].

The legal provisions concerning end-of-life issues in disorders of consciousness differ from country to country. In the United States, where a patient-centered medical framework has been adopted, the patient is allowed to participate in the regulation of her/his own course of the disease. In the case of disorders of consciousness, legal representatives in close collaboration with the clinical staff and in line with the patient's previously expressed wishes may decide together about the long-term care of irreversibly comatose patients. There are times, however, when conflicts of interests arise while making such decisions, either between family and physicians, such as in the Quinlan case [45], or among family members, like the more recent Schiavo case [46]. As most often such cases require the mediation of the court, they may have a wider publicity in which public opinion can come into play and may lead to societal movements on pro-life versus right-to-die action groups [47]. In Europe, there are more subtle differences in the way treatment limitation is perceived, especially between Northern (more right-to-die oriented) and Southern (more pro-life positioned) European countries [33]. In general, decisions for treatment limitation (usually concerning artifical nutrition and hydration) need to be taken after reference to the court. Exceptions are the Netherlands, Belgium, Switzerland and Scandinavian countries where no court mediation is needed for limiting treatment in disorders of consciousness [48]. Considering these different attitudes within and out of Europe, it has been suggested that an international consensus regarding standards of care for patients with disorders of consciousness needs to be reached [49].

Conclusion

The ethical issues accrued from the study and management of patients with disorders of consciousness are variant and multi-faceted. Medical, legal and public controversies are partly shaped by how different people think about these issues and in many cases are country-dependent. It is, therefore, evident that a uniform ethical framework needs to be shaped to guide clinicians and caregivers in terms of clinical outcome, prognosis, and medical management.

XV

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References

1. Laureys S, Boly M (2007) What is it like to be vegetative or minimally conscious? Curr Opin Neurol 20: 609 – 613
2. Report of the Ad Hoc Committee of the Harvard Medical School to Examine the Definition of Brain Death (1968) A definition of irreversible coma. JAMA 205: 337 – 340

3. Zeman A (2001) Consciousness. Brain 124: 1263 – 1289
4. Demertzi A, Liew C, Ledoux D, et al (2009) Dualism persists in the science of mind. Ann N Y Acad Sci 1157: 1 – 9
5. Posner J, Saper C, Schiff N, Plum F (2007) Plum and posner's diagnosis of stupor and coma. 4th edn. Oxford University Press, New York
6. Jennett B, Plum F (1972) Persistent vegetative state after brain damage. A syndrome in search of a name. Lancet 1: 734 – 737
7. Giacino JT, Ashwal S, Childs N, et al (2002) The minimally conscious state: Definition and diagnostic criteria. Neurology 58: 349 – 353
8. Schnakers C, Vanhaudenhuyse A, Giacino JT, et al (2009) Diagnostic accuracy of the vegetative and minimally conscious state: Clinical consensus versus standardized neurobehavioral assessment. BMC Neurology 9: 35
9. Owen AM, Coleman MR, Boly M, Davis MH, Laureys S, Pickard JD (2006) Detecting awareness in the vegetative state. Science 313: 1402
10. Monti MM, Vanhaudenhuyse A, Coleman MR, et al (2010) Willful modulation of brain activity in disorders of consciousness. N Engl J Med 362: 579 – 589
11. Horne M (2009) Are people in a persistent vegetative state conscious? Monash Bioeth Rev 28: 12 – 12
12. Kahane G, Savulescu J (2009) Brain damage and the moral significance of consciousness. J Med Philos 34: 6 – 26
13. The Multi-Society Task Force on PVS (1994) Medical aspects of the persistent vegetative state (2). N Engl J Med 330: 1572 – 1579
14. Demertzi A, Schnakers C, Ledoux D, et al (2009) Different beliefs about pain perception in the vegetative and minimally conscious states: A european survey of medical and paramedical professionals. Prog Brain Res 177: 329 – 338
15. Fins JJ (2006) Affirming the right to care, preserving the right to die: Disorders of consciousness and neuroethics after schiavo. Palliat Support Care 4: 169 – 178
16. Ahronheim JC, Gasner MR (1990) The sloganism of starvation. Lancet 335: 278 – 279
17. The Medical Task Force on Anencephaly (1990) The infant with anencephaly. N Engl J Med 322: 669 – 674
18. McQuillen MP (1991) Can people who are unconscious or in the "vegetative state" perceive pain? Issues Law Med 6: 373 – 383
19. Schnakers C, Chatelle C, Vanhaudenhuyse A, et al (2010) The nociception coma scale: A new tool to assess nociception in disorders of consciousness. Pain 148: 215 – 219
20. Laureys S, Faymonville ME, Peigneux P, et al (2002) Cortical processing of noxious somatosensory stimuli in the persistent vegetative state. NeuroImage 17: 732 – 741
21. Boly M, Faymonville ME, Schnakers C, et al (2008) Perception of pain in the minimally conscious state with pet activation: An observational study. Lancet Neurol 7: 1013 – 1020
22. Demertzi A, Vanhaudenhuyse A, Bruno MA, et al (2008) Is there anybody in there? Detecting awareness in disorders of consciousness. Expert Rev Neurother 8: 1719 – 1730
23. Poldrack RA (2008) The role of fmri in cognitive neuroscience: Where do we stand? Curr Opin Neurobiol 18: 223 – 227
24. Schnakers C, Zasler ND (2007) Pain assessment and management in disorders of consciousness. Curr Opin Neurol 20: 620 – 626
25. Bernat JL (2004) Ethical issues in the perioperative management of neurologic patients. Neurol Clin 22: 457 – 471
26. Youngner SJ (1987) Do-not-resuscitate orders: No longer secret, but still a problem. Hastings Cent Rep 17: 24 – 33
27. Laureys S (2005) Science and society: Death, unconsciousness and the brain. Nat Rev Neurosci 6: 899 – 909
28. Boveroux P, Kirsch M, Boly M, et al (2008) Évaluation du pronostic neurologique dans les encéphalopathies postanoxiques. Réanimation 17: 613 – 617
29. Bernat JL, Beresford HR (2006) The controversy over artificial hydration and nutrition. Neurology 66: 1618 – 1619
30. Rosner F (1993) Why nutrition and hydration should not be withheld from patients. Chest 104: 1892 – 1896

31. Steinbrook R, Lo B (1988) Artificial feeding--solid ground, not a slippery slope. N Engl J Med 318: 286–290
32. Royal College of Physicians (2003) The vegetative state: Guidance on diagnosis and management. Clin Med 3: 249–254
33. Demertzi A, Bruno MA, Ledoux D, et al (2009) Attitudes towards disorders of consciousness: Do europeans disentangle vegetative from minimally conscious state? Paper presented at the Nineteenth Meeting of the European Neurological Society, Milan, Italy, 22 June
34. Vincent JL (1999) Forgoing life support in western european intensive care units: The results of an ethical questionnaire. Crit Care Med 27: 1626–1633
35. Bernat JL, Steven L (2005) The concept and practice of brain death. Prog Brain Res 150: 369–379
36. Bernat JL (2002) Ethical issues in neurology. Second edn. Butterworth Heinemann, Boston
37. Brierley JB, Graham DI, Adams JH, Simpsom JA (1971) Neocortical death after cardiac arrest. A clinical, neurophysiological, and neuropathological report of two cases. Lancet 2: 560–565
38. Bernat JL (1998) A defense of the whole-brain concept of death. Hastings Cent Rep 28: 14–23
39. Engelhardt K (1998) Organ donation and permanent vegetative state. Lancet 351: 211
40. Truog RD, Robinson WM (2003) Role of brain death and the dead-donor rule in the ethics of organ transplantation. Crit Care Med 31: 2391–2396
41. Bernat JL (2002) Clinical ethics and the law. In: Ethical Issues in Neurology. Second edn. Butterworth Heinemann, Boston, pp 79–107
42. Bernat JL (2002) The persistent vegetative state and related states. In: Ethical issues in neurology. 2nd edn. Butterworth Heinemann, Boston, pp 283–305
43. Emanuel EJ, Emanuel LL (1994) The economics of dying. The illusion of cost savings at the end of life. N Engl J Med 330: 540–544
44. Jennett B (1976) Editorial: Resource allocation for the severely brain damaged. Arch Neurol 33: 595–597
45. Beresford HR (1977) The quinlan decision: Problems and legislative alternatives. Ann Neurol 2: 74–81
46. Quill TE (2005) Terri Schiavo – a tragedy compounded. N Engl J Med 352: 1630–1633
47. Wijdicks EFM (2008) Law and bioethics. In: The Comatose Patient. Oxford University Press, New York, pp 201–216
48. Jennett B (2002) Ethical issues. In: Jennett B (ed) The vegetative state. Medical facts, ethical and legal dilemmas. Cambridge University Press, Cambridge, pp 97–125
49. Yaguchi A, Truog RD, Curtis JR, et al (2005) International differences in end-of-life attitudes in the intensive care unit: Results of a survey. Arch Intern Med 165: 1970–1975

XVI Metabolic Disorders and Nutrition

Metformin and Lactic Acidosis

S. Vecchio, P. Papa, and A. Protti

Introduction

Metformin is currently the first-line drug of choice for the treatment of adults with type 2 diabetes and might be also used in other conditions characterized by insulin resistance, such as the polycystic ovarian syndrome [1, 2]. It is the 10th most frequently prescribed generic drug in the USA (> 40 million prescriptions in 2008) and is taken by almost 1.5 % of the Italian population [3, 4].

Several clinical trials have shown that metformin is a safe drug, when correctly used. In particular, in properly selected patients, it does not seem to increase the risk of lactic acidosis, a well known side effect of other biguanide compounds [5]. Real life, however, can differ from research settings and lactic acidosis has been repeatedly, although rarely, observed in patients treated with metformin. When lactic acidosis occurs in the presence of hypoxia, tissue hypoperfusion or liver failure, then the most probable diagnosis is metformin-*associated* lactic acidosis. In these cases, lactic acidosis is likely to develop independently of metformin use. Conversely, when lactic acidosis occurs in the absence of any other major risk factor, then metformin accumulation is likely the cause of the syndrome and the most probable diagnosis is metformin-*induced* lactic acidosis [6]. The distinction between these two entities is sometimes very subtle and metformin accumulation may coexist with other risk factors, all contributing to the pathogenesis of lactic acidosis. Since metformin use is constantly increasing (10 – 15 % rise in prescriptions per year in the USA and Italy [3, 4]), related cases of lactic acidosis may become more common.

The aim of this present work is to summarize our current knowledge of lactic acidosis during metformin use and provide some new insight into the way in which the drug may induce a rise in blood lactate levels. Data of accidentally intoxicated patients referred to the Poison Control Center of Pavia, Italy, in the last few years will be also presented.

Epidemiology and Risk Factors

According to the most recent systematic review of literature performed by the Cochrane collaboration, no cases of lactic acidosis (usually defined as pH< 7.35 and lactatemia > 5 mmol/l) were reported in 347 trials with 70,490 patient-years of metformin use. The upper limit of the true incidence of cases per 100,000 patient-years was estimated to be 4 [5]. Of note, 57 % of the prospective studies included in the work did not enroll patients with renal insufficiency.

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However, the number of inquires to the Swedish Poison Information Center for metformin intoxication has increased ten fold during the last decade, with 25 cases of severe lactic acidosis reported in 2007–2008 [7]. According to the American Association of Poison Control Centers, metformin may have contributed to 21 fatalities in the USA in 2008 [8]. Forty-nine cases of lactic acidosis and accidental metformin accumulation were reported to the Poison Control Center of Pavia from January 2005 to August 2010, resulting in 11 deaths. Patients were on average 65 ± 10 years old, mainly females (61 %). Serum metformin levels were on average 48 ± 27 μg/ml (therapeutic level is < 4 μg/ml). Complete data recording was available in 21 cases (14 metformin-induced and 7 metformin-associated lactic acidosis), that will be further analyzed in the following sections. Nineteen additional cases of lactic acidosis were classified as 'probably' due to metformin accumulation, based only on anamnesis and clinical findings. In these cases, serum metformin levels were not available. Whether similar data reflect the real incidence of lactic acidosis during metformin accumulation remains unclear. Underestimation cannot be excluded, depending on lack of recognition of the syndrome or unavailability of confirmatory tests.

Aside from cases of voluntary overdose, metformin accumulation is usually accidental and occurs when the drug is regularly taken (at therapeutic dose) despite impaired renal elimination. Once absorbed from the intestinal tract, metformin does not undergo any metabolism and is both filtered and actively excreted by the kidney. Renal dysfunction is present in virtually all cases of unintentional metformin accumulation and is usually attributed to dehydration secondary to a few days history of nausea, vomiting and diarrhea [9]. Whether these symptoms depend on an initial metformin accumulation, development of lactic acidosis or other intercurrent illness remains unclear. Nephrotoxic drugs, such as non-steroidal anti-inflammatory compounds, may act as a trigger. Genetic variants of the organic cation transporter (OCT)-2 on renal tubules might affect drug clearance and relate to individual risk [10]. Creatininemia can be exceptionally high in patients with accidental intoxication (not unusually > 10 mg/dl) and hypovolemia may not be the sole explanation. Since renal secretion of creatinine is also mediated by OCT-2 [11], it is possible that increasing blood levels of metformin interfere with creatinine clearance, further aggravating the rise in creatininemia. Moreover, metformin may directly affect renal function. In fact, acute renal failure sometimes occurs in otherwise healthy subjects following intentional metformin overdose. The recovery is usually complete once the intoxication is resolved [12, 13].

Since metformin has a short half-life (around 6 hours), drug accumulation can become severe only if renal dysfunction develops over several days. Early recognition of renal damage may lead to reduction or suspension of metformin use. Calculation of creatinine clearance or estimation of glomerular filtration rate (GFR) may be better, although more complex, alternatives to the sole determination of blood creatinine levels [14].

According to Italian labeling instruction, metformin should not be prescribed in the presence of diabetic ketoacidosis or pre-coma; renal failure or dysfunction (with creatinine clearance < 60 ml/min); any acute condition that may impair renal function (dehydration, sepsis, shock, intravenous injection of contrast medium); tissue hypoxia due to heart or respiratory failure, recent myocardial infarction, shock; liver failure; alcohol abuse; lactation. Most of the listed contraindications increase the risk of metformin accumulation and/or lactic acidosis. Of

note, lactic acidosis may develop even in patients without any contraindication at the time the drug was first prescribed, due to intercurrent acute deterioration of renal, cardiovascular or liver function. Out of 21 cases of lactic acidosis due to metformin accumulation notified to our Poison Control Center, with sufficient details about pre-existing health status, 10 (48 %) patients had initially no contraindication to drug use. Even so, all the patients presented to hospital with overt renal failure (see below).

Pathophysiology

Lactic acidosis develops whenever lactate production exceeds elimination [15]. Most of the cases of metformin-associated lactic acidosis occur in the presence of hypoxia or tissue hypoperfusion. Metformin use may be coincidental, or, in case of drug accumulation, variably (although usually marginally) co-causative. When cellular oxygenation is inadequate, lactate production increases. In fact, in physiological conditions, mitochondria consume oxygen to produce most of the energy the cell needs. The overall process depends on the transfer of electrons from reducing equivalents derived from metabolism, down the mitochondrial respiratory chain, to molecular oxygen. Electron transfer is coupled to proton extrusion and generation of a mitochondrial membrane potential. Protons then flow back into the mitochondria through the permeable pore of adenosine triphosphate (ATP) synthase, while the catalytic subunit of the enzyme produces energy in form of ATP. When hypoxia or tissue hypoperfusion impairs cellular oxygenation, mitochondria can no longer function normally and cellular energy generation becomes variably dependent on anaerobic lactate overproduction. Metabolic acidosis then develops. Metformin-associated lactic acidosis may also occur in the absence of cellular hypoxia. During liver failure, for example, blood lactate levels increase mainly because of impaired elimination [15].

Conversely, the pathophysiology of metformin-induced lactic acidosis remains poorly understood. Metformin exerts its therapeutic effects mainly by inhibiting the hepatic production of glucose from substrates other than sugar (gluconeogenesis), which can be abnormally high in patients with type 2 diabetes [16]. Metformin can accumulate in virtually every tissue but hepatocyte uptake is greatly facilitated by a transporter known as OCT-1 (similar to the one on renal tubules) [17]. At a cellular level, metformin mildly inhibits mitochondrial respiratory chain complex I, thus decreasing hepatocyte energetic charge [18, 19]. Rate of gluconeogenesis then diminishes, since glucose generation is an energetically costly process; expression and activities of related enzymes are inhibited, either in response to, or independently from, activation of AMP kinase [20–22]. Since the liver can use lactate to produce glucose, any abnormal decrease in hepatic gluconeogenesis due to metformin is likely to impair lactate clearance. Moreover, hepatocyte lactate output can increase in response to partial inhibition of aerobic metabolism [18, 19]. That the liver has a key role in the pathogenesis of metformin-induced lactic acidosis has been clearly demonstrated by Wang and colleagues [23]. These authors reported that blood lactate levels significantly increase when wild-type mice are infused with high doses of metformin. On the other hand, lactatemia remained normal in OCT-1 deficient animals, with much lower hepatic metformin uptake despite similar plasma drug levels. Of note, these experiments lasted 210 minutes, thus providing insight mainly on the early phase

of intoxication, when changes (if any) in other tissues may not have already occurred. Accordingly, despite plasma metformin levels as high as 100 μg/ml, lactatemia in wild-type animals only rose from 0.5 to 3 mmol/l [23].

Increased lactate output from extra-hepatic tissues may have an additional role. In fact, metformin can increase intestinal lactate generation [24]. Moreover, several *in vitro* studies, mainly performed using animal tissues, suggest that metformin might dose-dependently impair mitochondrial respiration even in skeletal muscle, kidney, pancreas, neural tissue, endothelium and white blood cells [25–30]. It may then be hypothesized that energy metabolism in these same peripheral tissues may become variably dependent on increased lactate generation.

We have recently noted that patients admitted to intensive care with severe lactic acidosis due to metformin intoxication consume, on average, half the oxygen of other critically ill subjects. Oxygen extraction, but not delivery, is usually diminished, at least after adequate fluid resuscitation. As long as drug accumulation is resolved, global oxygen consumption increases and blood lactate levels return to normal (**Fig. 1**) [9]. It is hard to believe that only inhibition of hepatic mitochondrial respiration accounts for such a large decrease in global oxygen consumption. We may rather suspect that when metformin serum levels are abnormally high, mitochondrial respiration is inhibited even in extra-hepatic tissues. Widespread lactate overproduction, in the presence of diminished clearance, may be the full explanation for metformin-induced lactic acidosis. We have now confirmed these clinical, retrospective findings, in a much more controlled experimental setting. In otherwise healthy, metformin-intoxicated pigs, global oxygen extraction and consumption markedly declined, despite a grossly preserved delivery, while blood lactate levels progressively increased (unpublished data). We are now measuring the respiratory chain enzyme activities in different tissue specimens collected from these same animals, to clarify whether diffuse mitochondrial damage has occurred. Preliminary results suggest that mitochondrial function similarly declines in skeletal muscle, heart, liver, kidney and platelets.

We are also currently running a multicenter prospective observational trial, aimed at clarifying whether platelet (easily obtainable) mitochondrial function declines during human metformin-induced lactic acidosis (ClinicalTrials.gov identifier: NCT00942123). Patients will be enrolled if they suffer from otherwise

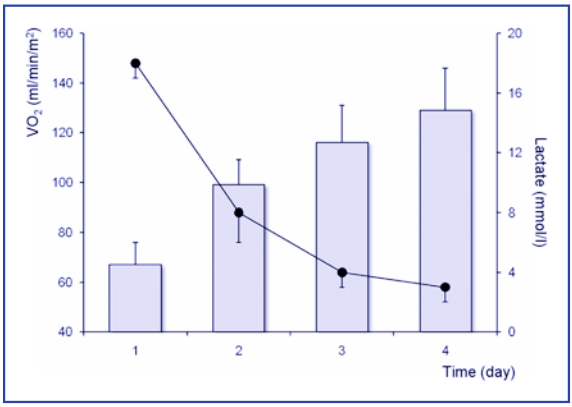

Fig. 1. Oxygen consumption is abnormally low during metformin-induced lactic acidosis. Global oxygen consumption (blue bars, VO_2) and blood lactate levels (black circles) measured in 11 patients with metformin-intoxication during the first 4 days of stay in the intensive care unit. Data are presented as mean and standard error of the mean. The increase in VO_2 and the decrease in lactatemia over time were both significant ($p < 0.001$, one way repeated measure ANOVA). Data from [9].

unexplained lactic acidosis and have abnormally high serum metformin levels. Blood will be taken at different time points, platelets isolated and their mitochondrial function assessed. In a preliminary phase, we incubated platelets from healthy donors with increasing doses of metformin. As a result, platelet complex I activity and oxygen consumption decreased and lactate generation increased, in a time and drug-dose dependent manner [31].

Clinical Presentation

Clinical presentation of lactic acidosis during metformin accumulation is not specific. Out of 21 patients referred to the Poison Control Center of Pavia, 17 (81 %) had a recent history of vomiting, nausea and/or diarrhea. On average, symptoms began 4 (range 1 – 20) days before lactic acidosis was diagnosed. At the time of hospital admission, oligo-anuria and hypercreatininemia (8 ± 3 mg/dl) were always observed. Other findings included lethargy or coma (71 %), dyspnea (38 %), hypotension (19 %), arrhythmias (19 %). Nine patients (42 %) presented to the emergency room in overt shock or cardiac arrest. Initial arterial pH was 6.85 ± 0.21 (range 6.55 – 7.30) and lactatemia was 17 ± 5 (range 6 – 26) mmol/l. Serum metformin level at admission ranged between 20 and 100 μg/ml; it correlated positively with lactatemia ($p < 0.05$) but not creatininemia. Following adequate fluid resuscitation, the hemodynamic state of the most severe cases usually resembled that of septic shock: increased heart rate and cardiac output, decreased systemic vascular resistances and mean arterial pressure, unexpectedly high mixed or central venous oxygen saturation. Seventeen patients (81 %) had leukocytosis at admission although infection was diagnosed in only two patients. Of note, body core temperature was usually abnormally low (a finding further corroborating the hypothesis of a hypometabolic state). Regardless of any hemodynamic optimization, lactic acidosis tended to become progressively more severe. Hypoglycemia (< 60 mg/dl), was noted in 6 (28 %) patients, even when no other antidiabetic drugs were used (4 patients).

Diagnosis

Lactic acidosis can be easily diagnosed by performing a blood gas analysis (arterial pH < 7.35 and elevated anion gap) and measuring lactatemia (> 5 mmol/l). However, recognition of the role of metformin use (coincidental versus causative) can be extremely complex. Lactic acidosis can be reasonably attributed to metformin accumulation once other risk factors (such as hypoxia, tissue hypoperfusion and liver failure) have been excluded based on clinical and instrumental findings, and renal failure and continued drug intake have been documented. In diabetic patients already known for alcohol abuse, methanol and ethylene glycol intoxication should be ruled out by performing appropriate urinary and blood levels. Metformin accumulation can be confirmed by measuring blood and urinary drug levels. However, this dosage is rarely available in an emergency setting.

Treatment

The therapeutic approach to lactic acidosis should always be directed towards the correction of the causative mechanism. When lactic acidosis is induced by metformin accumulation, then drug removal is the mainstay of therapy. When renal insufficiency is present, hemodialysis should be used to remove metformin (and lactate) from blood. Seidowsky and colleagues recently reported their ten years' experience with patients admitted to intensive care with lactic acidosis and metformin accumulation (mean plasma level at admission 27 ± 25 μg/ml). On average, a cumulative duration of hemodialysis of 15 hours was associated with complete removal of metformin from blood. Blood flow was usually set at around 200 ml/min and dialysate flow was 500 ml/min [32]. Continuous renal replacement therapy may be a valid option when hemodynamic instability is a major concern, although drug removal is less efficient and duration of treatment longer (3–4 days in our experience). Case reports suggest that combining intermittent and continuous renal replacement therapy, using separate venous catheters, may expedite metformin clearance [33, 34].

Supportive care can include mechanical ventilation, hemodynamic optimization, correction of fluid deficits, electrolyte abnormalities, and hypoglycemia. The use of buffer therapy is controversial and is no longer recommended when pH is ≥ 7.15 [35, 36]. Sodium bicarbonate may paradoxically lower cerebrospinal and intracellular fluid pH; increase hemoglobin affinity for oxygen thus impairing peripheral oxygen delivery; cause hypernatremia and volume overload, severe hypokalemia and hypocalcemia; and increase cellular membrane permeability to metformin, with the risk of precipitating lactate overproduction. Nonetheless, due to the extreme severity of acidosis, metformin-intoxicated patients do usually receive bicarbonate, along with hemodialysis or hemofiltration. Whether buffer therapy exerts a beneficial effect that is independent from dialysis remains unknown.

We are currently evaluating the potential use of succinate in metformin-intoxicated animals. As reported above, metformin seems to only inhibit complex I and succinate is a complex II specific electron donor. In other words, electrons are passed from succinate to complex II and then transferred down the respiratory chain, bypassing complex I. Succinate has been proven to ameliorate mitochondrial respiration and cellular energy charge in other situations characterized by complex I inhibition [37, 38]. *In vitro*, any decrease in hepatocyte mitochondrial respiration due to metformin is reversed after addition of succinate [18, 19]. In pancreatic cells, succinate can attenuate the mitochondrial toxicity of metformin and prevent cell death [27]. Whether succinate can similarly work in animals or humans strictly depends on the demonstration that, even *in vivo*, metformin does not critically inhibit any respiratory chain enzyme distal to complex I.

Prognosis

Despite the dramatic severity of clinical presentation, most patients survive to hospital discharge, provided lactic acidosis is really due to metformin accumulation and no other underlying pathology. In the series of 21 patients referred to our Poison Control Center, with complete follow-up, survival was 72 % (6 deaths) despite arterial pH at admission of on average 6.85 ± 0.21 and lactatemia of

17 ± 5 mmol/l. In one fatal case, a concomitant accumulation of acenocoumarol was noted (550 ng/ml; therapeutic range is < 200 ng/ml) resulting in a prothrombin time, expressed as international normalized ratio (INR), equal to 17. A second fatal case had concomitant digoxin intoxication (9.2 ng/ml; therapeutic level 0.6–2.0 ng/ml) and received the specific antidote. Caution is warranted if metformin is used with other cationic drugs, eliminated by the kidney. For example, cimetidine may favor metformin accumulation [39]. Because digoxin is also a cationic drug, it might similarly diminish metformin clearance.

That lactic acidosis carries a poor prognosis has been known for decades [40]. However, lactic acid *per se* is unlikely the explanation of this association. Why would evolution have selected such a strategy, if it were harmful? Growing evidence suggests that lactate can no longer be merely considered as a waste product; lactate production may be rather an adaptive response to impending energetic failure. By producing lactate, cells can gain some energy and survive for a limited period of time even when mitochondria get damaged. According to the theory of 'lactate shuttles' proposed by Brooks and colleagues, lactate should be considered as an oxidative substrate exchanged between cells and tissues [41]. Acidosis itself may arise as an adaptive response to inadequate energy provision and may extend cellular viability [42].

Accordingly, the prognosis of lactic acidosis depends primarily on the causative mechanism and not just on the severity of hyperlactatemia. When lactic acidosis is due to metformin accumulation, then prognosis is good since its treatment is straightforward (once diagnosis has been made). Things are more complex when lactic acidosis is primarily due to prolonged hypoxia or tissue hypoperfusion. Of note, patients admitted soon after acute metformin overdose usually present with much higher serum drug levels but less severe lactic acidosis (if present at all) than cases of chronic, accidental, intoxication. Slow tissue penetration of metformin is the most likely explanation. As a result, high serum metformin levels may not necessarily predict the severity of clinical presentation and can be associated with a favorable outcome [11, 32].

Conclusion

Metformin is a safe drug and lactic acidosis an extremely rare complication. Usually other concomitant risk factors, such as hypoxia, tissue hypoperfusion or liver failure, are the most plausible explanation for the rise in blood lactate levels. However, lactic acidosis may sometimes develop in response to isolated metformin intoxication. Prompt identification of initial, subtle, changes in renal function may represent an important tool to prevent inadvertent drug accumulation and toxicity. Inhibition of mitochondrial respiration is likely to be a key event in the pathogenesis of metformin-induced lactic acidosis and may result in both cellular lactate overproduction and impaired clearance. Drug removal is the cornerstone of therapy; when instituted early, prognosis is likely to be favorable, in face of the extreme severity of initial clinical presentation.

References

1. Nathan DM, Buse JB, Davidson MB, et al (2009) Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 32: 193 – 203
2. Nestler JE (2008) Metformin for the treatment of the polycystic ovary syndrome. N Engl J Med. 358: 47 – 54
3. 2008 Top 200 generic drugs by total prescriptions. [http://drugtopics.modernmedicine.com/drugtopics/data/articlestandard//drugtopics/222009/599844/article.pdf] Accessed Nov 2010
4. Gruppo di lavoro OsMed (2010) L'uso dei farmaci in Italia. Rapporto nazionale gennaio-settembre 2009. Available at: http://www.epicentro.iss.it/farmaci/pdf/OsMed/OsMed%20primi%209 %20mesi%202009.pdf Accessed Nov 2010
5. Salpeter SR, Greyber E, Pasternak GA, Salpeter EE (2010) Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus. Cochrane Database Syst Rev 4: CD002967
6. Lalau JD, Race JM (2001) Lactic acidosis in metformin therapy: searching for a link with metformin in reports of 'metformin-associated lactic acidosis'. Diabetes Obes Metab 3: 195 – 201
7. Personne M (2009) [Alarming increase of the number of metformin intoxications. Ten times doubled number of inquiries to the Swedish Poison Information Center since 2000]. Lakartidningen 106: 994
8. Bronstein AC, Spyker DA, Cantilena LR Jr, Green JL, Rumack BH, Giffin SL (2009) 2008 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 26th Annual Report. Clin Toxicol 47: 911 – 1084
9. Protti A, Russo R, Tagliabue P, et al (2010) Oxygen consumption is depressed in patients with lactic acidosis due to biguanide intoxication. Crit Care 14: R22
10. Song IS, Shin HJ, Shim EJ, et al (2008) Genetic variants of the organic cation transporter 2 influence the disposition of metformin. Clin Pharmacol Ther 84: 559 – 562
11. Urakami Y, Kimura N, Okuda M, Inui K (2004) Creatinine transport by basolateral organic cation transporter hOCT2 in the human kidney. Pharm Res 21: 976 – 981
12. Guo PY, Storsley LJ, Finkle SN (2006) Severe lactic acidosis treated with prolonged hemodialysis: recovery after massive overdoses of metformin. Semin Dial 19: 80 – 83
13. Lacher M, Hermanns-Clausen M, Haeffner K, Brandis M, Pohl M (2005) Severe metformin intoxication with lactic acidosis in an adolescent. Eur J Pediatr 164: 362 – 365
14. Holstein A, Stumvoll M (2005) Contraindications can damage your health – is metformin a case in point? Diabetologia 48: 2454 – 2459
15. Kreisberg RA (1980) Lactate homeostasis and lactic acidosis. Ann Intern Med 92: 227 – 237
16. Hundal RS, Krssak M, Dufour S, et al (2000) Mechanism by which metformin reduces glucose production in type 2 diabetes. Diabetes 49: 2063 – 2069
17. Shu Y, Sheardown SA, Brown C, et al (2007) Effect of genetic variation in the organic cation transporter 1 (OCT1) on metformin action. J Clin Invest 117: 1422 – 1431
18. El Mir MY, Nogueira V, Fontaine E, Averet N, Rigoulet M, Leverve X (2000) Dimethylbiguanide inhibits cell respiration via an indirect effect targeted on the respiratory chain complex I. J Biol Chem 275: 223 – 228
19. Owen MR, Doran E, Halestrap AP (2000) Evidence that metformin exerts its anti-diabetic effects through inhibition of complex 1 of the mitochondrial respiratory chain. Biochem J 348: 607 – 614
20. Zou MH, Kirkpatrick SS, Davis BJ, et al (2004) Activation of the AMP-activated protein kinase by the anti-diabetic drug metformin in vivo. Role of mitochondrial reactive nitrogen species. J Biol Chem 279: 43940 – 43951
21. He L, Sabet A, Djedjos S, et al (2009) Metformin and insulin suppress hepatic gluconeogenesis through phosphorylation of CREB binding protein. Cell 137: 635 – 646
22. Foretz M, Hébrard S, Leclerc J, et al (2010) Metformin inhibits hepatic gluconeogenesis in mice independently of the LKB1/AMPK pathway via a decrease in hepatic energy state. J Clin Invest 120: 2355 – 2369

23. Wang DS, Kusuhara H, Kato Y, Jonker JW, Schinkel AH, Sugiyama Y (2003) Involvement of organic cation transporter 1 in the lactic acidosis caused by metformin. Mol Pharmacol 63: 844 – 848
24. Bailey CJ, Wilcock C, Scarpello JH (2008) Metformin and the intestine. Diabetologia 51: 1552 – 1553
25. Brunmair B, Staniek K, Gras F, et al (2004) Thiazolidinediones, like metformin, inhibit respiratory complex I: a common mechanism contributing to their antidiabetic actions? Diabetes 53: 1052 – 1059
26. Morales AI, Detaille D, Prieto M, et al (2010) Metformin prevents experimental gentamicin-induced nephropathy by a mitochondria-dependent pathway. Kidney Int. 77: 861 – 869
27. Hinke SA, Martens GA, Cai Y, et al (2007) Methyl succinate antagonises biguanide-induced AMPK-activation and death of pancreatic beta-cells through restoration of mitochondrial electron transfer. Br J Pharmacol 150: 1031 – 1043
28. El Mir MY, Detaille D, Villanueva G, et al (2008) Neuroprotective role of antidiabetic drug metformin against apoptotic cell death in primary cortical neurons. J Mol Neurosci 34: 77 – 87
29. Detaille D, Guigas B, Chauvin C, et al (2005) Metformin prevents high-glucose-induced endothelial cell death through a mitochondrial permeability transition-dependent process. Diabetes 54: 2179 – 2187
30. Zmijewski JW, Lorne E, Zhao X, et al (2008) Mitochondrial respiratory complex I regulates neutrophil activation and severity of lung injury. Am J Respir Crit Care Med 178: 168 – 179
31. Protti A, Lecchi A, Fortunato F, et al (2010) Metformin increases platelet lactate production by inhibiting mitochondrial function. Crit Care 14 (Suppl 1): P162 (abst)
32. Seidowsky A, Nseir S, Houdret N, Fourrier F (2009) Metformin-associated lactic acidosis: a prognostic and therapeutic study. Crit Care Med 37: 2191 – 2196
33. Panzer U, Kluge S, Kreymann G, Wolf G (2004) Combination of intermittent haemodialysis and high-volume continuous haemofiltration for the treatment of severe metformin-induced lactic acidosis. Nephrol Dial Transplant 19: 2157 – 2158
34. Friesecke S, Abel P, Kraft M, Gerner A, Runge S (2006) Combined renal replacement therapy for severe metformin-induced lactic acidosis. Nephrol Dial Transplant 21: 2038 – 2039
35. Dellinger RP, Levy MM, Carlet JM, et al (2008) Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. Intensive Care Med 34: 17 – 60
36. Forsythe SM, Schmidt GA (2000) Sodium bicarbonate for the treatment of lactic acidosis. Chest 117: 260 – 267
37. Doctor RB, Bacallao R, Mandel LJ (1994) Method for recovering ATP content and mitochondrial function after chemical anoxia in renal cell cultures. Am J Physiol 266: C1803 – 1811
38. Protti A, Carré J, Frost MT, et al (2007) Succinate recovers mitochondrial oxygen consumption in septic rat skeletal muscle. Crit Care Med 35: 2150 – 2155
39. Somogyi A, Stockley C, Keal J, Rolan P, Bochner F (1987) Reduction of metformin renal tubular secretion by cimetidine in man. Br J Clin Pharmacol 23: 545 – 551
40. Vitek V, Cowley RA (1971) Blood lactate in the prognosis of various forms of shock. Ann Surg 173: 308 – 313
41. Brooks GA (2009) Cell-cell and intracellular lactate shuttles. J Physiol 587: 5591 – 5600
42. Gores GJ, Nieminen AL, Wray BE, Herman B, Lemasters JJ (1989) Intracellular pH during "chemical hypoxia" in cultured rat hepatocytes. Protection by intracellular acidosis against the onset of cell death. J Clin Invest 83: 386 – 396

Energy Goals in the Critically Ill Adult

S.L. Peake, E. Ridley, and M. Chapman

Introduction

The nutrition literature is replete with observational studies, small randomized trials, systematic reviews and consensus guidelines on how best to provide nutrition support to critically ill patients. Nevertheless, many questions remain unresolved including: What are the most appropriate substrates, when is the right time to commence feeding, which route should be used (enteral, parenteral or a combination), what is the ideal method for assessing energy requirements and what are the optimal nutritional goals?

In order to avoid the complications of both over- and under-feeding, the traditional approach has been to provide sufficient nutrition to meet either measured energy requirements (based on indirect calorimetry) or estimated requirements (based on predictive equations developed in the non-critically ill); the assumption being that meeting energy expenditure is ideal. However, there is no convincing evidence to show that this approach improves important clinical outcomes following admission to the intensive care unit (ICU). In particular, there are no large scale randomized controlled trials in which an increased or decreased amount of energy delivery has been associated with improved survival.

Confounding the issue further, is the fact that, despite aiming for eucaloric feeding, usual clinical practice typically results in critically ill patients receiving only 50 to 70 % of prescribed energy requirements (approximately 1000 kcal/day) [1, 2]. Furthermore, evidence-based guidelines for nutrition support have not been shown to increase the amount of energy delivered in two cluster-randomized trials conducted under the auspices of the Australian and New Zealand Intensive Care Society Clinical Trials Group [3] and the Southwestern Ontario Critical Care Research Network [4]. In the study by Doig et al. [3], critically ill patients randomized to receive nutrition according to guidelines received 1241 (95 % confidence interval [CI] 1121 – 1374) kcal/patient-day compared to 1065 (95 CI 961 – 1179) kcal/patient-day in non-guideline ICUs (p = 0.14) [3]. Similar hypocaloric energy delivery was also observed in the Canadian ACCEPT trial [4].

So, should clinicians be trying to achieve predicted or measured caloric goals that, until now, have been difficult to achieve, particularly in the context of declining mortality following ICU admission over the last 15 years [5]? Or, instead, should we be considering alternative nutrition strategies such as permissive hypocaloric feeding, which has been advocated by a number of authors [6, 7] and for which there is some evidence [8], albeit predominantly in the obese [9]?

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Determination of Energy Goals

Indirect Calorimetry

Indirect calorimetry is considered to be a 'gold standard' for the determination of energy needs in the critically ill. There are a number of proposed benefits of using regular indirect calorimetry, especially for patients in whom it is difficult to predict energy requirements and who fail to respond to nutrition, and in those who are particularly catabolic and therefore require specialized and accurate nutrition delivery [10]. The concept of individualized tailoring of nutrition is also gaining popularity, with a growing body of data demonstrating the possible deleterious effects of under- and over-feeding [1, 11–13].

To better understand the utility of indirect calorimetry in the critically ill, there are some important technical considerations which must be appreciated. Heat is produced as a result of substrate oxidation during metabolism [14]. By measuring pulmonary gas exchange (CO_2 production and O_2 consumption [VO_2]) and applying the Weir equation, energy use is approximated by indirect calorimetry [14, 15].

In the critical care setting, indirect calorimetry measurement determines the patient's resting metabolic rate, which makes up approximately 70 % of the total daily energy expenditure. In the healthy adult, the total daily energy expenditure consists of three main components; basal metabolic rate (BMR), diet-induced energy expenditure and the most variable of all, activity-induced energy expenditure. Diet-induced energy expenditure contributes approximately 10 % of total daily energy expenditure in the healthy adult and is not accounted for with indirect calorimetry measurement; albeit the contribution is thought to be less during continuous enteral nutrition [14]. In the critically ill, the reduction in physical activity and continuous enteral nutrition as standard practice ensure that most variable components of energy expenditure (diet-induced energy expenditure and activity-induced energy expenditure) are minimized [14].

The total daily energy expenditure of hospitalized patients is decreased so that the resting metabolic rate (BMR + diet-induced energy expenditure) approximates total daily energy expenditure. This was demonstrated by McClave et al. in 22 mechanically ventilated patients where the addition of a 10 % adjustment factor to measured resting metabolic rate decreased prediction accuracy [16]. Therefore, what is actually measured by indirect calorimetry in the critically ill is BMR or the energy actually expended at that point in time, incorporating basal requirements and any metabolic changes due to the acute illness [17].

With repeated measurements over time, valuable information about the energy expenditure of the patient can be determined using indirect calorimetry and nutrition tailored accordingly. In a small, single-center, prospective, randomized, non-blinded, pilot study, Anbar et al. reported that nutrition targeted to indirect calorimetry measurements was associated with improved clinical outcomes compared to a standard, fixed prescription (see below) [18]. These results are currently being tested in a multicenter trial, but there are not yet any results from large scale trials demonstrating the beneficial effect of routine indirect calorimetry use on important clinical outcomes (e.g., infectious complications, length of stay [LOS], mortality).

The recommended indirect calorimetry study length is also not established. Measurement periods of 15 minutes have been demonstrated to estimate resting energy expenditure within 4 % and several groups have shown < 10 % error from

a 5 minute measurement [10, 16]. Length of measurement is also correlated with patient acuity [16]. If steady state cannot be achieved (defined as a change in VO_2 < 5–10 % for 5–10 minutes) the measurement period should be extended up to 24 hourly measurement [16].

Finally, despite the potential advantages of indirect calorimetry, there are limitations to its use. Accuracy of measurements is affected by patient and therapeutic factors. High inspired fraction of oxygen (FiO_2) requirements (> 0.60) can lead to an error in indirect calorimetry measurement as the Haldane transformation (used in the prediction of inspired and expired air volume) assumes that nitrogen concentration is constant in both inspired and expired gases. Thus, whilst high FiO_2 requirements are not an absolute contraindication to indirect calorimetry measurement, this limitation reinforces the need to have experienced practitioners applying and interpreting indirect calorimetry results. Proper maintenance and calibration by trained personnel is also essential to ensure accuracy. Other factors contributing to inaccuracy of measurement include known air leaks in the ventilation circuit and treatments such as continuous veno-venous hemodialysis and extracorporeal membrane oxygenation (ECMO) which modify inspiratory and expiratory gas losses.

Predictive Equations

Predictive equations are the most common method for determining energy requirements in the critically ill. Notwithstanding their ease of application, most of the formulas were designed for use in a healthy population and there remains no consensus as to the most accurate equation for predicting nutritional requirements in the critically ill.

The most commonly used predictive equations, the Harris-Benedict and Schofield equations, were derived in a lean, healthy population in 1919 and 1985, respectively. The Harris-Benedict equation has been evaluated in the critically ill, consistently performing poorly compared to measured requirements and, hence, not recommended for use in this patient cohort [19]. For example, in a study using continuous calorimetry for 5 days in 27 mechanically ventilated patients, the Harris-Benedict equation provided estimates within 80–110 % of total daily energy expenditure, and would have resulted in clinically significant under- or over-feeding in 16 % and 18 % of patients, respectively [20]. Frankenfield et al. found that the Harris-Benedict equation was more accurate with an adjustment factor of 1.2; although this should not be regarded as a blanket adjustment [19]. The Schofield equation, most commonly used in Europe and Australia, is less well validated in the critically ill and has been shown to yield similar inaccuracies to the Harris-Benedict equation [20].

Due to the difficulties with using the above predictive equations in the critically ill, several groups have developed their own specific equations. These include: The Ireton-Jones equations, developed in 1992 and reworked in 1997; the Penn State equation derived in 1998; the Swinamer equation published in 1990 and; the Faisy equation, developed in 2003. Although some of these equations more accurately predict the energy consumption of the critically ill, the results of validation studies are divergent and complexities of the equations are often impractical at the patient's bedside.

In their evaluation of the eight most commonly used equations in the critically ill compared with calometric measurements, Frankenfield et al. found that accu-

racy rates (defined as < 15 % error in the square root of the mean prediction) ranged from 18 – 67 % [21]. In particular, accuracy became increasingly difficult to predict as patients became more obese or elderly. They concluded that the Penn State equation, which was derived from a mixed ICU population, was the most unbiased and precise across all groups (except the elderly obese in whom no equation performed well). Of note, however, accuracy of the Penn State equation ranged from 62 – 67 % (depending on the form of the equation used) and the incidence of large errors (> 15 % difference from measured requirements) was 19 – 22 %.

The most significant source of error in predictive equations is the use of estimated, rather than measured, weight due to the impracticality and inaccuracies of actual weight in the critically ill. Age, gender, and heterogeneity of this population also complicate the accuracy of predictive equations. Finally, the changing nature of critical illness means that what may be an accurate estimate soon after injury can quickly become a significant overestimate. Nonetheless, the addition of injury factors that adjust the predicted energy requirements for the degree of metabolic stress caused by injury or illness can also affect accuracy and complicate usage.

Fixed Prescription

Another popular choice for determination of energy requirements in the critically ill is fixed prescription, usually in the order of 20 – 35 kcal/kg/day. Several studies have used indirect calorimetry to measure the energy expenditure in the critically ill and values of 21 – 35 kcal/kg/day have commonly been reported. In 1997, the American College of Chest Physicians (ACCP) also published their consensus statement recommending that a fixed prescription of 25 kcal/kg of ideal body weight (IBW)/day "appears to be adequate for most patients" [22].

Whereas fixed prescription is more easily applied at the patient bedside than either indirect calorimetry or predictive equations, accuracy is generally reported to be poor. Using 25 kcal/kg/day, only 35 % of delivered calories are within 10 % of measured requirements and 65 % are within 80 – 110 % of measured requirements. Moreover, 25 kcal/kg/day fixed prescription results in underfeeding in 22 % of critically ill patients and overfeeding in 13 % [20, 23]. Although metabolically active weight, rather than actual weight, may improve accuracy, a reliable definition of metabolically active weight is problematic [21].

Effect of Energy Delivery on Clinical Outcomes

There is little reliable information on either the amount or types of nutrition (energy and nitrogen) required to optimize outcomes in the critically ill. As noted above, current energy goals are commonly based on studies using indirect calorimetry and calculated using predictive equations. Several professional organizations have also developed guidelines and consensus statements regarding determination of nutrition requirements during critical illness [24 – 27] (**Table 1**). Importantly, however, these recommendations are conflicting. Furthermore, there is an assumption that meeting energy expenditure is ideal but there are no convincing data to support this practice.

Table 1. Recommended caloric intake for critically ill patients according to published guidelines

Society	Year	Recommendations
ACCP [22]	1997	25 kcal/kg/day
CCCPG [24]	2003	No recommendation (insufficient evidence)
ESPEN [25]	2006	Enteral nutrition Acute phase 20 – 25 kcal/kg/day (Grade C) Anabolic recovery phase 25 – 30 kcal/kg/day (Grade C) Patients with malnutrition 25 – 30 kcal/kg/day (Grade C)
ESPEN [26]	2009	Parenteral nutrition According to calorimetric calculations if available (Grade B)* 25 kcal/kg/day (if IC not available) (Grade C)
ASPEN [27]	2009	According to calorimetric calculations or equations or 25 kcal/kg/day

ACCP: American College of Chest Physicians; CCCPG: Canadian Critical Care Practice Guidelines; ESPEN: European Society of Parenteral and Enteral Nutrition; ASPEN: American Society of Parenteral and Enteral Nutrition; IC: indirect calorimetry.
Evidence grades: B, supported by at least one well-designed randomized controlled trial or other with sound methodology; C, based on expert opinion or advice.
* single center pilot study published in abstract form

Hypocaloric Feeding

When the ACCP consensus conference guidelines were published in 1997, they were based on limited evidence [22]. Unfortunately, little progress has been made since that time in our understanding of nutritional goals in critical illness. Consequently, the recommendation of 25 kcal/kg/day for all ICU patients is still commonly used by many clinicians.

Following publication of the ACCP guidelines, a prospective observational study involving 187 medical ICU patients examined the relationship between energy delivery according to ACCP guidelines and survival [8]. These data suggested that the best patient outcomes were associated with delivery of 33 – 65 % of ACCP goals (approximately 9 – 18 kcal/kg/day) [8]. Patients receiving 33 – 65 % of recommended caloric intake had increased likelihood of survival to hospital discharge compared to those receiving a lower delivery of nutrition (< 33 % of ACCP goal), odds ratio (OR) 1.22 (95 % CI 1.15 – 1.29). In contrast, delivery of ≥ 66 % of ACCP recommended intake was associated with a lower likelihood of survival to hospital discharge, OR 0.82 (95 % CI 0.70 – 0.94).

Hypocaloric feeding occurs frequently in the critically ill but is usually inadvertent as most patients fail to achieve nutritional goals during the enteral delivery of nutrition. In a prospective, observational study conducted in 167 ICUs across 37 countries, Alberda et al. reported that mechanically ventilated patients received just over 1000 kcal/day (14 kcal/kg/day) when averaged over the first 12 days of ICU stay [1]. While it may seem logical to attempt to meet energy goals, there are theoretical arguments to support hypocaloric feeding early in critical illness.

Short periods of hypocaloric feeding may not be expected to affect clinical outcomes and would be considered a 'normal' response to acute illness in which loss of appetite and reduced intake would be usual. There is a teleological argument that the anorexia associated with illness indicates metabolic change where the

body does not require, and may not be able to utilize, energy at that time. In addition, feeding is associated with complications which may affect clinical outcomes. The most topical of these is hyperglycemia. Both enteral and parenteral nutrition cause hyperglycemia which is associated with mortality; suggesting that nutrition should be modified to control glycemia.

Further clinical evidence that it may be advantageous to deliver less nutrition is provided in a retrospective observational study undertaken in severely injured patients [28]. Sena et al. reported that increased nutrient delivery with parenteral nutrition (supplementing enteral nutrition) was associated with an increased risk of infection (blood stream infection risk ratio 2.8 [1.5–5.3], p = 0.002) and a trend to increased risk of death (adjusted OR 2.7 [0.8–8.8], p = 0.10) [28]. Energy delivery with enteral nutrition alone increased from 15 kcal/kg/day on day 3 to 30 kcal/kg/day on day 7, whereas energy delivery from combined feeding increased from 20 kcal/kg/day on day 3 to 35 kcal/kg/day on day 7. The energy delivery in the enteral feeding group was close to goal feeding while the supplemented group could be considered overfed. Although the authors adjusted for other factors that may have contributed to a worse outcome, the observational nature of the study further limits the conclusions and there remains a possibility that the combined group was sicker. Finally, it is unclear whether the worse outcomes were because of increased energy delivery *per se* or the use of intravenous feeding which is associated with infection.

A randomized, controlled trial published by Taylor et al. in 1999 [29] supports the finding by Krishnan et al. [8] that moderate hypocaloric feeding is preferable to underfeeding. In this study, patients with traumatic brain injury were randomized to either standard or enhanced enteral nutrition; the enhanced feeding group received 60 % of nutritional goals (calculated by Schofield equation) over 7 days and the control group received less than 40 % of goals. The intervention group had fewer infective complications (61 % vs. 85 %, p = 0.02) but neurological recovery and mortality were unaffected [29].

The Canadian ACCEPT trial [4] suggested an improvement in outcomes with protocol-based management of nutrition. Paradoxically, the implementation of nutrition guidelines did not result in a significant improvement in energy delivery. Although both treatment groups received calories within the hypocaloric range (1266 vs. 995 kcal/day, p = 0.31 in guideline and non-guideline ICUs respectively), hospital LOS was shorter (25 vs. 35 days, p = 0.003) and there was a trend to reduced mortality (27 % vs. 37 %, p = 0.06) in the protocol-treated group [4].

While it may appear logical that feeding during critical illness is important, it is likely that a brief period of reduced intake may have no effect on outcome. It is also plausible that some variation in calories within a defined range, delivered over a variable time frame, is not going to influence clinical outcomes. Many factors, both illness and treatment related, affect outcomes during critical illness and nutrient delivery may or may not be important. It is also plausible however that at some point cumulative malnutrition and muscle mass loss will impact on recovery.

Although the enteral route is considered preferable to the intravenous route in the provision of nutrition to the critically ill, enteral delivery frequently does not achieve prescribed nutritional goals [30, 31]. To ensure adequate delivery of nutrition, combined feeding with both parenteral and enteral nutrition has been advocated in some centers (particularly in Europe). However, to date, the addi-

tional nutrient delivery has not been associated with improved outcomes. For example, a study that examined the effect of supplemental parenteral nutrition on clinical outcomes showed that supplementing enteral nutrition with parenteral nutrition could increase energy delivery from 10–15 kcal/kg/day to 25 kcal/kg/day with no effect on mortality (40 % in both groups). However, a reduction in hospital stay was observed in the supplemented group (31 ± 19 vs. 34 ± 28 days, $p = 0.002$) [32]. In a subsequent meta-analysis, which included this and four other studies involving differing groups of critically ill patients (severe burns 1, trauma 1, mixed 2), no clinical benefit was demonstrated by supplementing enteral with parenteral nutrition despite more successful nutritional delivery [33]. However, the use of parenteral nutrition was not associated with increased complications.

Energy dose has also been examined when nutrition has been provided solely by the intravenous route. McCowen et al. randomized 40 ICU patients to 25 kcal/kg/day or 1000 kcal/day in a non-blinded trial. Patients received 1410 versus 1000 kcal at goal but there were no differences in any clinical outcomes, including glucose control, between the two groups [34].

Overall, these studies suggest that supplementing enteral energy delivery with parenteral nutrition in order to achieve nutritional goals does not affect survival; however, it is clear that studies examining nutritional goals are small and possibly underpowered to show a benefit with increased or reduced calorie delivery. It is also possible that increased calories delivered by resorting to parenteral nutrition administration alone, or in combination with enteral nutrition, may expose the patient to complications of intravenous delivery such that any improvement in outcome from increased calorie delivery will be counterbalanced by complications from parenteral nutrition. Larger studies are currently underway aimed at addressing these questions (e.g. ClinicalTrials.gov: NCT00512122).

Evidence that Achieving Nutritional Goals may Improve Outcomes

Whereas the study by Krishnan et al. [8] suggests that mild underfeeding is optimal for survival, other observational studies have suggested that underfeeding is associated with an inability to wean from mechanical ventilation and an increase in complications, particularly infections [13]. Severe underfeeding (less than 25 % requirements) is associated with increased risk of nosocomial blood stream infections, independent of illness severity, compared with feeding > 25 % of requirements (relative risk of death of 0.27 [0.11–0.68] compared to < 25 % of requirements) [35].

Alberda et al. reported that reduced energy delivery was associated with worse clinical outcomes in ventilated patients with a body mass index (BMI) < 25 and > 35 kg/m^2 [1]. While the suggestion that reduced energy delivery may worsen clinical outcomes in patients with a lower BMI is entirely plausible, this finding in patients with a higher BMI conflicts with previous studies [36]. The observational nature of Alberda's study means that a causal association cannot be established between underfeeding and outcome. It is possible that, in these cohorts, the sicker and dying patients receive less nutrition because of more deranged gastrointestinal function, nutrition may not be a treatment priority and, in the case of palliation, there may be a conscious decision not to administer nutrition.

An additional argument against hypocaloric feeding is the concept of the development of energy debt over time and the understanding that deficits in energy delivery cannot be recouped because of the fear of complications from overfeed-

ing. Hence, while a brief period of underfeeding may not have any negative consequences, it is often unclear how long a patient will stay in the ICU and reduced nutrient delivery may result in a significant cumulative energy debt over time.

This concept of cumulative energy debt was explored by Villet et al. in a prospective observational study examining energy expenditure and matching it to energy delivered in 48 critically ill surgical patients [13]. Energy goal was 1.3 times the resting energy expenditure (i.e., 29 kcal/kg/day). Cumulative energy debt was calculated as −12,600 ± 10,520 kcal over the first week and there was a strong relationship between ICU complications and LOS and energy debt. These data were not corrected for illness severity. So, again, these observational data, while interesting, may merely reflect an association between illness severity and difficulties with feeding. In particular, it is also important to note that the energy debt is dependent on the energy goal (which was higher than the 25 kcal/kg/day generally recommended).

In the pilot study reported by Anbar et al., increased energy delivery was demonstrated when indirect calorimetry was used to determine caloric goals, compared to a fixed prescription of 25 kcal/kg/day (daily energy balance 212 ± 63 kcal/day indirect calorimetry group vs. −362 ± 67 kcal/day, $p = 0.001$). Hospital mortality was also improved in patients receiving calories according to indirect calorimetry (28 % vs. 51 %, $p = 0.03$), albeit the control arm mortality appears excessive. The results of the ongoing trial are awaited with interest [18].

Overfeeding

Hyperalimentation was in vogue in the 1970s and 1980s in an effort to reverse the nitrogen loss and subsequent cachexia associated with critical illness. However, it became clear that overfeeding not only failed to reverse muscle mass loss but also had several negative consequences and this technique was abandoned. The subsequent swing in opinion may in part explain the current acceptance of less than normal nutritional goals.

Examples of problems associated with overfeeding include increased inotrope requirement, increased O_2 requirements and CO_2 production, increased metabolic rate and measured energy expenditure, and increased body temperature. In addition, increased mortality has been demonstrated in association with increased energy delivery in a group of critically ill burns patients randomized to receive enteral nutrition with or without supplemental parenteral nutrition [37]. However, the study was published in 1989 and the approach to feeding at that time was different; energy goals were 25 kcal/kg/24h plus 40 kcal per % total burnt surface area burned per day, resulting in calorie goals of 4700 – 4800 per day.

Energy Delivery in The Malnourished Patient

Malnutrition is common in the acute care setting and is often poorly recognized. No longer are the elderly and the cachectic the only patient cohorts at risk. Obesity is a new challenge in the assessment of malnutrition. One recent cross-sectional study in 57 ICU patients aimed to assess whether nutritional status could be determined using the subjective global assessment (SGA) tool [38]. Using two independent assessors, 50 % of patients were malnourished (95 % agreement [$\kappa = 0.90$]).

Adequate nutrition delivery during critical illness is essential as malnutrition is both a cause and a consequence of disease which can greatly affect outcome. Nonetheless, defining the amount of energy required for the malnourished critically ill patient is also challenging and there are several important considerations, including the issue of refeeding syndrome which is characterized by potentially life-threatening clinical and biochemical abnormalities. Those at highest risk of refeeding syndrome are those with a low body weight or BMI < 18 kg/m^2, a history of weight loss of ≥ 10 % of total body weight over 3 months, poor oral intake for > 5 days and a history of poor nutritional intake or conditions that may be associated with malnutrition (e.g., alcoholism). There is general consensus that nutrition should be introduced cautiously over an extended period of time with close monitoring of electrolytes and replacement as required.

Energy Delivery in Obesity

Population-based studies demonstrate that the prevalence of obesity is progressively increasing in developed countries such as the United States, Canada and Australia. More importantly, obesity (BMI ≥ 30 kg/m^2) may be present in up to 30 % of ICU patients [39]. An understanding of the nutritional requirements and feeding goals in this important patient cohort is, therefore, essential.

Metabolic Changes Associated With Obesity

The metabolic and endocrine consequences of obesity in non-stressed individuals include glucose intolerance, insulin resistance, type 2 diabetes mellitus, metabolic syndrome, dyslipidemia, non-alcoholic fatty liver disease, and steatohepatosis. Obesity is also associated with an increase in both adipose tissue and lean body mass, with lean body mass contributing approximately 30 % of excess weight. Consequent upon the increase in lean body mass, there is also a concomitant increase in BMR and resting energy expenditure compared with lean individuals. However, it should be noted that as the degree of obesity increases, the relative contribution of lean body mass to total body weight progressively decreases.

In ICU patients, obesity-related metabolic and endocrine changes are further exacerbated by critical illness. The well-described increase in protein and energy requirement that occurs in response to physiologic stress in the non-obese ICU population may also be modified, with a greater increase in net glucose and protein oxidation and reduction in fat oxidation compared to lean individuals. Jeevenanadam et al. reported that non-obese trauma patients (BMI < 30 kg/m^2) preferentially used fat oxidation (61 % of resting energy expenditure); whereas carbohydrate and protein oxidation were the main fuel sources in obese trauma patients (only 39 % of resting energy expenditure derived from fat oxidation) [40]. Obese individuals are, therefore, potentially at greater risk of energy and protein malnutrition. Moreover, obesity and pre-morbid malnutrition are not mutually exclusive.

Notwithstanding the risk of malnutrition, the presence of co-morbidities, such as diabetes, fatty liver and obesity-related hypoventilation syndrome, may place obese patients at increased risk of overfeeding compared to the non-obese. Stress-induced hyperglycemia may be exacerbated by obesity-related glucose intolerance and excessive glucose (caloric) load may further increase the risk of

lipogenesis, hepatic steatosis, increased CO_2 production and increased work of breathing. Accordingly, careful consideration must be given to the desired nutritional support goals. Unfortunately, both a paucity of data and conflicting evidence provide little guidance for clinicians. Two important questions remain unanswered; namely, "How many calories should be administered?" and "How to estimate caloric goals?".

How Many Calories should be Administered?

Provision of nutritional support for obese critically ill patients must be cognizant of the recognized differences in metabolic response as described above and the potential complications of both under- and over-feeding.

The recently published Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (ASPEN) guidelines recommend limiting target energy goals to 60–70 % of energy requirements (i.e., 11–14 kcal/kg actual body weight/day or 22–25 kcal/kg ideal body weight/day) (Grade D recommendation supported by at least two level III non-randomized contemporaneous trials) [27]. Importantly, however, this recommendation remains to be validated in a large scale, multicenter, prospective, blinded, randomized, controlled trial of obese critically ill patients.

Conversely, the observational study conducted by Alberda et al. suggested that increased caloric intake may be associated with improved clinical outcomes in obese mechanically ventilated patients [1]. On average, obese patients were prescribed almost 2000 kcal/day. However, only 1000 kcal/day was actually delivered; predominantly as enteral nutrition. The adjusted OR for 60-day mortality per increase of 1000 kcal/day delivered for patients with a BMI of 35 to < 40 kg/m^2 (n = 132) was 0.36 (95 % CI 0.16–0.80). Notably, however, this same relationship between mortality and energy delivery did not exist in obese patients with a BMI of 30 to < 35 kg/m^2 (n = 395, OR 1.04 [95 % CI 0.64–1.68]) or ≥ 40 kg/m^2 (n = 171, OR 0.63 [95 %CI 0.32–1.24]). Inconsistent effects on ventilator-free days in the various obesity categories were also observed. Finally, the inherent bias in observational nutrition studies reinforces the need for a prospective, randomized trial of hypocaloric versus eucaloric feeding.

The putative benefits of hypocaloric feeding in obese critically ill patients include [41–43]:

i) reducing obesity- and stress-induced hyperglycemia, exogenous insulin requirements, hepatic gluconeogenesis and lipogenesis
ii) promoting endogenous fat oxidation
iii) limiting protein oxidation and muscle breakdown and promoting protein anabolism
v) preventing the complications of overfeeding
vi) reducing infectious complications
vii) supporting weight loss and inducing favorable changes in body composition

Dickerson et al. reported that obese trauma and surgical ICU patients receiving hypocaloric, high protein enteral feeding (< 20 kcal/kg adjusted body weight/day) had a significantly reduced ICU LOS and duration of antibiotic therapy and a trend towards decreased length of mechanical ventilation compared to obese patients receiving eucaloric enteral feeding (25–30 kcal/kg adjusted body weight/day). Of note, however, the number of infectious complications, hospital LOS and

survival were not different [44]. Moreover, the retrospective nature of this small (n = 40), unblinded, non-randomized, single center study and the potential for selection bias, particularly in the assignation of feeding regimens, limit the study's findings.

The beneficial effects of hypocaloric feeding on various clinical outcomes in obese patients have also been reported in several small parenteral nutrition studies. However, not all of these studies have been conducted in ICU patients. In 13 obese surgical patients with post-operative complications (mean weight 127 ± 60 kg), the administration of only 51 % of measured energy expenditure as non-protein calories (average intake 881 ± 393 kcal/day) resulted in both weight loss and positive nitrogen balance [45]. A prospective, randomized, blinded trial of obese, non-ICU patients (n = 16) receiving either 50 % of measured energy expenditure as non-protein calories or a eucaloric regimen (100 % of measured energy expenditure) for 14 days also reported that nitrogen balance was not different between the two feeding groups [46]. A similar effect on nitrogen balance has been reported in another prospective, blinded study of thirty patients (average BMI 35 kg/m^2) randomized to receive either hypocaloric (22 kcal/kg ideal body weight/day) or eucaloric (36 kcal/kg ideal body weight/day) parenteral nutrition; albeit the study cohort included only 13 ICU patients [42].

In twenty non-surgical, mechanically ventilated patients with multiple organ failure, Muller et al. measured the metabolic effects of a 12 hour hypocaloric, eucaloric or hypercaloric parenteral nutrition infusion (14, 28, and 56 kcal/kg per day, respectively) [48]. Energy expenditure and lactate and glucose levels were significantly lower in patients receiving a hypocaloric regimen. Conversely, protein breakdown was significantly elevated with hypercaloric nutrition. In contrast, McCowen et al. were unable to demonstrate that hypocaloric parenteral nutrition was associated with lower blood glucose levels or reduced insulin requirements [34].

It should be noted, however, that although both these studies were conducted in ICU patients, neither was specifically designed to address the question of hypocaloric feeding in the obese critically ill population; accordingly, the implications for feeding strategies in this specific patient group are limited. Moreover, separating out the deleterious effects of excessive caloric load from the specific effect of parenteral nutrition-induced hyperglycemia (e.g., infectious complications) is problematic.

How to Estimate Caloric Goals?

Notwithstanding the unresolved controversy surrounding how many calories should be delivered to obese critically ill patients, considerable debate also exists regarding the most accurate method for estimating energy requirements and, hence, caloric goals in this patient cohort. In 2007, a systematic review conducted by the American Dietetic Association assessed the validity of various formulae to accurately predict resting metabolic rate in ICU patients, including the obese. The authors concluded that the Ireton-Jones (1992 version) and Penn State (1998 version) equations are the most useful in obese patients. In particular, Ireton-Jones may be more accurate in obese, than non-obese, patients; albeit predicted estimates of energy estimates for both formulae are > 15 % different to measured energy in nearly 30 % of obese patients and validation data are limited [19].

Irrespective of which predictive equation clinicians use, obesity-related changes in body composition and resting energy expenditure, in particular the

reduced metabolic demands of adipose tissue and the variable increase in lean body mass with increasing weight, lead to difficulties in accurately determining both actual and ideal body weight, thereby placing obese patients at particular risk of inadvertent overfeeding and underfeeding.

Using actual body weight has been shown to overestimate energy requirements whereas ideal body weight generally underestimates measured energy expenditure [7]. Consequently, formulae exist for calculating an 'adjusted body weight' (e.g., adjusted body weight = [actual body weight x 0.25] + ideal body weight) that take into account the increase in metabolically active lean body mass that occurs with obesity. Currently, however, there is no consensus as to which of these weights (actual, ideal or adjusted) should be used to predict energy requirements in obese patients. Finally, an alternative proposal advocated by some authors is to simply deliver a fixed amount of calories per day (e.g., 21 kcal/kg actual weight/day in obese ventilated patients) [7].

Ultimately, all the proposed methods for estimating energy requirements are inherently biased with considerable error, particularly for the individual patient. In fact, the SCCM and ASPEN guidelines advocate using indirect calorimetry instead of formulae in obese patients as predictive equations in this patient population are "even more problematic" than in non-obese ICU patients (Grade E recommendation supported by studies of non-historical controls, case series, uncontrolled studies or expert opinion) [27]. However, this recommendation does not acknowledge that accurate and reproducible measurement of resting energy expenditure with indirect calorimetry is often problematic in the critically ill. Limited availability of metabolic carts in most ICUs also prevents widespread usage.

Conclusion

In summary, it is as yet unknown what nutritional goals should be used in the critically ill. There is limited evidence suggesting that hypocaloric feeding may be superior to both severe underfeeding and goal feeding and stronger evidence that overfeeding is associated with poor outcomes. Based on the limited data available, we can hypothesize that: 1) energy delivery will have no impact on outcome in short stay ICU patients; 2) differences in energy delivery within a certain range may have no impact on outcome; 3) cumulative energy delivery below and above that range will cause worse outcomes including increased mortality; 4) different energy goals may apply when patients are malnourished or obese prior to ICU admission; 5) energy goals may change over time as metabolism changes in response to hormonal change associated with critical illness. Before further research is performed aimed at defining methods of improving energy delivery to the critically ill it is important to establish what nutritional goals will optimize clinical outcomes.

References

1. Alberda C, Gramlich L, Jones N, et al (2009) The relationship between nutritional intake and clinical outcomes in critically ill patients: results of an international multicenter observational study. Intensive Care Med 35: 1728 – 1737
2. NICE-SUGAR Study Investigators, Finfer S, Chittock DR, et al (2009) Intensive versus conventional glucose control in critically ill patients. N Engl J Med 360: 1283 – 1297

3. Doig GS, Simpson F, Finfer S, et al (2008) Effect of evidence-based feeding guidelines on mortality of critically ill adults: a cluster randomized controlled trial. JAMA 300: 2731–2741
4. Martin CM, Doig GS, Heyland DK, Morrison T, Sibbald WJ (2004) Multicentre, cluster-randomized clinical trial of algorithms for critical-care enteral and parenteral therapy (ACCEPT). CMAJ 170: 197–204
5. Moran JL, Bristow P, Solomon PJ, George C, Hart GK (2008) Mortality and length-of-stay outcomes, 1993–2003, in the binational Australian and New Zealand intensive care adult patient database. Crit Care Med 36: 46–61
6. Miller JP, Choban PS (2006) Feeding the critically ill obese patient: the role of hypocaloric nutrition support. Respir Care Clin N Am 12: 593–601
7. Port AM, Apovian C (2010) Metabolic support of the obese intensive care unit patient: a current perspective. Curr Opin Clin Nutr Metab Care 13: 184–191
8. Krishnan JA, Parce PB, Martinez A, Diette GB, Brower RG (2003) Caloric intake in medical ICU patients: consistency of care with guidelines and relationship to clinical outcomes. Chest 124: 297–305
9. Dickerson RN, Boschert KJ, Kudsk KA, Brown RO (2002) Hypocaloric enteral tube feeding in critically ill obese patients. Nutrition 18: 241–246
10. da Rocha EE, Alves VG, da Fonseca RB (2006) Indirect calorimetry: methodology, instruments and clinical application. Curr Opin Clin Nutr Metab Care 9: 247–256
11. Petros S, Engelmann L (2006) Enteral nutrition delivery and energy expenditure in medical intensive care patients. Clin Nutr 25: 51–59
12. Rubinson L, Diette GB, Song X, Brower RG, Krishnan JA (2004) Low caloric intake is associated with nosocomial bloodstream infections in patients in the medical intensive care unit. Crit Care Med 32: 350–357
13. Villet S, Chiolero RL, Bollmann MD, et al (2005) Negative impact of hypocaloric feeding and energy balance on clinical outcome in ICU patients. Clin Nutr 24: 502–509
14. Haugen HA, Chan LN, Li F (2007) Indirect calorimetry: a practical guide for clinicians. Nutr Clin Pract 22: 377–388
15. Weir JB (1949) New methods for calculating metabolic rate with special reference to protein metabolism. J Physiol 109: 1–9
16. McClave SA, Spain DA, Skolnick JL, et al (2003) Achievement of steady state optimizes results when performing indirect calorimetry. JPEN J Parenter Enteral Nutr 27: 16–20
17. Holdy KE (2004) Monitoring energy metabolism with indirect calorimetry: instruments, interpretation, and clinical application. Nutr Clin Pract 19: 447–454
18. Anbar R TM, Fisher H, Madar Z, Cohen J, Singer P (2009) Tight calorie balance control decreases hospital mortality in a prospective randomised controlled study: The final single center TICACOS results. Clin Nutr Suppl 4: 7 (abst)
19. Frankenfield D, Hise M, Malone A, Russell M, Gradwell E, Compher C (2007) Prediction of resting metabolic rate in critically ill adult patients: results of a systematic review of the evidence. J Am Diet Assoc 107: 1552–1561
20. Reid CL (2007) Poor agreement between continuous measurements of energy expenditure and routinely used prediction equations in intensive care unit patients. Clin Nutr 26: 649–657
21. Frankenfield DC, Coleman A, Alam S, Cooney RN (2009) Analysis of estimation methods for resting metabolic rate in critically ill adults. JPEN J Parenter Enteral Nutr 33: 27–36
22. Cerra FB, Benitez MR, Blackburn GL, et al (1997) Applied nutrition in ICU patients. A consensus statement of the American College of Chest Physicians. Chest 111: 769–778
23. MacDonald A, Hildebrandt L (2003) Comparison of formulaic equations to determine energy expenditure in the critically ill patient. Nutrition 19: 233–239
24. Heyland DK, Dhaliwal R, Drover JW, Gramlich L, Dodek P (2003) Canadian clinical practice guidelines for nutrition support in mechanically ventilated, critically ill adult patients. JPEN J Parenter Enteral Nutr 27: 355–373
25. Kreymann KG, Berger MM, Deutz NE, et al (2006) ESPEN Guidelines on Enteral Nutrition: Intensive care. Clin Nutr 25: 210–223
26. Singer P, Berger MM, Van den Berghe G, et al (2009) ESPEN Guidelines on Parenteral Nutrition: intensive care. Clin Nutr 28: 387–400

27. Martindale RG, McClave SA, Vanek VW, et al (2009) Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient: Society of Critical Care Medicine and American Society for Parenteral and Enteral Nutrition: Executive Summary. Crit Care Med 37: 1757 – 1761
28. Sena MJ, Utter GH, Cuschieri J, et al (2008) Early supplemental parenteral nutrition is associated with increased infectious complications in critically ill trauma patients. J Am Coll Surg 207: 459 – 467
29. Taylor SJ, Fettes SB, Jewkes C, Nelson RJ (1999) Prospective, randomized, controlled trial to determine the effect of early enhanced enteral nutrition on clinical outcome in mechanically ventilated patients suffering head injury. Crit Care Med 27: 2525 – 2531
30. Adam S, Batson S (1997) A study of problems associated with the delivery of enteral feed in critically ill patients in five ICUs in the UK. Intensive Care Med 23: 261 – 266
31. De Jonghe B, Appere-De-Vechi C, Fournier M, et al (2001) A prospective survey of nutritional support practices in intensive care unit patients: what is prescribed? What is delivered? Crit Care Med 29: 8 – 12
32. Bauer P, Charpentier C, Bouchet C, Nace L, Raffy F, Gaconnet N (2000) Parenteral with enteral nutrition in the critically ill. Intensive Care Med 26: 893 – 900
33. Dhaliwal R, Jurewitsch B, Harrietha D, Heyland DK (2004) Combination enteral and parenteral nutrition in critically ill patients: harmful or beneficial? A systematic review of the evidence. Intensive Care Med 30: 1666 – 1671
34. McCowen KC, Friel C, Sternberg J, et al (2000) Hypocaloric total parenteral nutrition: effectiveness in prevention of hyperglycemia and infectious complications – a randomized clinical trial. Crit Care Med 28: 3606 – 3611
35. Rubinson L, Diette GB, Song X, Brower RG, Krishnan JA (2004) Low caloric intake is associated with nosocomial bloodstream infections in patients in the medical intensive care unit. Crit Care Med 32: 350 – 357
36. Dickerson, R.N, Boschert KJ, Kudsk KA, Brown RO (2002) Hypocaloric enteral tube feeding in critically ill obese patients. Nutrition 18: 241 – 246
37. Herndon DN, Barrow RE, Stein M, et al (1989) Increased mortality with intravenous supplemental feeding in severely burned patients. J Burn Care Rehabil 10: 309 – 313
38. Sheean PM, Peterson SJ, Gurka DP, Braunschweig CA (2010) Nutrition assessment: the reproducibility of subjective global assessment in patients requiring mechanical ventilation. Eur J Clin Nutr 64: 1358 – 1364
39. Peake SL, Moran JL, Ghelani DR, Lloyd AJ, Walker MJ (2006) The effect of obesity on 12-month survival following admission to intensive care: a prospective study. Crit Care Med 34: 2929 – 2939
40. Jeevanandam M, Young DH, Schiller WR (1991) Obesity and the metabolic response to severe multiple trauma in man. J Clin Invest 87: 262 – 269
41. Klein CJ, Stanek GS, Wiles CE (1998) Overfeeding macronutrients to critically ill adults: metabolic complications. J Am Diet Assoc 98: 795 – 806
42. Choban PS, Burge JC, Scales D, Flancbaum L (1997) Hypoenergetic nutrition support in hospitalized obese patients: a simplified method for clinical application. Am J Clin Nutr 66: 546 – 550
43. Miller JP, Choban PS (2006) Feeding the critically ill obese patient: The role of hypocaloric nutrition support. Respir Care Clin 12: 593 – 601
44. Dickerson RN, Boschert KJ, Kudsk KA, Brown RO (2002) Hypocaloric Enteral tube feeding in critically ill obese patients. Nutrition 18: 241 – 246
45. Dickerson RN, Rosato EF, Mullen JL (1986) Net protein anabolism with hypocaloric parenteral nutrition in obese stressed patients. Am J Clin Nutr 44: 747 – 755
47. Burge JC, Goon A, Choban PS, Flancbaum L (1994) Efficacy of hypocaloric total parenteral nutrition in hospitalized obese patients: a prospective, double-blind randomized trial. JPEN J Parenter Enteral Nutr 18: 203 – 207
48. Müller TF, Müller A, Bachem MG, Lange H (1995) Immediate metabolic effects of different nutritional regimens in critically ill medical patients. Intensive Care Med 21: 561 – 566

XVII ICU Organization and Management

Frailty: A New Conceptual Framework in Critical Care Medicine

R.C. McDermid and S.M. Bagshaw

A Brief History of Critical Care: How Did We Get Here?

From its inception, the practice of critical care medicine has been focused on prolonging life, based on the assumption that reducing mortality outweighs the potential morbidity in survivors. In broad terms, its goal is to avoid unnecessary suffering and untimely death by aggressively treating potentially curable or reversible illnesses for an suitable period of time [1]. From its humble beginnings in 1854, with Florence Nightingale's vision for hospital reform in the British Scutari Barracks in Istanbul during the Crimean war [2], through the polio epidemic of the 1950s and the development of mechanical ventilatory support, critical care medicine has since evolved into a distinct specialty [3]. This has occurred in an assimilatory fashion with the introduction of new medical treatments and technologies such as pulse oximetry, continuous hemodynamic monitoring, vasoactive drugs, renal replacement therapy, and extracorporeal membrane oxygenation.

In general, effective critical care support is time-dependent, and treatment must be instituted rapidly and aggressively in order to positively influence outcome. Alternatively, critical care also has the potential to cause harm if these therapies are applied at an inappropriate time or for an inadequate duration or intensity [4, 5]. Despite the utility of life support at temporarily prolonging short-term survival, no therapy has demonstrated unequivocal effectiveness. Furthermore, the benefits of many of our most commonly employed therapies, in terms of intermediate and long-term outcome, remain uncertain or questionable [4, 6–9]. An unintended consequence of our capacity to prolong life is that increasing numbers of critically ill patients survive, but are also left with significant psychosocial or functional impairment [10, 11]. This begs the question: Is our current therapeutic model of focusing treatment on acute physiologic derangement sufficient, or have we been neglectful of the other factors that influence outcome from critical illness?

What Can We Learn From Other Specialties?

What is clear is that individual patients with the same disease process may have very different trajectories of illness and prognoses. Patients admitted to ICU are heterogeneous in terms of demographics, primary diagnosis, illness severity, and extent of comorbidity [12], which raises the possibility that factors other than adequacy of organ support may strongly influence death and quality of survival.

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Chronological age has been found to be an independent predictor of survival following an episode of critical illness [13, 14]. Although appealing in its simplicity, this finding has not been shown to be consistent [15]. On the other hand, recent studies have suggested that proxy measures of physiologic reserve, such as baseline functional status and burden of comorbid illness, are important determinants of survival after an episode of critical illness [16–19]. It is in this regard that a proxy measure of 'physiologic' rather than 'chronologic' age may have clinical utility for use in critically ill patients. The concept of measuring a patient's level of 'frailty' may represent just such a novel and suitable proxy metric.

Over the past decade, gerontologists have defined 'frailty' as a multi-dimensional syndrome characterized by the loss of physical and cognitive reserve that leads to increased vulnerability to adverse events [20]. In this physiologic state, individually reversible deficits collectively can result in an insurmountable burden of disease, leading to increased vulnerability to adverse outcomes [21, 22] (**Fig. 1**). This syndrome is distinct from, but overlaps with disability (i.e., functional impairment) and comorbidity (i.e., co-existence of two diseases). One proposed mechanism relates to 'inflammaging' or the balance between the protective pro-inflammatory response to invading microorganisms and the similarly protective compensatory anti-inflammatory system [23]. Genetic polymorphisms in pro- and anti-inflammatory cytokines and their receptors may modify individual susceptibility to inflammation-related damage and alter the rate of relative 'aging'. This may partially explain the poor discriminatory power of age alone to predict outcome [14]. A recent study on protein oxidation also suggests a possible causal relationship between inflammation and frailty: Protein carbonylation, a process that is a known marker of oxidative stress and interferes with normal cellular function, has shown close correlation with grip strength in a group of frail elderly patients [24]. Hence, imbalance in inflammation may play an important role in potentiating a vicious cycle of decreasing muscle mass (i.e., sarcopenia), malnutrition, and reduced energy expenditure that eventually culminates in a frail state [21, 22].

Frailty is recognized as a major determinant of mortality, hospitalization, institutionalization and functional outcome in geriatric patients [25–27]. In fact, frailty may represent a surrogate for many of the difficult-to-measure aspects of a patient's pre-hospital health state [25, 26]. Consequently, it has been suggested that the syndrome of frailty may be just such a measure of 'physiologic age'.

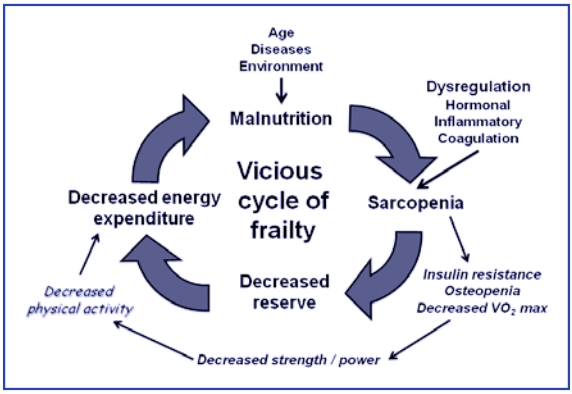

Fig. 1. Vicious cycle of frailty. Adapted from Fried et al [22]

Although the concept of frailty has existed for some time, its syndromic nature has made it challenging to operationalize. One of the most widely adopted tools in geriatric medicine is the 'frail phenotype' (**Box 1**) [22]. The Frailty Index, a detailed 70-item inventory of clinical deficits, is also broadly employed but is cumbersome and challenging to use in a busy clinical practice [28]. A more subjective judgment-based 7-point Clinical Frailty Scale (CFS) has also been developed and validated by Rockwood and colleagues (**Table 1**) [20]. Each of these tools appears to perform similarly well in identifying frailty in elderly patients and risk for adverse outcomes, but to date have not been evaluated in other populations [20, 22, 29, 30].

Box 1. A proposed clinical definition of the phenotype of frailty. Adapted from [22]

Presence of 3 or more of the following features:
Decreased grip strength
Self-reported exhaustion
Unintentional weight loss of more than 4.5 kg over the past year
Slow walking speed
Low physical activity

Table 1. Clinical Frailty Score [20].

Score	Frailty Grade	Description
1	Very fit	People who are robust, active, energetic and motivated. These people commonly exercise regularly. They are among the fittest for their age.
2	Well	People who have no active disease symptoms but are less fit than category 1. Often, they exercise or are very active occasionally (e.g., seasonally).
3	Managing well	People whose medical problems are well controlled, but are not regularly active beyond routinely walking.
4	Vulnerable	While not dependent on others for daily help, often symptoms limit activities. A common complaint is being "slowed up", and/or being tired during the day.
5	Mildly frail	These people often have more evident slowing, and need help in high order instrumental activities of daily living (finances, transportation, heavy housework, medications). Typically, mild frailty progressively impairs shopping and walking outside alone, meal preparation and housework.
6	Moderately frail	People need help with all outside activities and with keeping house. Inside, they often have problems with stairs and need help with bathing and might need minimal assistance (cuing, standby) with dressing.
7	Severely frail	Completely dependent for personal care, from whatever cause (physical or cognitive). Even so, they seem stable and not at high risk of dying (within $\sim$ 6 months)
8	Very severely frail	Completely dependent, approaching the end of life. Typically, they could not recover even from a minor illness.
9	Terminally ill	Approaching the end of life. This category applies to people with a life expectancy < 6 months, who are not otherwise evidently frail.

How Might Frailty Be Applicable To Critical Care?

Regardless of the tool used to define frailty, it is the concept that may have direct relevance to critical care. Based on data from the Canadian Study of Health and Aging, the prevalence of frailty in the elderly demographic may be as high as 43 % [20]. Utilization of ICU resources by the elderly is rising, and consequently the prevalence of pre-existing frailty in patients admitted to the ICU is also likely increasing [14]. Additionally, simple measures of burden of pre-existing disease and global function such as residency in a nursing home facility have also been shown to correlate with mortality and post-ICU quality of life [31, 32]. Validated measures of frailty have also been shown to have added discriminatory value for postoperative complications, delirium or poor outcomes when used in conjunction with established perioperative risk scales or in estimating survival for patients admitted to ICU with severe pneumonia [13, 33–35]. Consequently, pre-existing frailty may significantly impact health resource utilization in critical illness, in both the short-term (i.e., increased length of ICU stay, prolonged hospitalization) and long-term (i.e., rehabilitation, institutionalization, rehospitalization, reduced quality of life).

Independent of age and pre-morbid functional reserve, critically ill patients are at increased vulnerability to adverse clinical outcomes. This may be characterized by intermittent deteriorations in clinical status requiring increases in the degree of organ support, without which the critically ill patient may die [36]. Furthermore, severe sarcopenia, motor weakness, and functional impairment that would normally take years to develop in the outpatient setting in a 'frail' patient, may develop over markedly reduced time frames (i.e., days to weeks) in 5–10 % of critically ill patients [37–39]. This so-called syndrome of chronic critical illness shares many features with frailty in elderly patients and is associated with both increased risk of ICU death and, in survivors to hospital discharge, significantly reduced quality of life. Chronic critical illness also chokes health resources, resulting in prolonged durations of hospitalization and rehabilitation [40]. In fact, functional dependence after critical illness is correlated with two of the more prominent phenotypic features of characterizing frailty: Inability to walk and poor upper extremity strength [37]. Although these complications are often viewed as an unavoidable consequence of critical illness, we hypothesize that they may actually be an unintended byproduct of our current conceptual model of ICU therapy.

How Might We Treat Critical Illness More Effectively?

Recognition of the complex nature of frailty in the elderly has resulted in the investigation of multi-dimensional home-based interventions intended to interrupt the vicious cycle. In the ongoing British Frailty Intervention Trial (FIT) [41], individualized nutritional, social, psychological and physical interventions targeted at the core dimensions of frailty are being evaluated in a group of elderly adults who are considered frail by the operational definition proposed by Fried et al. [22]. These interventions include nutritional intake analysis, home meal delivery and high calorie/high protein meal supplementation, day activity groups, psychiatric referral and home physiotherapy.

A similar approach may have value for interrupting the development of new or exacerbation of existing frailty in the critically ill. The potential role of inflamma-

tion in the development of acquired muscle weakness is being emphasized in the critically ill [42]. Other elements that may contribute to the development of weakness and frailty in the ICU include immobilization, suboptimal nutritional supplementation and ineffective substrate utilization, all of which may be further compounded by the effects of medications such as neuromuscular blockers and corticosteroids [43]. The importance of adequate nutritional support, daily sedation interruption, early mobilization and physiotherapy to prevent physical deconditioning, and the psychological consequences of critical illness for both patients and their caregivers are being increasingly recognized as important determinants of quality-adjusted survival in critically ill patients [44–48]. Perhaps other multi-modality therapies targeting the vicious cycle of frailty, such as neuroendocrine manipulation and attenuation of the catabolic response are important adjuncts [49, 50].

The challenge remains how to organize and deliver the complex web of interventions that are required for the critically ill patient. Care maps for managing the process rather than the content of care for the chronic critically ill are being developed, due to the exorbitant associated costs of care [51]. It is hoped that similar benefits in terms of length of stay, costs of care, and overall patient satisfaction that have been demonstrated in other medical specialties will be seen in the critically ill [52].

How Might Frailty Change Our Current Understanding Of Critical Care?

In our current conceptual paradigm, a major role of the critical care specialist is to minimize the injurious effects of somatic support and interventions for acute physiologic derangement. However, given the modifying impact that functional status and co-morbidity likely exert on prognosis, the development of frailty and the effects of restorative therapies may be viewed as tempering the gains achieved by advanced life supportive therapy. Perhaps it is the inattention to pre-existing frailty and the processes and treatments that affect its development during critical illness that have contributed to the difficulty in evaluating the efficacy of selected critical care therapies. Specifically, while our organ support technologies will temporarily sustain life for our patients, this is not synonymous with healing and recovery. Consequently, this conceptual model may not be complete (**Fig. 2**).

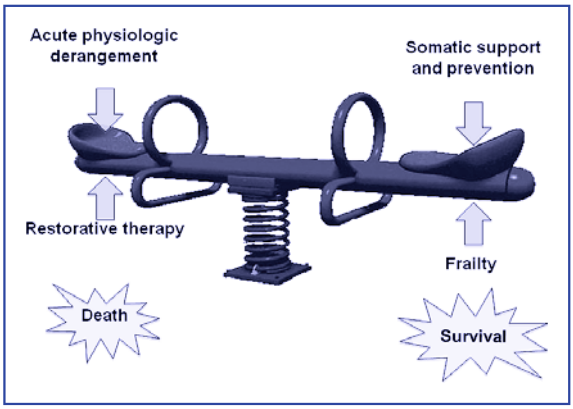

Fig. 2. 'Opposing forces' model.

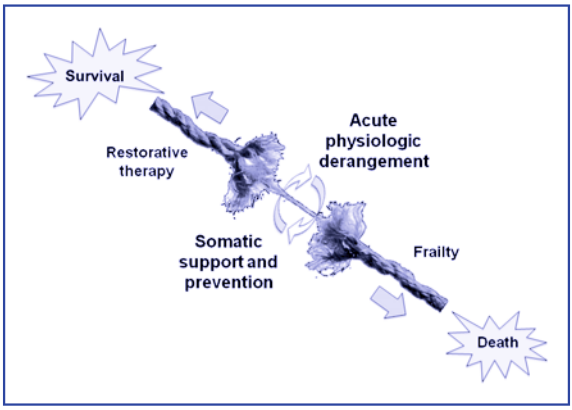

Fig. 3. 'Dimensions of care' model.

Conceivably the impact of critical illness and its treatment on functional reserve is a poorly recognized but fundamental determinant of survival or death. Restorative therapies that aim to improve reserve, such as physiotherapy, early mobilization and nutritional support, are being increasingly recognized as important components of critical care treatment [44–47]. Thus, restoration of reserve could conceptually be considered a principle objective of critical care support; appropriate and skillful application of somatic support may be a means to provide adequate time for recovery of physiologic reserve while minimizing iatrogenic injury.

Accordingly, the critically ill patient could be viewed as being in a homeostatic tug-of-war, with depletion of reserve and restorative therapies pulling the patient towards death and survival, respectively. In this model, critical illness may represent an acute 'unraveling of homeostasis', whereas the role of somatic support could be seen as bolstering homeostasis and allowing the tug-of-war to continue (**Fig. 3**). Life supportive treatments do not necessarily result in survival unless the acute insult is treated before physiologic reserve is depleted or restorative treatments have improved pre-existing and/or acquired frailty. If this model proves valid, objective measures of diminishing reserve despite optimal restorative therapy may provide much needed support and reinforcement for clinicians engaged in end-of-life decisions [1].

Conclusion

Critical care practitioners clearly recognize that patient-centered outcomes, such as quality of life and functional status post-ICU discharge, are as important to patients as survival itself [53–55]. The short-term successes of life supportive therapy do not necessarily always translate into optimal long-term survival. The current subspecialty-based focus on short-term treatment during each stage of illness results in therapeutic fragmentation. Together, patients and their physicians must share responsibility for reconciling short- and long-term treatment objectives in the context of a continual assessment of trajectory of illness. Acceptable health outcomes for each individual may change with time, but should remain clearly defined during the journey from acute decompensation to either death or recovery. This requires the creation of a more complete conceptual para-

digm that includes those processes that may influence the transition from health to illness and back, such as pre-existing frailty and its development during critical illness. Hopefully, the result will be a philosophical and ethical framework that allows physicians to identify what technology can and can not accomplish, thereby facilitating the delivery of more effective and just health care.

References

1. McDermid RC, Bagshaw SM (2009) Prolonging life and delaying death: the role of physicians in the context of limited intensive care resources. Philos Ethics Humanit Med 4: 3
2. Aravind M, Chung KC (2010) Evidence-based medicine and hospital reform: tracing origins back to Florence Nightingale. Plast Reconstr Surg 125: 403 – 409
3. Richmond C (2007) Obituary – Bjorn Ibsen. BMJ 335: 674
4. The Acute Respiratory Distress Syndrome Network (2000)Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med 342: 1301 – 1308
5. Finfer S, Chittock DR, Su SY, et al (2009) Intensive versus conventional glucose control in critically ill patients. N Engl J Med 360: 1283 – 1297
6. Rivers E, Nguyen B, Havstad S, et al (2001) Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med 345: 1368 – 1377
7. Van den Berghe G, Wouters P, Weekers F, et al (2001) Intensive Insulin Therapy in Critically Ill Patients. N Engl J Med 345: 1359 – 1367
8. Annane D, Sebille V, Charpentier C, et al (2002) Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. JAMA 288: 862 – 871
9. Bernard GR, Vincent JL, Laterre PF, et al (2001) Efficacy and safety of recombinant human activated protein C for severe sepsis. N Engl J Med 344: 699 – 709
10. Unroe M, Kahn JM, Carson SS, et al (2010) One-year trajectories of care and resource utilization for recipients of prolonged mechanical ventilation: a cohort study. Ann Intern Med 153: 167 – 175
11. Myhren H, Ekeberg O, Toien K, Karlsson S, Stokland O (2010) Posttraumatic stress, anxiety and depression symptoms in patients during the first year post intensive care unit discharge. Crit Care 14: R14
12. Knaus WA, Draper EA, Wagner DP, Zimmerman JE (1985) APACHE II: a severity of disease classification system. Crit Care Med 13: 818 – 829
13. Sligl WI, Eurich DT, Marrie TJ, Majumdar SR (2011) Only severely limited premorbid functional status is associated with short- and long-term mortality in critically ill patients with pneumonia: A prospective observational study. Chest (in press)
14. Bagshaw SM, Webb SA, Delaney A, et al (2009) Very old patients admitted to intensive care in Australia and New Zealand: a multi-centre cohort analysis. Crit Care 13: R45
15. Boumendil A, Aegerter P, Guidet B (2005) Treatment intensity and outcome of patients aged 80 and older in intensive care units: a multicenter matched-cohort study. J Am Geriatr Soc 53: 88 – 93
16. Vazquez Mata G, Rivera Fernandez R, Gonzalez Carmona A, et al (1992) Factors related to quality of life 12 months after discharge from an intensive care unit. Crit Care Med 20: 1257 – 1262
17. Poses RM, McClish DK, Smith WR, Bekes C, Scott WE (1996) Prediction of survival of critically ill patients by admission comorbidity. J Clin Epidemiol 49: 743 – 767
18. Dowdy DW, Eid MP, Sedrakyan A, et al (2005) Quality of life in adult survivors of critical illness: a systematic review of the literature. Intensive Care Med 31: 611 – 620
19. Ho KM, Finn J, Knuiman M, Webb SA (2007) Combining multiple comorbidities with Acute Physiology Score to predict hospital mortality of critically ill patients: a linked data cohort study. Anaesthesia 62: 1095 – 1100
20. Rockwood K, Song X, MacKnight C, et al (2005) A global clinical measure of fitness and frailty in elderly people. CMAJ 173: 489 – 495
21. Lunney JR, Lynn J, Foley DJ, Lipson S, Guralnik JM (2003) Patterns of functional decline at the end of life. JAMA 289: 2387 – 2392

22. Fried LP, Tangen CM, Walston J, et al (2001) Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci 56: M146–156
23. Franceschi C (2007) Inflammaging as a major characteristic of old people: can it be prevented or cured? Nutr Rev 65: S173–176
24. Howard C, Ferrucci L, Sun K, et al (2007) Oxidative protein damage is associated with poor grip strength among older women living in the community. J Appl Physiol 103: 17–20
25. Schuurmans H, Steverink N, Lindenberg S, Frieswijk N, Slaets JP (2004) Old or frail: what tells us more? J Gerontol A Biol Sci Med Sci 59: M962–965
26. Mitnitski AB, Mogilner AJ, MacKnight C, Rockwood K (2002) The mortality rate as a function of accumulated deficits in a frailty index. Mech Ageing Dev 123: 1457–1460
27. Mitnitski AB, Graham JE, Mogilner AJ, Rockwood K (2002) Frailty, fitness and late-life mortality in relation to chronological and biological age. BMC Geriatr 2: 1
28. Rockwood K, Andrew M, Mitnitski A (2007) A comparison of two approaches to measuring frailty in elderly people. J Gerontol A Biol Sci Med Sci 62: 738–743
29. Fried LP, Ferrucci L, Darer J, Williamson JD, Anderson G (2004) Untangling the concepts of disability, frailty, and comorbidity: implications for improved targeting and care. J Gerontol A Biol Sci Med Sci 59: 255–263
30. Rockwood K, Mitnitski A, MacKnight C (2002) Some mathematical models of frailty and their clinical implications. Rev Clin Gerontol 12: 109–117
31. Kothe H, Bauer T, Marre R, Suttorp N, Welte T, Dalhoff K (2008) Outcome of community-acquired pneumonia: influence of age, residence status and antimicrobial treatment. Eur Respir J 32: 139–146
32. Orwelius L, Nordlund A, Nordlund P, et al (2010) Pre-existing disease: the most important factor for health related quality of life long-term after critical illness: a prospective, longitudinal, multicentre trial. Crit Care 14: R67
33. Dasgupta M, Rolfson DB, Stolee P, Borrie MJ, Speechley M (2009) Frailty is associated with postoperative complications in older adults with medical problems. Arch Gerontol Geriatr 48: 78–83
34. Makary MA, Segev DL, Pronovost PJ, et al (2010) Frailty as a Predictor of Surgical Outcomes in Older Patients. J Am Coll Surg 210: 901–908
35. Robinson TN, Eiseman B, Wallace JI, et al (2009) Redefining geriatric preoperative assessment using frailty, disability and co-morbidity. Ann Surg 250: 449–455
36. Levin PD, Worner TM, Sviri S, et al (2003) Intensive care outflow limitation--frequency, etiology, and impact. J Crit Care 18: 206–211
37. van der Schaaf M, Dettling DS, Beelen A, Lucas C, Dongelmans DA, Nollet F (2008) Poor functional status immediately after discharge from an intensive care unit. Disabil Rehabil 30: 1812–1818
38. De Jonghe B, Sharshar T, Lefaucheur JP, et al (2002) Paresis acquired in the intensive care unit: a prospective multicenter study. JAMA 288: 2859–2867
39. Seneff MG, Zimmerman JE, Knaus WA, Wagner DP, Draper EA (1996) Predicting the duration of mechanical ventilation. The importance of disease and patient characteristics. Chest 110: 469–479
40. Garnacho-Montero J, Amaya-Villar R, Garcia-Garmendia JL, Madrazo-Osuna J, Ortiz-Leyba C (2005) Effect of critical illness polyneuropathy on the withdrawal from mechanical ventilation and the length of stay in septic patients. Crit Care Med 33: 349–354
41. Fairhall N, Aggar C, Kurrle SE, et al (2008) Frailty Intervention Trial (FIT). BMC Geriatr 8: 27
42. Winkelman C (2010) The role of inflammation in ICU-acquired weakness. Crit Care 14: 186
43. Griffiths RD, Hall JB (2010) Intensive care unit-acquired weakness. Crit Care Med 38: 779–787
44. Doig GS, Simpson F, Finfer S, et al (2008) Effect of evidence-based feeding guidelines on mortality of critically ill adults: a cluster randomized controlled trial. JAMA 300: 2731–2741
45. Schweickert WD, Pohlman MC, Pohlman AS, et al (2009) Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial. Lancet 373: 1874–1882

46. Kress JP (2009) Clinical trials of early mobilization of critically ill patients. Crit Care Med 37: S442 – 447
47. Salisbury LG, Merriweather JL, Walsh TS (2010) The development and feasibility of a ward-based physiotherapy and nutritional rehabilitation package for people experiencing critical illness. Clin Rehabil 24: 489 – 500
48. Davydow DS, Gifford JM, Desai SV, Bienvenu OJ, Needham DM (2009) Depression in general intensive care unit survivors: a systematic review. Intensive Care Med 35: 796 – 809
49. Van den Berghe G (2003) Endocrine evaluation of patients with critical illness. Endocrinol Metab Clin North Am 32: 385 – 410
50. Mechanick JI, Nierman DM (2006) Gonadal steroids in critical illness. Crit Care Clin 22: 87 – 103
51. Glouberman S, Mintzberg H (2001) Managing the care of health and the cure of disease--Part II: Integration. Health Care Manage Rev 26: 70 – 84
52. DeMonaco HJ (2000) Guidelines, pathways, and the end result. Crit Care Med 28: 889 – 890
53. Hopkins RO, Jackson JC (2006) Long-term neurocognitive function after critical illness. Chest 130: 869 – 878
54. Cuthbertson BH, Roughton S, Jenkinson D, Maclennan G, Vale L (2010) Quality of life in the five years after intensive care: a cohort study. Crit Care 14: R6
55. The SUPPORT Principal Investigators (1995) A controlled trial to improve care for seriously ill hospitalized patients. The study to understand prognoses and preferences for outcomes and risks of treatments (SUPPORT). JAMA 274: 1591 – 1598

Access Block and Emergency Department Overcrowding

R. Forero, S. McCarthy, and K. Hillman

Introduction

Access block affecting the emergency department (ED), also known as boarding in the United States and Canada, can be described as a phenomenon comprising almost all the challenges in the world of modern EDs. We use the analogy of parallel universes to illustrate both the complexity and the severity of the problem. In the world of physics, many attempts have been made to create a mathematical solution that can answer the more basic questions about physical phenomena in the universe. This has been known as 'Theory of Everything'. Albert Einstein spent 30 years of his life trying to solve this 'Theory of Everything', but failed [1].

In the parallel universe of emergency medicine, access block, or delays in admission of patients to hospital inpatient areas from EDs, can be described as a whole system problem, the equivalent to the 'Theory of Everything'. It remains a fundamental challenge, prompting comments such as: "Access Block and ED overcrowding have created a dynamic tension and the future of emergency medicine will be determined by the resolution of this conflict" [2].

Despite access block and overcrowding in EDs being redefined, investigated and managed in multiple ways, it is far from being resolved [3, 4]. This chapter summarizes the evidence from access block studies, exploring hospital, patient or medical interventions to reduce the impact of access block in terms of ambulance diversion, impaired access to emergency care, compromised clinical care, prolonged pain and suffering as well as increased comorbidity and mortality associated with prolonged ED length of stay.

According to the Australasian College for Emergency Medicine (ACEM) access block is defined as "the situation where patients are unable to gain access to appropriate hospital beds within a reasonable amount of time, no greater than 8 hours" and 'overcrowding' refers to "the situation where ED function is impeded by the number of patients waiting to be seen, undergoing assessment and treatment, or waiting for departure, exceeding the physical or staffing capacity of the department" [5, 6].

Access block has been linked to increased ED waiting time for medical care and leads to ED overcrowding. This overcrowding is generally accepted as a reason for decreased efficiency and quality of care, and has also been linked to an increased incidence of adverse events [5, 6]. It has been indicated that the 'Theory of Everything' has some fundamental problems [1]. Access block is also full of them. The first problem is that most interventions produced to date have had some positive effects, although not necessarily on access block itself; however, they have been of short duration or have had limited or short term impact [7].

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In the last decade, the UK reduced the acceptable waiting time for admission to hospital from the ED to four hours. This is known as the 'Four-Hour Target', where 98 % of patients must be seen and treated within four hours. It has produced significant effects (both positive and negative). In Australia and New Zealand, the positive effect generated in the UK prompted the New Zealand government to implement a similar version – or a 'six-hour target'. In Australia, the State of Western Australia decided to implement the 'four hour target' and its implementation is in the final stages. The South Australian health system is also in the process of implementing it. In relation to the negative effect, in the UK it has been reported that the 'four hour target' has been overused in an inflexible way by some hospitals. A Mid-Staffordshire Trust report claimed that many patients died because of substandard care driven by the Trust management's wish to achieve Key Performance Indicators (KPIs) at any cost. This report has been tabled in the British parliament and the continuation of this policy has been reconsidered by the new UK government [8, 9]. However, the dilemma remains – is the four or six hour rule going to achieve its purpose?

The second problem is that access block has been described as a disease where the symptoms can be managed but the fundamental problem remains as yet unsolved [10].

The third problem is that access block is frequently associated with bed capacity and there are studies confirming that hospital wards cannot be run at around 100 % occupancy for long without considerable risk to patients as a result of delayed admission from the ED [11, 12]. Most hospitals are run at full capacity and the problem is exacerbated by significant pressures in health care, such as natural events (earthquakes, flu pandemics, floods, bushfires, etc.) or long waiting lists for elective surgery. It has been demonstrated that a finite-capacity system with variable demand cannot sustain both full utilization and full availability. A single level of ideal or safe occupancy suitable for all situations is a simplistic interpretation and application of the underlying science [12]. Therefore, specific studies and actions are necessary to understand and deal with the problems of long waiting lists and access block in any given health care facility [12].

Magnitude of the Problem

Recent literature reviews have demonstrated that most authors agree on three things [7, 13–15]:

A. the problem is getting worse
B. it is associated with poor health outcomes, and
C. there are mainly three levels or factors associated with the problem, namely patient centered, hospital/system and clinical factors

In relation to patient-centered factors, we are interested in understanding the operation of EDs and how this is impacted by access block and overcrowding, and the resulting effects on patients and staff. To do so we need to identify clinical/system factors, and which interactions may be influenced across departments, such as EDs, medical and surgical wards, intensive care units (ICUs), operating rooms, radiology departments and ambulance services.

It has been confirmed that in Australia, the ED rate of presentation per 1,000

population increased by 35 % between 2003 and 2008. There were 1.98 million more presentations to Australian EDs in 2006 – 2007 (6.7 million) compared to the 2005 – 2006 financial year (4.8 million) [7]. As a result of the increased demand and co-incident bed shortages, occupancy rates in most hospitals were greater than 85 %, which has been considered the maximum level for efficiency [6, 11 – 15].

Hospital and System Factors

In order to understand the complexity of the problem, we need to understand the flow on effect of access block on EDs and the cascading effect on other services.

Policy Interventions

Easy answers are elusive (**Fig. 1**). The literature has identified multiple policy interventions that have temporarily reduced the impact of access block and ED crowding. However, one of the challenges is to identify which interventions have been implemented and how they have affected specific areas, namely EDs, ambulance services, radiology, operating rooms, medical and/or surgical wards, and ICUs.

There is strong evidence suggesting that initiatives to avoid or reduce the duration of hospital admission such as transit lounges, observation wards, multidisciplinary team interventions, additional ED staff and rescheduling of some services have produced positive effects, while ED expansion on its own has not been demonstrated to have a significant effect on hospital diversion nor length of stay [16 – 21].

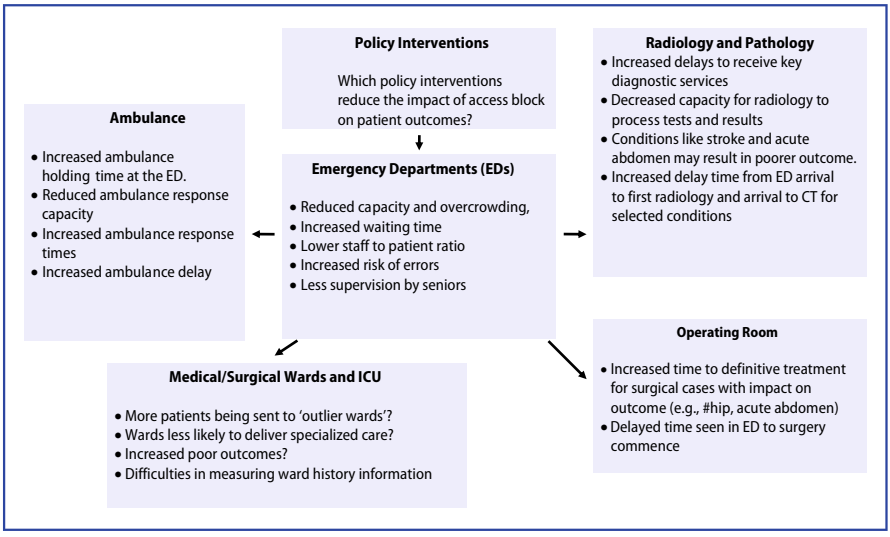

Fig. 1. Effect of access block on other parts of the hospital. Diagram of the flow-on effect of access block to other parts of the hospital, including ambulance, radiology and pathology, operating rooms, medical, surgical wards and ICU. CT: computed tomography

Many hospitals have reported that, by increasing staff capacity, they have been able to reduce ED length of stay [22]. In addition, other initiatives have combined multiple strategies to avoid admission such as transit lounges, short stay wards, and transit bays with alternatives to admission such as fast track and ambulance diversion [16, 23–27]. Other initiatives have transcended from the ED to other services. For example, it has been found that interventions initiated by nurses, such as nurse initiated X-ray services improve patient satisfaction, without impact on access block or ED crowding. Mental health patients can benefit from the co-location of psychiatric emergency services within the ED, by the earlier delivery of specialist mental health care [28–30].

In a recent literature review, it was confirmed that at least 62 % of interventions reporting strategies to manage existing resources, had at least one positive effect on different parts of the health system [7]. Hospital restructuring has also been found to have a positive effect in Canada [31]. However, not all interventions have had the same effect. Access to general practitioner services within the hospital has had mixed results. It has been considered unsuccessful in some hospitals in Australia and New Zealand but has been reported effective in diverting patients from EDs in the Netherlands [32–34]. No Australasian study has reported any effect on the availability of co-located services at reducing access block or ED crowding, but they have shown that very low acuity patients consume a minimal part of ED resources and are cheaply and quickly treated at hospital EDs [7].

Individual initiatives, such as expanding the ED capacity from 24 to 54 beds, in isolation, without addressing other bottlenecks in the hospital, are ineffective and insufficient to produce significant changes on ambulance diversion or the proportion of patients who left without being seen [21].

In general, policies to reduce or control overcrowding have been associated with the majority of access block cases in Canada. They are perceived by ED directors as largely ineffective [35]. In the UK, policies such as early hospital discharge and the four hour target have had unintended consequences, such as the creation of incomplete episodes of care that have resulted in increases in the percentage of readmissions [8–9, 13].

Emergency Departments

Access block and consequent ED overcrowding constitute the greatest threat to quality emergency care. Inadequate hospital bed capacity and flexibility, or lack of an available bed when it is needed, result in the delay of transfer of patients from ED to an appropriate in-hospital bed, particularly to medical and surgical wards as well as ICUs [5–7].

Access block and the ED overcrowding it causes, constitute the greatest threat to quality emergency care, being associated with increased risk of errors, delayed time-critical care, increased morbidity and excess deaths [7, 10, 11, 31, 36–40].

There is evidence that ED length of stay targets such as the ‘four hour target’ can produce important changes in work practices, hospital and system processes, and discharge planning, leading to more efficient use of resources and reducing ED overcrowding [41]. However, evidence also demonstrates that emphasis on time alone, rather than quality of patient care, can adversely affect patient safety and staff morale [8, 9].

Ambulance Service

Ambulance bypass or diversion is the situation where ambulances cannot deliver patients to the closest hospital as a result of overcrowding in that hospital. It has been identified especially in urban areas as one of the more serious issues resulting from access block [7]. Access block and overcrowding have also resulted in extended delays either at the scene in the community or in transport time from the scene to hospital. Simple expansion of the ED does not have a significant effect on ambulance diversion [21]; instead, ED length of stay increased [21]. In addition, the improvement in the proportion of patients who left the ED without being seen was minimal. Internet-accessible emergency department workload information may reduce ambulance diversion [27]. The main effects of access block on ambulance services include increased ambulance holding time at the ED, reduced ambulance response capacity, increased ambulance response times, increased ambulance delays, and increased mortality [38].

Radiology and Pathology

Rapid access to diagnostic services from EDs is important [42]. It has been found that radiology and pathology tests initiated by nurses improve patient satisfaction [28, 29]. There is evidence of increased test ordering using these providers [43]. It has also been documented that EDs and inpatient units are facing challenges associated with the impact of access block and ED overcrowding on radiology and pathology. Increased demand for imaging can result in delays to receiving those services as well as errors in the production and processing of radiology orders [6, 7]. The same has been reported for pathology services, resulting in poor health outcomes for certain conditions such as stroke and acute abdominal conditions [43, 44].

Operating Room

Access block can cause delays to definite treatment for surgical cases with adverse impact on outcome, such as hip fractures and acute abdominal conditions. This is often exacerbated by operating room closures during holiday periods such as Christmas and the New Year periods. In addition, access block may interrupt elective surgery which may have escalating effects on the whole system. Cancellation of elective surgery, for example, has been found to have an important effect on funding arrangements, hospital capacity and the way operating rooms are utilized [45].

Medical, Surgical Wards and the ICU

Pressure to admit patients more rapidly from the ED can result in patients being sent to 'outlier wards'; wards less likely to deliver specialized care. When bed occupancy rates are reduced, patient flow improves by allowing patient transfer to the wards, which, in turn, frees up EDs, so that patients from the waiting room or ambulance bay can be seen and processed, reducing ED length of stay, ambulance diversion and operating room cancellations [20, 46–48].

Potential Solutions

It has been reported that the efficiencies gained from successful implementation of national access targets, such as the 'four hour target', may lead to a one off improvement in capacity and access to beds through improvement in processes, possibly the equivalent of 5–8 % capacity [8, 49]. Access targets may help our health systems deal more effectively with the long-term growth in demand for acute beds of about 2–4 % per year but cannot be the only solution. Increased physical bed capacity in hospitals in order to reduce bed occupancy levels is required.

Out of hospital, demand management strategies and improved community support are also necessary. In particular, the demand associated with aged care and mental health must be addressed as a matter of urgency so that sufficient resources are available for these patients to be treated in the community, thus avoiding acute hospital admission where appropriate.

Accurate audit or research data for the benefits/risks of introducing these targets are limited. Evaluation, continuous audit, and transparent dissemination of results are essential to allow flexible changes in response to outcomes at the local level, and across the system. Consideration of each hospital's differing circumstances, for example, local populations and disease severity, availability of specialized resources or staffing models, must guide local implementation. Rigorous and independent monitoring at the national level must be mandatory to safeguard quality clinical care, and to ensure optimal use of health system resources [49].

In summary, the patients most affected by access block and overcrowding are those who, because of their medical condition require unplanned admission to hospital [6, 7, 10, 13–15]. The reasons for some patient groups being more affected by access block are multifactorial and complex. Deleterious effects as a result of overcrowding and access block have been found in trauma patients [39], and include: Increased delays in transfer to ICU [46–48]; delays in pain treatment [6, 7]; increased numbers of patients who did not wait for treatment [36]; increase in patient adverse events [37]; and increased mortality [38, 39].

Additional resources will be required for redesigning current processes, improving access to diagnostic and other support services and making effective use of hospital infrastructure over extended hours. In particular, appropriate, and improved, staffing of EDs, general wards and diagnostic and support services is necessary to ensure prompt, timely and safe care for patients, 24 hours per day, every day [49].

Resources must support the continued ability of the ED, hospital and community providers to fulfill clinical education, training and supervisory obligations in accordance with national professional guidelines and standards [49]. In relation to the evidence about what works and what does not work, the majority of the evidence on interventions comes from single hospital rather than multicenter studies. In order to improve the type and success of access block interventions more multilevel studies are needed instead of retrospective or observational/descriptive studies.

Conclusion

If we considered access block as a disease then we would be forced to treat only some of the symptoms, but the fundamental condition would remain unaffected [7, 10]. As indicated above, many interventions have been partially successful, but as long as the fundamental causes remain, the symptoms sooner or later will re-emerge [7].

In large EDs, 40 % or more of staff time is spent caring for patients who are waiting for a bed, rather than looking after new emergency patients [50]. An emphasis on what is clinically appropriate for patients underpins success in improving access to care. In relation to potential solutions, in addition to adequate mental health and transitional care beds (flexible beds) there is a need for robust, long-term data collection and system dynamic analysis [42]. Finally, transparency and free access to data must be made available to those who understand the health care system and can provide possible ways to improve the system. This must include researchers and clinicians as well as policy makers and bureaucrats.

References

1. Ellis J (1986) The superstring: theory of everything, or of nothing? Nature 323: 595 – 598
2. Sklar DP, Handel DA, Hoeskstra I, Baren J, Zink B, Hedges J (2010) The future of Emergency Medicine: an Evolutionary Perspective. Acad Med 85: 490 – 495
3. Scott I, Vaughan L, Bell D (2009) Effectiveness of acute medical units in hospitals: a systematic review. Int J Qual Health Care 21: 397 – 407
4. Walters EH, Dawson DJ (2009) Whole-of-hospital response to admission access block: the need for a clinical revolution. Med J Aust 191: 561 – 563
5. Australasian College for Emergency Medicine (2006) Standard Terminology. Available at: http://www.acem.org.au/media/policies_and_guidelines/P02_-_Standard_Terminology_16.04.09.pdf Accessed November 2010.
6. Australasian College for Emergency Medicine (2004) Access Block and overcrowding in emergency departments. Online report. Available at: http://www.acem.org.au/media/Access_Block1.pdf Accessed November 2010.
7. Forero R, Hillman K, McCarthy S, Fatovich D, Joseph A, Richardson DW (2010) Access block and ED overcrowding. Emerg Med Australas 22: 119 – 135
8. Orr J (2008) The good, the bad, and the four hour target. BMJ 337: a195
9. Commission for Healthcare Audit and Inspection (2009) Investigation into Mid Staffordshire NHS Foundation Trust. Available at: http://www.cqc.org.uk/_db/_documents/Investigation_into_Mid_Staffordshire_NHS_Foundation_Trust.pdf Accessed November 2010
10. Braitberg G (2007) Emergency department overcrowding: dying to get in? Med J Aust 187: 624 – 625
11. Fatovich DM, Hughes G, McCarthy SM (2009) Access block: it's all about available beds. Med J Aust 190: 362 – 363
12. Bain CA, Taylor PG, Mcdonell G, Georgiou A (2010) Myths of ideal hospital occupancy. Med J Aust 192: 42 – 43
13. Cooke M, Fisher J, Dale J, McLeod E, Szczepura A, Walley P, Wilson S (2005) Reducing attendances and waits in emergency departments. A systematic review of innovations. Report to the national coordinating centre for NHS Service Delivery and Organisation R&D (NCCSDO). SDO, London, Available at: http://wrap.warwick.ac.uk/134/1/WRAP_Szczepura_29-final-report.pdf Accessed November 2010.
14. Anderson J, Bernath V, Davies J, Greene L, Ludolf S (2001) Literature Review on Integrated Bed and Patient Management. Centre for Clinical Effectiveness Monash Institute of Public Health and Planning and Development Unit Southern Health: Melbourne, Australia
15. Dwyer J, Jackson T (2001) Literature Review: Integrated Bed and Patient Management.

Commissioned by the Patient Management Task Force, Department of Human Services Victoria, Australia
16. Mace SE, Graff L, Mikhail M, Ross M (2003) A national survey of observation units in the United States. Am J Emerg Med 21: 529 – 533
17. Caplan GA, Williams AJ, Daly B, Abraham K (2004) A randomized, controlled trial of comprehensive geriatric assessment and multidisciplinary intervention after discharge of elderly from the emergency department--the DEED II study. J Am Geriatr Soc 52: 1417 – 1423
18. Dunn R (2003) Reduced access block causes shorter emergency department waiting times: An historical control observational study. Emerg Med (Aust) 15: 232 – 238
19. Donald KJ, Smith AN, Doherty S, Sundararajan V (2005) Effect of an on-site emergency physician in a rural emergency department at night. Rural and Remote Health Available at: http://www.rrh.org.au/publishedarticles/article_print_380.pdf Accessed November 2010.
20. Levin SR, Dittus R, Aronsky D, et al (2008) Optimizing cardiology capacity to reduce emergency department boarding: a systems engineering approach. Am Heart J 156: 1202 – 1209
21. Han JH, Zhou C, France DJ, et al (2007) The effect of emergency department expansion on emergency department overcrowding. Acad Emerg Med 14: 338 – 343
22. Cameron PA, Campbell DA (2003) Responses to access block in Australia: Royal Melbourne Hospital. Med J Aust 178: 109 – 110
23. Ruffin RE, Hooper JK (2003) Responses to access block in Australia: Queen Elizabeth Hospital Medical Division. Med J Aust 178: 104 – 105
24. Ashby RH (2003) Responses to access block in Australia: Queensland. Med J Aust 178: 107 – 108
25. Combs S, Chapman R, Bushby A (2007) Evaluation of fast track. Accid Emerg Nurs 15: 40 – 47
26. O'Brien D, Williams A, Blondell K, Jelinek GA (2006) Impact of streaming "fast track" emergency department patients. Aust Health Rev 30: 525 – 532
27. Sprivulis P, Gerrard B (2005) Internet-accessible emergency department workload information reduces ambulance diversion. Prehospital Emerg Care 9: 285 – 291
28. Tambimuttu J, Hawley R, Marshall A (2002) Nurse-initiated x-ray of isolated limb fractures in the emergency department: research outcomes and future directions. Aust Crit Care 15: 119 – 122
29. Cooper MA, Lindsay GM, Kinn S, Swann IJ (2002) Evaluating emergency nurse practitioner services: a randomized controlled trial. J Adv Nurs 40: 721 – 730
30. American College of Emergency Physicians (2008) ACEP psychiatric and substance abuse survey 2008. Available at: http://www.acep.org/uploadedFiles/ACEP/Advocacy/federal_issues/PsychiatricBoardingSummary.pdf Accessed November 2010
31. Schull MJ, Szalai JP, Schwartz B, Redelmeier DA (2001) Emergency department overcrowding following systematic hospital restructuring: trends at twenty hospitals over ten years. Acad Emerg Med 8: 1037 – 1043
32. Takakuwa KM, Shofer FS, Abbuhl SB (2007) Strategies for dealing with emergency department overcrowding: a one-year study on how bedside registration affects patient throughput times. J Emerg Med 32: 337 – 342
33. Wilson H (2005) Co-locating primary care facilities within emergency departments: brilliant innovation or unwelcome intervention into clinical care? NZ Med J 118: U1633
34. Van Uden CJT, Crebolder HFJM (2004) Does setting up out of hours primary care cooperatives outside a hospital reduce demand for emergency care? Emerg Med J 21: 722 – 723
35. Bond K, Ospina MB, Blitz S, et al (2007) Frequency, determinants and impact of overcrowding in emergency departments in Canada: a national survey. Healthc Q 10: 32 – 40
36. Mohsin M, Forero R, Ieaci S, Bauman A, Young L, Santiano N (2007) A population follow up study of patients who left an emergency department without being seen by a medical officer. Emerg Med J 24: 175 – 179
37. Foster AJ, Murff HJ, Peterson JF, Gandhi TK, Bates DW (2005) The incidence and severity of adverse events affecting patients after discharge from the hospital. Ann Intern Med 138: 161 – 167
38. Fatovich DM (2005) Effect of ambulance diversion on patient mortality: how access block can save your life. Med J Aust 183: 672 – 673

39. Richardson DB (2006) Increase in patient mortality at 10 days associated with emergency department overcrowding. Med J Aust 184: 213 – 216
40. Sprivulis PC, Da Silva JA, Jacobs IG, Frazer AR, Jelinek GA (2006) The association between hospital overcrowding and mortality among patients admitted via Western Australian emergency departments. Med J Aust 184: 208 – 212
41. The College of Emergency Medicine (2008) The Way Ahead 2008 – 2012. Strategy and guidance for Emergency Medicine in the United Kingdom and the Republic of Ireland. Available at: http://www.collemergencymed.ac.uk/CEM/About%20the%20College/Current%20Issues%20and%20Statements/The%20Way%20Ahead/default.asp Accessed November 2010
42. Australian Medical Association (2006) Position statement on quality and safety in public hospitals. Kingston, ACT, 2006. Available at: http://ama.com.au/node/2540 Accessed November 2010
43. Imaging Performance Partnership (2009) Elevating Interdepartmental Workflow: Best Practices for Optimizing Emergency and Patient Radiology Throughput. The Advisory Board Company, Washington
44. Worster A, Fernandes CBM, Malcolmson C, Eva K, Simpson D (2006). Identification of root causes for emergency diagnostic imaging delays at three Canadian hospitals. J Emerg Nursing 32: 276 – 280
45. Thomas J, Nicholas C (2007) Effect of a holiday services reduction period on a holspital's emergency department access block. Emerg Med Australas 19: 136 – 142
46. Ou L, Young l, Chen J, Santiano N, Baramy LS, Hilman K (2009). Discharge delay in acute care: reasons and determinants of delay in general ward patients. Aust Health Rev 33: 513 – 521
47. Frost SA, Alexandrou E, Bogdanovski T, Salamonson Y, Parr MJ, Hillman KM (2009) Unplanned admission to intensive care after emergency hospitalisation: Risk factors and development of a nomogram for individualised risk. Resuscitation 80: 224 – 230
48. Carr BG, Kaye AJ, Wiebe DJ, Gracias VH, Schwab CW, Reilly PM (2007) Emergency department length of stay: a major risk factor for pneumonia in intubated blunt trauma patients. J Trauma 63: 9 – 12
49. Australasian College for Emergency Medicine (2010) ACEM Statement on National Time Based Emergency Access Targets in Australia and New Zealand. Available at: http://www.acem.org.au/media/media_releases/Statement_4hr_target.pdf Accessed November 2010
50. Richardson D (2009) Access block point prevalence survey. Carried out by the Road Trauma and Emergency Medicine Unit, Australian National University on behalf of the Australasian College for Emergency Medicine. Available at: http://www.acem.org.au/media/Access_Block_Update_2009 – 2_201109_.pdf Accessed November 2010

Triage of High-risk Surgical Patients for Intensive Care

J. Sobol and H. Wunsch

Introduction

Patients who undergo high-risk non-cardiac surgical procedures represent a large proportion of admissions to intensive care units (ICUs) in the developed world [1]. Ideally, surgeons, anesthesiologists, and intensivists admitting surgical patients to ICUs target the patients who will benefit most from this highest level of postoperative care. However, accurately identifying which patients are at high risk of complications or death after major surgery remains difficult. For example, a recent study in the United Kingdom demonstrated that patients undergoing high-risk general surgical procedures comprised only 12.5 % of surgical admissions to hospitals but over 80 % of deaths, with less than 15 % of these high-risk patients admitted to the ICU postoperatively [2].

Postoperative outcomes are a result of the complex interplay between the exact general surgical procedure performed, the previous health of the patient, and specific intra- and postoperative events. Outcomes may also be influenced by aspects of the particular healthcare system, such as the surgical procedure volume at different hospitals [3], as well as care options, such as the availability and suitable use of intensive care beds. Appropriate triage of patients to intensive care postoperatively may have a large impact on outcomes after non-cardiac surgery. This chapter reviews the patient factors and scoring systems developed to help with triage, describes current ICU triage recommendations for postsurgical patients, and identifies potential ways to improve evaluation and management of high-risk postoperative patients.

Prediction of Postoperative Outcomes

Predictors of postoperative outcomes may be divided into three categories: Known preoperative risk factors; the risk associated with the specific surgical procedure; and the unique aspects of each operative case that may contribute to a particular patient being at high risk for complications or death after surgery.

Preoperative Evaluation

Many preoperative risk factors can help distinguish which patients are most likely to experience poor postoperative outcomes. In particular, preoperative comorbidities are well-established as predictors of both morbidity and mortality after surgery and can be measured in different ways (**Table 1**). Perhaps the best known is

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Table 1. Select scoring systems available for assessment of postoperative risk

Scoring system	Year	Number of variables	Inclusion of intraoperative variables	Outcomes predicted	Simplicity	Objectivity
Preoperative						
ASA	1941	Unlimited	No	None	Simple	Subjective
Charlson Comorbidity Index	1987	19	No	Mortality	Mildly complex	Objective
RCRI	1999	6	No	Major cardiac complication	Simple	Objective
Postoperative						
P-POSSUM	1998	12 physiologic, 6 operative	Yes	Morbidity & mortality	Complex	Objective
E-PASS	2001	6 preoperative, 3 operative	Yes	Morbidity & mortality	Complex	Subjective (includes ASA)
NSQIP	1997	57 preoperative, 15 operative	Yes	Morbidity & mortality	Complex	Subjective (includes ASA)
SAS	2007	3 operative	Yes	Morbidity & mortality	Simple	Objective
Intensive care						
APACHE I-IV*	1981 – 2006	> 10*	No	Mortality	Complex	Objective
SAPS I-III*	1983 – 2005	> 10*	No	Mortality	Complex	Objective
MPM I-III*	1985 – 2007	> 10*	No	Mortality	Complex	Objective
SOFA	1994	6	No	None	Mildly complex	Objective
MODS	1995	6	No	None	Mildly complex	Objective

* Dependent on the version of the scoring system used
ASA: American Society of Anesthesiologists' physical status; RCRI: Revised Cardiac Risk Index; APACHE: Acute Physiology and Chronic Health Evaluation; SAPS: Simplified Acute Physiology Score; MPM: Mortality Probability Model; SOFA: Sequential Organ Failure Assessment; MODS: Multiple Organ Dysfunction Score; P-POSSUM: Portsmouth Physiological and Operative Severity Score for the enUmeration of Mortality and morbidity; E-PASS: Estimation of Physiologic Ability and Surgical Stress; NSQIP: National Surgical Quality Improvement Program; SAS: Surgical Apgar Score.

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the American Society of Anesthesiologists' (ASA) physical status classification system. This is a widely used preoperative scoring system that describes the overall health of the patient and burden of comorbidities. The score is ideal in being simple to apply and requiring no laboratory data; however, it is also subject to substantial interobserver variation in score assignment [4]. Despite this inherent

subjectivity, the ASA classification has been recognized as a helpful predictor of potential postoperative morbidity and mortality [5]. Another scoring system of preoperative comorbidities is the Charlson Comorbidity Index, which assigns weights to a variety of systemic diseases and predicts long-term survival [6]. While more detailed than the ASA classification, this score is usually considered more useful for research purposes than for risk stratification in real time. There are also organ system-specific scores, most notably the Revised Cardiac Risk Index (RCRI), a scoring system that incorporates six factors to predict the risk of major cardiac events after non-cardiac surgery [7]. None of these scoring systems alone is generally sufficient to provide adequate information regarding the risk for an individual patient. The RCRI predicts only cardiac risk, while the ASA and Charlson Comorbidity Index do not incorporate variables specific to the surgical procedure.

These preoperative scoring systems encompass a wide range of patient variables to produce a composite score. Individual patient factors have also been identified in large studies as independently predicting increased risk of morbidity and mortality after surgery, including age and poor nutritional and functional status [8, 9]. Functional capacity at baseline may indicate how a patient will respond to surgical stress in the perioperative period. Recent guidelines from the American College of Cardiology Foundation (ACCF) and the American Heart Association (AHA) for preoperative cardiovascular risk evaluation in non-cardiac surgery rely on a modified version of the Duke Activity Status Index. This questionnaire estimates energy requirements for various patient activities. Depending on a patient's functional capacity, clinical risk factors, and type of surgery, the ACCF/AHA guidelines recommend either proceeding with surgery or further cardiac evaluation prior to the planned procedure. Clinical risk factors include active cardiac conditions and elements of the RCRI, and surgical procedures are divided into those that are low, intermediate, or high risk [10]. While these guidelines only address cardiovascular risk, they illustrate the importance of including both the patient's preoperative status and the particular surgical procedure for evaluation of the risk of poor postoperative outcomes.

Intraoperative Events

Surgical duration and urgency have both been shown to impact postoperative outcomes, with longer duration and emergent procedures associated with worse outcomes [2, 9, 11]. Preoperative patient characteristics were the most important predictors of postoperative mortality in a large study of the Veterans Affairs database, but operative complexity became a significant predictor with highly complex procedures [12]. Pearse et al. defined high-risk surgical procedures as those with at least a 5 % risk of mortality and found that these procedures, in combination with advanced age, comorbidities, and emergency surgery, were highly predictive of increased risk of death postoperatively [2]. While the weight of the effects of patient- and surgery-specific factors on postoperative outcomes varies across different studies, it is clear that it is ultimately the combination of the two that contributes to morbidity and mortality after surgery.

Surgical patients are unique as hospital patients in having a prolonged period of time in the operating room when they are closely monitored, providing detailed information on the physiologic perturbations associated with the anesthesia and surgery itself. The individual experience of a patient during surgery

may have a large impact on outcomes. In particular, hemodynamic stresses to the body manifested as extremes of vital signs may influence the postoperative course. One study demonstrated that intraoperative tachycardia in long, complicated surgical procedures was independently associated with a composite measure of poor outcome [13]. In another case-control study, intraoperative tachycardia requiring treatment was associated with a significantly increased risk of ICU admission, prolonged hospital stay, and hospital mortality [14]. A prospective cohort study in elderly patients showed that ASA class, emergency surgery, and intraoperative tachycardia were the most important predictors of adverse outcomes after surgery [11]. These three studies indicate that intraoperative tachycardia is associated with a wide spectrum of poor postoperative outcomes. Unanswered questions raised by these studies are whether tachycardia represents inadequate preoperative beta-blockade for high-risk patients or whether better control of intraoperative tachycardia would improve postoperative outcomes.

In addition to heart rate, blood pressure extremes may also predict outcomes after surgery. A prospective evaluation of over 1,000 patients revealed only three significant independent predictors of one-year mortality after major general surgery: The Charlson Comorbidity Index, the cumulative deep hypnotic time, and intraoperative hypotension [15]. Other researchers found that the risk of one-year mortality in elderly patients may be influenced not only by the presence or absence of hypotension but by its duration as well. The cut-off value associated with an increased risk of one-year mortality was only 5 minutes for mean blood pressure less than 50 mmHg but 30 minutes for mean blood pressure less than 60 mmHg [16]. It is important to note, however, that intraoperative hypertension has also been associated with poor outcome [13], suggesting that it is not just a single hemodynamic response but many different types of physiologic stress that may affect postoperative morbidity and mortality in surgical patients.

Perioperative Scoring Systems

A number of scores aid in prediction of death specifically for patients admitted to the ICU (**Table 1**). While not developed solely for surgical patients, all of these scores account for postsurgical patients and provide risk prediction. The most commonly used scores are the Acute Physiology and Chronic Health Evaluation (APACHE) score, the Simplified Acute Physiology Score (SAPS), and the Mortality Probability Model (MPM) [17, 18]. The Sequential Organ Failure Assessment (SOFA) and the Multiple Organ Dysfunction Score (MODS) are two other ICU scoring systems used to describe organ dysfunction over the course of the ICU stay [19, 20]. The main problem with all of these scoring systems for triage of patients is that they were developed and validated on patients already admitted to the ICU, and they do not necessarily provide adequate prediction for a broader range of patients. Moreover, none of the ICU scoring systems takes into account specific intraoperative data from the surgical procedure itself.

Other scoring systems were created specifically for surgical populations to aid in postoperative predictions of morbidity and mortality, regardless of admission to the ICU. These scores incorporate patient and surgical factors to predict postoperative outcomes (**Table 1**). One of the most widely used is the Portsmouth Physiological and Operative Severity Score for the enUmeration of Mortality and morbidity (P-POSSUM), comprised of twelve physiological variables and six operative variables. The Estimation of Physiologic Ability and Surgical Stress (E-PASS)

is another system calculated from six preoperative variables and three intraoperative variables [17]. In the United States, the National Surgical Quality Improvement Program (NSQIP) was developed to allow comparison of risk-adjusted surgical outcome data between hospitals. The risk prediction requires collection of 97 perioperative variables [21]. Finally, the Surgical Apgar Score (SAS) was derived to provide a simple postoperative assessment of patients at the end of a surgical procedure. The score is calculated from three intraoperative variables and predicts those patients at highest risk of postoperative complications and mortality [22]. All of these surgery-specific scoring systems can be applied to patients postoperatively irrespective of patient location. Indeed, none use ICU admission as a variable or as an outcome measure.

A major concern is that most of these scoring systems were created and evaluated for the purpose of audit, benchmarking, and assessment of quality of care. As such, they are valid for predicting outcomes in groups of patients, but they may not be useful or accurate for individual patients [18]. In addition, some of the scores, such as SOFA, MODS, and SAS, are much easier to implement in real time compared with others (such as NSQIP) to allow for an understanding of a patient's current status and to potentially assist in individual triage decisions.

Postoperative Complications

Despite increasing recognition of the importance of postoperative complications as outcomes, previous research and scoring systems primarily focused on short-term (hospital or 30-day) mortality as the main postoperative outcome measure [18]. However, complications potentially result in greater morbidity for patients, increased length of hospital stay, and higher hospital costs. The focus in U.S. healthcare has recently shifted towards an increased emphasis on measuring complications because of a change in hospital reimbursements in 2008 by the Centers for Medicaid and Medicare Services (CMS). The CMS implemented a pay-for-performance initiative designed to improve the quality of health care delivered to patients. Hospitals no longer receive additional reimbursement when Medicare patients experience certain 'preventable' complications, some of which are clearly postoperative concerns, such as mediastinitis after cardiac surgery or an object retained inside the patient after surgery [23]. While increasing attention to these outcomes, it is unclear whether these economic incentives will result in a reduced incidence of postoperative complications.

Data also suggest a link between the development of postoperative complications and long-term outcomes. In recognition of the potential importance of complications, NSQIP provides prospective data collection on postoperative morbidity as well as mortality. Using the NSQIP dataset merged with a Veterans Benefits Administration database, a multicenter study of over 100,000 Veterans Affairs hospital patients undergoing eight different surgical procedures demonstrated that the presence of any complication within the first 30 postoperative days was an important predictor of 5-year survival, independent of preoperative risk [24]. Recognition and avoidance of postoperative complications may thus reduce short-term morbidity and costs of care, and also impact long-term outcomes.

"Failure to Rescue"

In two large studies of U.S. hospitals, Ghaferi et al. found that patients undergoing general and vascular surgical procedures had similar postoperative complication rates across hospitals but a very wide range of postoperative 30-day mortality rates [25, 26]. The rates of "failure to rescue" (proportion of deaths in patients who developed a postoperative complication out of the total number of patients who developed a postoperative complication) were much higher in high-mortality hospitals. The authors suggest that rather than differences in complication rates, it is differences in rates of "failure to rescue" that better explain hospital variation in post-surgical mortality; those hospitals with higher mortality may not properly recognize and manage postoperative complications when they occur [25, 26]. This concept of "failure to rescue" shifts some of the focus from preventing the development of complications to improving the care provided to manage complications.

Intensive Care Triage

Improved Outcomes with Intensive Care

Routine postoperative care in an ICU after high-risk surgical procedures may allow for greater recognition and correct management of postoperative complications, thereby reducing long-term morbidity and mortality. While there is an assumption that ICU admission may improve postoperative outcomes, no randomized trials have addressed this issue. Given the limitations and variability of ICU bed availability worldwide [27], many patients referred for ICU admission must ultimately be refused. The potential benefit of intensive care in reducing mortality for some groups of high-risk surgical patients is, therefore, suggested by multiple observational studies primarily examining patients refused admission to an ICU. In one prospective study that took place in seven countries, ICU admission of mixed medical and surgical patients was associated with a substantial reduction in 28- and 90-day mortality compared with patients refused admission. However, surgical patients were significantly less likely to be refused admission to an ICU than medical patients [28]. This discrepancy may be explained by the fact that many patients with severe systemic illness who undergo surgical procedures for acute problems are still deemed to have a reasonable chance of recovery. Moreover, curative surgery often represents an investment of resources in a patient that may carry over to priority admission to an ICU.

Until recently, few studies emphasized the potentially different nature and practice of triage decisions for postoperative patients compared with medical patients. One recent study of patients in two British hospitals that did focus solely on postoperative admission practices for high-risk surgical patients found that only one-third of these patients received intensive care. Furthermore, patients admitted to the ICU immediately after surgery had greatly improved survival compared with patients who were re-admitted or had delayed admission to the ICU postoperatively [29]. This study showed the potential drawbacks of ICU underuse, but it did not include details of the triage decision-making process for postoperative ICU admission. Objective, evidence-based criteria for ICU admission after surgery may facilitate resource allocation and potentially help identify patients who would benefit most from admission to the ICU, with the ultimate goal of improving postoperative outcomes.

ICU Admission Guidelines

In 1994, the European Society of Intensive Care Medicine (ESICM) issued guidelines stating that patients should be admitted to the ICU if they have an unstable condition or if they are at high risk of developing a severe complication [30]. The American College of Critical Care Medicine then published broad guidelines for ICU admission in 1999 [31]. A prioritization model was described to aid with decision-making, ranging from Priority 1 (patients who will derive the most benefit from admission) to Priority 4 (those who will not benefit at all). Priority 1 patients include hemodynamically unstable or ventilator-dependent postoperative patients; Priority 2 patients are those who may need immediate intervention, such as patients with chronic comorbidities with an acute surgical problem [31]. The Italian intensivist group SIAARTI (Società Italiana di Anestesia Analgesia Rianimazione e Terapia Intensiva) published similar guidelines with specific recommendations for prioritization. A patient currently requiring intensive care should have priority for ICU admission over a patient who only needs intensive monitoring. This group also outlined a scale from Priority 1 (maximum benefit expected) to Priority 4 (little or no benefit expected) for determining which patients should take precedence for ICU admission [32]. Israeli consensus guidelines recommend ICU admission for all postoperative vascular or major general surgery patients with severe underlying systemic disease [33].

None of these sets of criteria, however, offers guidance as to how to triage patients of similar acuity. One method to allocate scarce ICU resources might be on a first-come, first-served basis, as suggested by the American Thoracic Society [34]. Current guidelines and studies also do not specifically target surgical populations. There are no universal criteria for postoperative admission of patients to the ICU. In a recent editorial, Goldhill and Down observed that postoperative critical care is highly inconsistent, with some groups of patients routinely admitted to the ICU postoperatively and others rarely admitted [35]. In some hospitals, patients are admitted postoperatively simply for monitoring, but it is unclear whether using the ICU for this purpose actually improves postoperative outcomes. While one early study found that a shortage of medical ICU beds led to restriction of admissions solely for monitoring purposes with no effect on mortality [36], no such study has been performed in surgical patients.

Alternatives to ICU Admission

Mandatory ICU admission could potentially lead to overuse of intensive care for postsurgical patients, and a shift has occurred away from this practice. As an alternative to intensive care, the high-dependency unit (HDU) provides a location for patients with a potential but low risk of major complications who require more care than the ward but less than that available in the ICU [37]. Over a 14-year period from 1991 to 2004, postoperative care of major vascular surgery patients in one center changed from mandatory ICU admission for all patients to care for more than two-thirds of postoperative patients in an HDU and ward [38]. Another group retrospectively examined patients who had undergone radical cystectomy with urinary diversion followed by mandatory admission to the ICU postoperatively. They identified a stratification system for triage of these patients to the ICU, HDU, or ward depending on the risk of requiring active treatment such as invasive monitoring, vasoactive medications, or mechanical ventilation.

However, there was no prospective evaluation of this postoperative risk stratification system [39]. Finally, an eight-year observational study compared ICU admissions for aortic abdominal surgery and surgery for lung cancer, two high-risk surgical procedures, before and after expansion of the hospital's post-anesthesia care unit (PACU). Admission rates to the ICU dropped significantly for both types of procedures, with no concomitant increase in postoperative morbidity or mortality [40]. These studies illustrate the possibility of caring for high-risk surgical patients in locations other than the ICU and highlight the potential for development of procedure-specific criteria for postoperative ICU admission.

Post-anesthesia Care Units

Individual hospital resources are extremely variable and not all centers have access to HDU facilities or proficient ward services. The PACU may often be used as an 'overflow' location for postoperative surgical patients who are not stable enough for ward care. Several issues may arise when a PACU is used to care for more severely ill patients. Physician coverage of these patients may be unclear, as anesthesia personnel, the primary surgical team, and/or an intensivist may all be involved in caring for such patients. In addition, PACU nurses must be fully competent and trained to care for ICU-level patients. Staffing patterns may need to be augmented, with increases in services from different provider types, such as respiratory therapists. Responsibility for record-keeping, daily progress notes, ordering systems, and flowsheets must all be clarified [41]. While the PACU can serve as a safety net for ICU patients during times of limited bed availability, patients who would most benefit from postoperative ICU care would ideally gain admission to the ICU immediately after surgery, as outcomes may be improved with immediate rather than delayed ICU admission [29]. Therefore, for high-risk patients, bypassing the PACU for immediate transfer to intensive care may ensure the most efficient use of resources with the best outcomes.

Improvement of Postoperative Outcomes

A number of interventions have the potential to improve postoperative outcomes, especially in high-risk patients.

Patient Interventions

Several studies show that hemodynamic optimization of high-risk surgical patients improves outcomes after surgery. The goal of hemodynamic optimization is to most efficiently match oxygen delivery to oxygen consumption. Tissue hypoxia due to surgical stress may not be adequately monitored by heart rate, blood pressure, or central venous pressure. Various invasive and non-invasive devices provide alternate means of assessing and optimizing oxygen delivery, including mixed or central venous oxygen saturation, cardiac index, pulse contour analysis, or other parameters indicating preload. Many of the studies using goal-directed hemodynamic therapy show decreased rates of postoperative complications, mortality, and hospital length-of-stay [42]. Individualized goal-directed therapy for high-risk surgical patients may improve outcome, but large, multicenter trials are necessary before widespread adoption can occur. British

consensus guidelines, however, do recommend preoperative therapy with intravenous fluids and inotropes to attain predetermined cardiac output and oxygen delivery targets in high-risk surgical patients as a way to reduce postoperative mortality [43].

Hospital Interventions

A simple way of improving surgical outcomes may include hospital-mandated use of a preoperative surgical safety checklist. A prospective study in eight countries looked at the rate of postoperative complications before and after implementing a checklist in all operating rooms. The checklist encompassed 19 items to ensure patient safety before induction of anesthesia, before surgical incision, and before exit from the operating room. All sites had reductions in major complication and mortality rates after implementation of the checklist [44].

Another method to reduce morbidity and mortality may be to improve ICU triage after surgery by creating and adhering to hospital guidelines that most efficiently use intensive care resources. These guidelines could include patient- and surgery-specific indications for admission to the ICU, HDU, or ward, and they could also delineate an ICU prioritization system for patients of similar acuity. 'Fast-track' surgery is a recent concept encompassing multimodal pre-, intra-, and postoperative interventions to improve outcomes after surgery. Each of these approaches must be specific to the surgical procedure and focus on enhancing postoperative recovery. Data are accumulating in a variety of surgical subspecialties that support the feasibility of 'fast-track' surgery [45]. Although practices vary, 'fast-track' surgery may mean more rapid progression through intensive care or admission to a specialized PACU.

Use of dedicated intensivists to staff ICUs may also help improve outcomes for high-risk surgical patients. In particular, intensivists may be the most appropriate practitioners to assist in ICU triage and bed allocation. Furthermore, dedicated intensivists may provide better care to ICU patients than non-specialized physicians. A survey of Maryland ICUs that provide postoperative care for patients undergoing abdominal aortic surgery showed that after adjusting for patient and hospital characteristics, the absence of daily rounds by an intensivist was associated with significantly increased morbidity and mortality after this high-risk surgery [46]. Similarly, rapid response teams with critical care-trained personnel may evaluate patients with complications on the ward to better identify those who might benefit from transfer to an ICU. Such teams may improve "failure-to-rescue" rates. Based on this concept, many hospitals have created rapid response teams [47], although their utility remains unproven in large multicenter studies.

Health Care System Interventions

On a health care system level, high volume hospitals and regionalization may also decrease the risk of postoperative morbidity and mortality. In an analysis of Medicare data, hospitals that performed a greater number of specific high-risk surgical procedures annually had lower hospital mortality rates [3]. A meta-analysis of the effects of surgical volume and specialization recently showed that high individual surgeon volume and surgeon specialization were independently associated with improved postoperative outcomes, but the relationship between high hospital volume overall and outcome remained unclear [48]. Regionalization to

high-volume centers or to individual specially trained surgeons for certain high-risk procedures may be another way to improve outcomes after surgery, as is now the model for trauma care [49].

Conclusion

High-risk surgical patients continue to make up a substantial proportion of ICU admissions in most developed countries. Identification and optimization of these patients prior to surgical interventions remains difficult. Pre-, intra-, and postoperative variables all play a role in the development of considerable morbidity and mortality for high-risk patients. Appropriate decisions relating to the need for intensive care after surgery are key for high-quality patient care, yet adequate systems for triage remain elusive. The potential exists for underuse of critical care resources, with inappropriate lack of admission to an ICU for high-risk patients, as well as overuse, with unnecessary admissions leading to increased length of stay and costs. With the wealth of data now available regarding the perioperative status of many of these patients, further research is needed to help facilitate optimal care for postsurgical patients.

References

1. Nathanson BH, Higgins TL, Kramer AA, Copes WS, Stark M, Teres D (2009) Subgroup mortality probability models: are they necessary for specialized intensive care units? Crit Care Med 37: 2375 – 2386
2. Pearse RM, Harrison DA, James P, et al (2006) Identification and characterisation of the high-risk surgical population in the United Kingdom. Crit Care 10: R81
3. Birkmeyer JD, Siewers AE, Finlayson EV, et al (2002) Hospital volume and surgical mortality in the United States. N Engl J Med 346: 1128 – 1137
4. Owens WD, Felts JA, Spitznagel EL Jr (1978) ASA physical status classifications: a study of consistency of ratings. Anesthesiology 49: 239 – 243
5. Wolters U, Wolf T, Stutzer H, Schroder T (1996) ASA classification and perioperative variables as predictors of postoperative outcome. Br J Anaesth 77: 217 – 222
6. Charlson ME, Pompei P, Ales KL, MacKenzie CR (1987) A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 40: 373 – 383
7. Lee TH, Marcantonio ER, Mangione CM, et al (1999) Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. Circulation 100: 1043 – 1049
8. McNicol L, Story DA, Leslie K, et al (2007) Postoperative complications and mortality in older patients having non-cardiac surgery at three Melbourne teaching hospitals. Med J Aust 186: 447 – 452
9. Turrentine FE, Wang H, Simpson VB, Jones RS (2006) Surgical risk factors, morbidity, and mortality in elderly patients. J Am Coll Surg 203: 865 – 877
10. Fleisher LA, Beckman JA, Brown KA, et al (2009) 2009 ACCF/AHA focused update on perioperative beta blockade incorporated into the ACC/AHA 2007 guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery: a report of the American college of cardiology foundation/American heart association task force on practice guidelines. Circulation 120: e169 – 276
11. Leung JM, Dzankic S (2001) Relative importance of preoperative health status versus intraoperative factors in predicting postoperative adverse outcomes in geriatric surgical patients. J Am Geriatr Soc 49: 1080 – 1085
12. Aust JB, Henderson W, Khuri S, Page CP (2005) The impact of operative complexity on patient risk factors. Ann Surg 241: 1024 – 1027

13. Reich DL, Bennett-Guerrero E, Bodian CA, Hossain S, Winfree W, Krol M (2002) Intraoperative tachycardia and hypertension are independently associated with adverse outcome in noncardiac surgery of long duration. Anesth Analg 95: 273 – 277
14. Hartmann B, Junger A, Rohrig R, et al (2003) Intra-operative tachycardia and peri-operative outcome. Langenbecks Arch Surg 388: 255 – 260
15. Monk TG, Saini V, Weldon BC, Sigl JC (2005) Anesthetic management and one-year mortality after noncardiac surgery. Anesth Analg 100: 4 – 10
16. Bijker JB, van Klei WA, Vergouwe Y, et al (2009) Intraoperative hypotension and 1-year mortality after noncardiac surgery. Anesthesiology 111: 1217 – 1226
17. Chandra A, Mangam S, Marzouk D (2009) A review of risk scoring systems utilised in patients undergoing gastrointestinal surgery. J Gastrointest Surg 13: 1529 – 1538
18. Higgins TL (2007) Quantifying risk and benchmarking performance in the adult intensive care unit. J Intensive Care Med 22: 141 – 156
19. Vincent JL, Moreno R, Takala J, et al (1996) The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. Intensive Care Med 22: 707 – 710
20. Marshall JC, Cook DJ, Christou NV, Bernard GR, Sprung CL, Sibbald WJ (1995) Multiple organ dysfunction score: a reliable descriptor of a complex clinical outcome. Crit Care Med 23: 1638 – 1652
21. Khuri SF, Henderson WG, Daley J, et al (2007) The patient safety in surgery study: background, study design, and patient populations. J Am Coll Surg 204: 1089 – 1102
22. Gawande AA, Kwaan MR, Regenbogen SE, Lipsitz SA, Zinner MJ (2007) An Apgar score for surgery. J Am Coll Surg 204: 201 – 208
23. Morse BC, Boland BN, Blackhurst DW, Roettger RH (2010) Analysis of Centers for Medicaid and Medicare Services 'never events' in elderly patients undergoing bowel operations. Am Surg 76: 841 – 845
24. Khuri SF, Henderson WG, DePalma RG, Mosca C, Healey NA, Kumbhani DJ (2005) Determinants of long-term survival after major surgery and the adverse effect of postoperative complications. Ann Surg 242: 326 – 341
25. Ghaferi AA, Birkmeyer JD, Dimick JB (2009) Complications, failure to rescue, and mortality with major inpatient surgery in medicare patients. Ann Surg 250: 1029 – 1034
26. Ghaferi AA, Birkmeyer JD, Dimick JB (2009) Variation in hospital mortality associated with inpatient surgery. N Engl J Med 361: 1368 – 1375
27. Wunsch H, Angus DC, Harrison DA, et al (2008) Variation in critical care services across North America and Western Europe. Crit Care Med 36: 2787 – 2793
28. Iapichino G, Corbella D, Minelli C, et al (2010) Reasons for refusal of admission to intensive care and impact on mortality. Intensive Care Med 36: 1772 – 1779
29. Jhanji S, Thomas B, Ely A, Watson D, Hinds CJ, Pearse RM (2008) Mortality and utilisation of critical care resources amongst high-risk surgical patients in a large NHS trust. Anaesthesia 63: 695 – 700
30. European Society of Intensive Care Medicine (1994) Guidelines for the utilisation of intensive care units. Intensive Care Med 20: 163 – 164
31. Task Force of the American College of Critical Care Medicine, Society of Critical Care Medicine (1999) Guidelines for intensive care unit admission, discharge, and triage. Crit Care Med 27: 633 – 638
32. SIAARTI (2003) SIAARTI guidelines for admission to and discharge from Intensive Care Units and for limitation of treatment in intensive care. Minerva Anestesiol 69: 101 – 111
33. Simchen E, Sprung CL, Galai N, et al (2007) Survival of critically ill patients hospitalized in and out of intensive care. Crit Care Med 35: 449 – 457
34. American Thoracic Society (1997) Fair allocation of intensive care unit resources. Am J Respir Crit Care Med 156: 1282 – 1301
35. Goldhill DR, Down JF (2008) Are we operating as well as we can? Critical care to minimise postoperative mortality and morbidity. Anaesthesia 63: 689 – 692
36. Singer DE, Carr PL, Mulley AG, Thibault GE (1983) Rationing intensive care--physician responses to a resource shortage. N Engl J Med 309: 1155 – 1160
37. Nasraway SA, Cohen IL, Dennis RC, et al (1998) Guidelines on admission and discharge

for adult intermediate care units. American College of Critical Care Medicine of the Society of Critical Care Medicine. Crit Care Med 26: 607 – 610
38. Teli M, Morris-Stiff G, Rees JR, Woodsford PV, Lewis MH (2008) Vascular surgery, ICU and HDU: a 14-year observational study. Ann R Coll Surg Engl 90: 291 – 296
39. Dahm P, Tuttle-Newhall JE, Nimjee SM, Byrne RR, Yowell CW, Price DT (2001) Indications for admission to the surgical intensive care unit after radical cystectomy and urinary diversion. J Urol 166: 189 – 193
40. Schweizer A, Khatchatourian G, Hohn L, Spiliopoulos A, Romand J, Licker M (2002) Opening of a new postanesthesia care unit: impact on critical care utilization and complications following major vascular and thoracic surgery. J Clin Anesth 14: 486 – 493
41. Lindsay M (1999) Is the postanesthesia care unit becoming an intensive care unit? J Perianesth Nurs 14: 73 – 77
42. Kirov MY, Kuzkov VV, Molnar Z (2010) Perioperative haemodynamic therapy. Curr Opin Crit Care 16: 384 – 392
43. Soni N (2009) British Consensus Guidelines on Intravenous Fluid Therapy for Adult Surgical Patients (GIFTASUP): Cassandra's view. Anaesthesia 64: 235 – 238
44. Haynes AB, Weiser TG, Berry WR, et al (2009) A surgical safety checklist to reduce morbidity and mortality in a global population. N Engl J Med 360: 491 – 499
45. Kehlet H (2009) Multimodal approach to postoperative recovery. Curr Opin Crit Care 15: 355 – 358
46. Pronovost PJ, Jenckes MW, Dorman T, et al (1999) Organizational characteristics of intensive care units related to outcomes of abdominal aortic surgery. JAMA 281: 1310 – 1317
47. Bellomo R, Goldsmith D, Uchino S, et al (2004) Prospective controlled trial of effect of medical emergency team on postoperative morbidity and mortality rates. Crit Care Med 32: 916 – 921
48. Chowdhury MM, Dagash H, Pierro A (2007) A systematic review of the impact of volume of surgery and specialization on patient outcome. Br J Surg 94: 145 – 161
49. Kahn JM, Branas CC, Schwab CW, Asch DA (2008) Regionalization of medical critical care: what can we learn from the trauma experience? Crit Care Med 36: 3085 – 3088

Transportation of the Critically Ill: Moving in the Right Direction

P.G. Brindley and T. O'Leary

Introduction

The goal of patient transportation is to enhance patient care by making investigations or treatments available that are not possible at the bedside or in the referring institution. Patient transport can be local, regional, national, and even international. Regardless, it requires the coordination of many teams, departments, and institutions. This is complex and potentially dangerous. As a result, proficiency should be taught not assumed. This manuscript offers a basic primer.

Transports can be divided into those within a single hospital site (intra-hospital transport) and those between different hospitals (inter-hospital transport). Unless transport is performed safely, benefits can easily be outweighed by the risks. In order to minimize patient risk during transport, regions should have suitable guidelines or protocols. Fortunately, many national societies have produced guidelines [1–3]; unfortunately, these are not well known, widely taught, or well practised.

In the same way that athletic relay races are often won or lost during handover of a baton, patients are probably at their most perilous during handover from one team to the next, or from one location to another. For over 30 years, the putative risks of transporting critically ill patients have been assumed, but insufficiently studied [4, 5]. It is widely assumed that critically ill patients are safer when static in the intensive care unit (ICU). Patients presumably benefit from the ICU's ready access to cutting-edge equipment, close monitoring, and a high-ratio of well-trained multidisciplinary staff. Critical care staff should make every effort to replicate these 'safety-nets' during transport.

Risks during transportation are compounded for critically ill patients with insufficient 'physiological reserve'. This is because patients may be additionally stressed when they are moved (even just between stretchers). They may also be disconnected from monitors (meaning that vital signs are temporarily unknown), and temporarily removed from positive pressure ventilation or placed on an inferior transport ventilator (with the risk of lung-derecruitment or relative hypoventilation). All these factors can result in increased morbidity and mortality for transfer patients [6, 7]. It also means that a medical transport is more than just a 'medical taxi'. Safe transport means optimizing the patient beforehand and also optimizing the team en route. As the saying goes, 'failure to prepare' is akin to 'preparing to fail'.

Transfer of critically ill patients uses time and resources. In one British survey, the average time from decision to arrival at the receiving hospital was approximately five hours, with an additional two hours for staff to return. Moreover,

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almost half (46 %) of these transfers occurred at night, or on weekends, when hospitals are relatively short-staffed [8]. Therefore, we should not forget the potential risk to patients who remain behind, especially in smaller centers. We should also not ignore risks to the transport team, especially during inclement weather. As such, part of safe patient-transfer is a judgment as to whether this is the 'right patient', at the 'right time', and to the 'right location'. This includes deciding whether to get the patient to treatment, i.e., 'scoop and run' or whether to get the treatment to the patient, i.e., '*in situ* resuscitation'. The demands of medical transportation require that we make a "science of human performance" and a "science of managing complexity" [9]. The goal is to make a "failure to rescue" unlikely, but also unacceptable. This starts by understanding the inherent risks.

Risks

Risks can be subdivided into four major categories: Patient-related, equipment-related; personnel-related (human factors); and process-related (organizational). Many studies have confirmed adverse events associated with both inter-hospital and intra-hospital transport of the critically ill patient [10–15]. Singh et al. [10] studied urgent air transportation within Ontario, Canada. Over 19,000 patients were transported over a two-and-a-half year period. These authors found that approximately 5 % of urgent air transports involved a critical incident, 0.1 % died, and the majority of adverse events involved cardiorespiratory deterioration. They recognized many independent risk factors for adverse events including mechanical ventilation, duration of transport, type of crew, and curiously female compared to male sex. An Australian analysis [16] of adverse events studied 191 submitted incident reports that arose over seven years of transports. Fifteen percent of patients showed major physiological derangement, 4 % had increased hospital stay, and 2 % died. This study also attempted to determine causation. Of 900 potential contributors, they concluded that 54 % of preventable errors were associated with human factors, and 46 % associated with process or organizational factors.

More data exist for intra-hospital than for inter-hospital transport. In fact, in a 2006 review, Fan et al. [17] found only five studies of inter-hospital transport. They reported that ventilation problems occurred in 5–28 % of transports, intravenous line disconnections in 8–34 %, and monitor disconnections in 15–74 %. If only serious adverse events were included (defined as 'life threatening' or where changes in vital signs necessitated treatment), then the rate dropped to 4–8 %. Predictably, the authors also found that the more equipment, the higher the risk of equipment-related adverse events. Similarly, for intra-hospital transfer, Szem et al. [18] found significantly higher all cause mortality when stationary patients were compared with transported patients (28.6 % vs 11.4 %).

It is difficult to compare studies given the many confounding variables, and the dearth of common definitions. This might also explain the wide variation in the incidence of adverse events. In addition, without knowing the denominator (i.e., the total number of transports rather than the total number of critical incidences) it is tough to estimate the independent risk associated with each adverse event. Error mitigation is also more complex than simply identifying one causative factor to fix...or one individual to blame. Transport errors are typically the

sum of several smaller – seemingly trivial – factors. Each of these errors, mistakes, or oversights rarely results in disaster on its own. Adverse outcomes with patient-transfer are better understood by the so-called 'Swiss cheese model', where concurrent small issues line up, even if only momentarily; therefore, it is typically the combination that results in an error [9].

While the data are imperfect, these studies do illustrate the potential perils of both intra-hospital and inter-hospital transport. They may also suggest where to channel our energy. For example, if the causes of error are multi-factorial then its mitigation must be equally multipronged. We will use a construct familiar to all critical care personnel, namely addressing the risks and strategies by organ system: Airway, breathing, circulation and the central nervous system.

Airway

Transportation to and from the ICU involves ventilated and non-ventilated patients. Each situation has its potential difficulties. For example, unplanned extubation still occurs. Excessive head flexion can also force an endotracheal tube (ETT) into the right main bronchus causing hypoxemia due to increased imbalance between ventilation and perfusion. Excessive head extension can lift the tube above the glottis, increasing the risk of unplanned extubation. Something as simple as assigning one person to be responsible for holding the tube during any patient movement may mitigate this. Targeted sedation also helps with tube tolerance. In addition, during unpressurized air transport, the ETT pilot balloon should be filled with fluid (i.e., saline), and not air. This is in order to prevent balloon distension, and dislodgement, due to the lower barometric pressure associated with increased altitude. Concurrent continuous end-tidal carbon dioxide monitoring ($ETCO_2$) is mandatory in most transport guidelines. Loss of $ETCO_2$ indicates that the patient may have self-extubated or the tube may have migrated out of the airway.

For non-intubated patients, the risks center more on decision making. For example, the sending and receiving doctor should decide in concert whether the patient should be intubated for transfer. Transportation, especially over large distances, represents a potentially perilous journey between two centers of relative control. As such, many accepting physicians have a very low threshold to request intubation, even if the patient is still in control of their airway. The rationale for pre-emptive intubation is that, once en-route, intubation is not easy in a cramped ambulance environment or with limited equipment. Furthermore, the intubated patient can be more readily sedated and fluid resuscitated en-route. Intubation may also facilitate tests when the patient arrives (e.g., if the patient must lie flat or be sedated in order to avoid respiratory motion). Mechanical ventilation may also lend more stability until the worst of the disease has abated. Regardless, the patient can be subsequently electively extubated by airway experts at the receiving hospital.

However, rather than automatic intubation for all patients (i.e., "intubate anyone that can't talk you out of it!"), physicians have to weigh factors such as the experience of the intubator, and the associated time delay. In addition they must be cognizant of the hypotension that often results with the change from negative to positive pressure breathing. In addition, the sending team must now have rudimentary experience with how to mechanically ventilate their patient. Inadequate

ventilation can exacerbate acidemia/acidosis, while overzealous ventilation can further impair hemodynamics. If concurrent hemodynamic support is required, then the sending team now also needs basic competence (and equipment) in order to titrate inotropes and vasopressors. Physicians, and transport crews, in rural areas may or may not have these tertiary care skills. If not, then the next question becomes whether skilled staff can be mobilized to offer assistance. In short, transportation medicine requires judgment and decision-making as much as it requires factual knowledge and procedural dexterity. Clearly, resuscitation is as much 'cerebral' as 'procedural'.

Breathing

Hypoxemia or low oxygen saturation has been reported in up to 86 % of transports [19]. Causes are multi-factorial, and the same diagnosis and treatment principles apply as for the static patient. However, there are specific transport considerations. Firstly, transportation means using portable equipment. Despite impressive advances, portable ventilators are often not able to deliver the advanced modes of ventilation achieved by their ICU counterparts. As such, oxygenation and ventilation may further worsen en-route. Therefore, it is incumbent to notify the transport team of significant concerns with pre-transport oxygenation and ventilation. It also means that the transport personnel must be vigilant during the transport. At the receiving end, there must also be staff prepared to receive an unstable patient.

For intra-hospital transfers from the ICU to operating room, the anesthesiologist should also receive advanced notice of any oxygenation or ventilation concerns. After all, the anaesthesiolgy ventilator is designed for the routine operative patient, not the ICU patient. It is not ideal in the setting of high oxygen requirements or with poorly compliant lungs. On occasion, the decision is made to keep the patient on the ICU ventilator. This means confirming that the anesthesiologist is comfortable with that machine or ensuring that personnel are available to assist. Very rarely – with a patient in extremis – the decision is made to perform the surgery in the ICU so that the patient is neither moved, nor temporarily disconnected. However, this requires a willing surgeon, extra equipment in the ICU, and efforts to ensure sterility. Explicit preparation and open communication are essential.

It is essential to insure that sufficient oxygen exists to last through the transport. Helpful websites do exist (http://manuelsweb.com/O2remaining.htm), but physicians should still know the rudiments. For example, we assume that a portable E-sized oxygen cylinder is full with a pressure of approximately 2000 pounds per square inch (PSI) (approximately 14,000 kilo Pascals). This means it contains (conservatively) 600 liters of oxygen. Therefore, the patient on 10 liters/minute will have 60 minutes of oxygen. Accordingly, if 1000 PSI remains then the patient has 30 minutes at 10 liters/minute, or 60 minutes at 5 liters/minute. It is prudent never to use a tank with < 500 PSI (approximately 3500 kPA).

It is important to humidify gases during transport. This is in order to prevent the drying of secretions, which can worsen gas exchange and airway patency, especially with infrequent suctioning. This is of particular concern during air transport due to the drier air associated with altitude and lower temperature. As a result, a heat and moisture exchanger is recommended. At least one study has

shown that intra-hospital transport of patients is an independent predictor for developing ventilator-associated pneumonia (VAP) [20]. It is speculated that this is due to aspiration resulting from suboptimal patient position and movement of the ETT during transport.

The equations used to precisely determine tissue oxygen at altitude are complex. Moreover, barometric pressure (Pb) fluctuates, and different patients have different compensatory mechanisms and metabolic demands. However, again, web-based guides do exist (http://www.altitude.org/oxygen_levels.php) and physicians should know the basics. These calculations are gross simplifications, but do facilitate decisions regarding how patients can be protected during flight (or if elective patients are safe to be moved). For example, while the fraction of oxygen is 0.21 regardless of altitude, Pb drops in a linear fashion with a rising altitude. If, at sea level, we assume a Pb of 760 mmHg, then by 5,000 ft (1524 m), it drops to approximately 639 mmHg. The partial pressure of oxygen in dry air (PO_2) is now approximately 134 (rather than 160 mmHg at sea level). However, water vapor pressure at a normal body temperature is 47 mmHg, regardless of altitude. This means a partial pressure of inspired oxygen (PiO_2) of 87 mmHg. Expressed another way, this means < 80 % of the oxygen available to the lungs compared to at sea level. At 10,000 ft (3048 m), Pb drops to 534 mmHg, meaning a dry air PO_2 of 112 mmHg, a PiO_2 of 65 mmHg, and < 60 % of the oxygen available at sea level. Calculations were shown for 5,000 and 10,000 feet because most planes, whether medical or commercial, are pressurized to approximately 8,000 feet (2438 m). In healthy individuals, this results in a small decrease in oxygen saturation to approximately 90 %. However, if a patient already has a reduced terrestrial PaO_2, then the decrease with altitude will be more significant [21]. This supplemental oxygen should be initiated before take-off, and followed in-flight with a saturation monitor.

Whichever mode of ventilation is used, it is again worth stressing that $ETCO_2$ is highly recommended. $ETCO_2$ is usually approximately 5 mmHg less than partial pressure of arterial CO_2 ($PaCO_2$). Therefore, $ETCO_2$ helps with targeted ventilation during transportation when arterial blood gas analysis is curtailed. While second nature to many, it is worth reminding inexperienced personnel that while a saturation monitor tracks oxygenation, only $ETCO_2$ approximates ventilation.

Circulation

Changes in blood pressure and heart rate are seen in almost 1-in-2 patient transports [7]. Predictably, hemodynamic disturbances occur more in those transported with cardiac pathology, poor cardiac reserve, or insufficient blood volume. The primary physiologic response to a lowered PaO_2 is chemoreceptor-induced hyperventilation, mediated by an increase in tidal volume. However, systemic hypoxia is also compensated for by increased cardiac output, mediated primarily through tachycardia. Therefore, it makes sense that altitude-related decreases in PiO_2 can decrease the ischemic-threshold in patients with exercise-induced angina. Hypoxia can also stimulate atrial arrhythmias and premature ventricular contractions [21]. Gravitational forces involved in vehicle transport (i.e., cornering, stopping, rapid acceleration and deceleration) can also exacerbate hemodynamic abnormalities either through increased sympathetic nervous system activation or vagal stimulation [4].

It is tougher to respond to hemodynamic changes in a cramped space or if the patient is tightly wrapped. Visualizing the monitor is also more difficult due to the shaking associated with either flight or road transport. It is also hard to communicate to other team members because of background noise. Patient temperature is also infrequently measured during transportation, despite evidence correlating hypothermia and worse outcome [22, 23]. Movement also increases the chance of intravenous access being lost, and reinsertion is more difficult. Monitors and infusion pumps rely upon limited battery power. Insufficient transport analgesia can also add to patient pain, anxiety and sympathetic stimulation.

It is essential to make sure that the patient has adequate venous access, and inotropes and vasopressors should be pre-mixed. Fluids should also be hanging, and blood products should have been checked. In short, a proactive plan is required in case of deterioration. Again, $ETCO_2$ is useful as it also offers a surrogate of cardiac output. For example, a large pneumothorax or a large pulmonary embolus can increase dead-space ventilation, which subsequently decreases $ETCO_2$. As such the $ETCO_2$ trend should be followed. The ultimate dead-space, namely cardiac arrest, substantially lowers $ETCO_2$. Recovery of $ETCO_2$ can guide resuscitative efforts and also prognosticate non-survival.

As outlined above, as altitude increases, Pb decreases. In accordance with Boyle's law, the volume of gas is inversely proportional to pressure. In an unpressurized plane at 30,000 ft (9144 m), gas trapped in the lung (or sinuses, or gastrointestinal tract) would expand to > 4 times its volume at sea level. Most air transports occur at lower altitude with cabins pressurized to 7,000 – 10,000 ft (2134 – 3048 m). This means that small pneumothoraces, and even blebs and bullae can expand from 30 – 40 %. Gas expansion can compress remaining lung and cause circulatory collapse (i.e., tension-pneumothorax). Therefore, the threshold to insert thoracostomy tubes prior to air transport must be low. Clinical suspicion en-route following any deterioration must also remain high. Chest tubes should never be clamped, and emergent needle decompression must be followed by tube thoracostomy [21].

Central Nervous System

In a study of 100 intra-hospital transports of brain-injured patients, 54 showed a > 5 % decrease in brain tissue partial pressure of oxygen, and longer episodes of brain tissue hypoxemia post-transport versus pre-transport [24]. Moreover, continuous intracranial pressure (ICP) monitoring is rarely available during transfer. This is all the more reason why pupillary reaction and, once again, $ETCO_2$ monitoring, should be followed. The team can also simply assume that the ICP is mildly elevated (i.e., 20 mmHg) and, therefore, aim for a mean arterial pressure (MAP) of approximately 85 mmHg. Because cerebral perfusion pressure (CPP) is MAP – ICP this approach targets a CPP of 65 mmHg. This is of course providing there is no contraindication to slightly elevated blood pressure such as penetrating trauma or an unsecured aneurysm.

The gravitational forces associated with transit may also worsen ICP. Therefore, in less time-critical transports it may be better to have slower transport with less directional forces than fast transport with high-speed cornering. External ventricular drains must be closed during any patient movement and then re-leveled with the tragus of the ear. If ICP cannot be monitored then, once the patient

is stationary, the external ventricular drain drip chamber can be placed 10 cm above the tragus, and in the open position. This permits cerebrospinal fluid (CSF) egress. If monitoring is available, then the external ventricular drain can be intermittently opened and closed (just as it would be in the ICU). This allows CSF drainage and ICP measurement, respectively.

Immobilization of the neck with a semi-rigid collar does not assure complete stabilization of the cervical-spine during transport. As a result, a long spine board is recommended along with a semi-firm collar, tapes, neck bolsters, and body straps. A transport stretcher, let alone a spine board, is harder than a standard bed. Both can cause discomfort and nerve damage. They can also cause pressure sores, especially after several hours. Therefore, it is important to periodically reassess the need for a spine board.

Transport Options

Definitive evidence regarding the most appropriate form of patient transport is lacking. [25, 26]. This may because generalizations are difficult, and the best transport is probably that which works for a particular patient, from a particular location, and at a particular time (**Table 1**). Regardless, Gray et al. [27] summa-

Table 1. Summary of the pros and cons concerning options for inter-hospital transport (United Kingdom units)

	Ground	Rotary-wing	Fixed-wing
Distance	< 50 miles	Up to 250 miles	Almost unlimited
Speed	Up to 60 mph	100 – 200 mph	> 100 mph depending on aircraft
Interior	Limited space, least noisy	Cramped space, noisy	Space depends on aircraft (small single engine up to commercial jet)
Number of patients	1	1 – 2	Multiple
Staff training	Less specialized transport training	Specialist air crew training	Specialist air crew training
Cost	Least expensive to purchase, maintain and operate (~£ 150 – 200 per transport)	Most expensive to purchase, maintain and operate (£ 10,000 – £ 20,000 per flight)	Most civilian transports are cheaper than rotary wing to maintain and operate
Limited by	Road access, traffic conditions	Weather conditions, specific landing requirements, noise can impair communication	Some weather conditions, need for a defined landing area, noise can impair communication
Effects on patients	Acceleration and deceleration forces may cause harm	Low flying so few altitude effects	Altitude effects may be of concern in unpressurized aircraft

mph: miles per hour

rized factors that influence the choice of transport; these were the apparent urgency, transport availability, geographical factors, traffic conditions, weather conditions, and cost.

Ground transportation is less expensive, offers door-to-door service, and there may be less delay in help arriving at the sending hospital. However, overall travel time may be increased due to traffic congestion. In remote areas or during inclement weather, road access can be limited. Staff (and awake patients) may also get travel-sickness. As mentioned above, there can also be adverse physiological ramifications from the gravitational forces associated with rapid road travel. As such, in non-time-critical transports, a slower smoother journey may be preferable to arriving at definite care sooner.

Air ambulances, either rotary- or fixed-wing, are employed over longer distances. However, they are more costly due to the expense of hardware, landing sites, and pilots. Personnel also require extra training because inexperience can compromise safety. As a result, many air transportation organizations employ specialist transport-teams. The advantage of fast air transport may be lost because of unavailable aircraft and longer mobilization time, and the distance of landing sites from institutions. Physicians should, therefore, know about local factors that affect the choice of rotary-wing versus fixed-wing aircraft. There are considerable variations depending upon the jurisdiction, but generally rotary-wing aircraft are considered for approximately 50–250 miles (80–400 km), and fixed wing aircraft for distances > 200 miles (> 300 km). For shorter distances, the speed advantage of air travel can be lost by the need for ground transportation at each end [25, 26].

Transport Education

Evidence suggests that transports performed by trained personnel reduce adverse events and improve patient outcome [28]. In contrast, in some jurisdictions, unsupervised and undertrained junior personnel perform transports [29, 30]. There may be a specious assumption that if individuals manage patients in a hospital then these skills will freely transfer elsewhere. However, transport is a specialized competency not well addressed by traditional curricula [9, 31].

Regular training – along with regular evaluation of transport equipment, routine audits, and efforts to learn from critical incidences – should be integral to a medical transport program. Chief amongst the required competencies are teamwork, communication, and medical decision-making. These skills are collectively known as crisis resource management (CRM). Curricula and validated evaluation-tools already exist. These competencies can be taught and assessed, and readers are encouraged to go beyond this manuscript [31–33]. Of note, CRM was co-opted from the civilian transport industry, and is therefore ideally suited to medical transportation [9].

XVII

Improving Teamwork and Communication

The impetus to improve teamwork outside of medicine coincided with the observation that the modern jet "is too much airplane for one man to fly" [31]. Similarly, the complexity of transport medicine means that it must be a viewed as a

team pursuit. Teams are more than just superiors and subordinates giving and receiving orders. One difference is that true teams possess a shared understanding of the situation, the task, and the available resources. This is also called a "shared mental model" [31, 33]. If time permits, the leader is responsible for sharing mental models. In time-critical situations leaders need to communicate a model that the team can share. In short, leaders ensure everyone is "on the same page". Otherwise the cognitive resources of the entire team cannot be fully leveraged [33].

The word 'communication' means to "share, join, unite, or make understanding common" [31]. Therefore, teamwork equates with good communication. Communication enables the team not only to establish a shared mental model, but also to coordinate tasks, to control the flow of information, to establish a structure for task-completion, and even to stabilize emotions [33]. As a result, safe critical care transportation really cannot be achieved without good communication skills.

Research shows that during crises, physicians commonly fail to communicate what they are doing, or why. For nurses, there are often lengthy delays between when a problem is first identified, and when this is shared [31]. Many practical strategies exist to close the 'communication gap'. These include SBAR (Situation-Background-Assessment-Recommendation), the read-back/hear-back technique, graded-assertiveness, and five-step advocacy [31]. Regardless of the strategy, acute care communication should include:

1. Who you are, and who you are communicating with
2. Relevant clinical details
3. How the problem is being currently addressed
4. What you require.
5. Confirmation that the request was understood
6. And confirmation that the action was completed.

The unique "verbal dexterity" [31] required during transportation should also be addressed. For example, non-transport medical communication often occurs face-to-face. This means that it includes non-verbal communication (e.g., facial expression, hand gestures) and is facilitated by visual clues (e.g., the appearance of the patient). In contrast, transport communication usually forces 'blind' communication, i.e., telephone and written communication; it also frequently occurs between relative strangers from unfamiliar locations. Therefore, the specific choice of words (i.e., verbal communication) and the tone, pitch and timing of speech (i.e., paraverbal communication) become even more important. Competence in transport communication should therefore be taught and practiced, rather than assumed. [31]

The loss of cues means it is beneficial to provide a predictable structure (or checklist) for communication. That way, both sender and receiver know what to expect and should be more likely to identify omissions. The 'sender' must learn to be unambiguous and concise. The 'receiver' must learn to demonstrate that the information is understood, or demand clarification. It is worth remembering the adage: "meant is not said; said is not heard; heard is not understood and understood is not done" [31]. Communication can breakdown anywhere along this chain, but, again, numerous strategies exist. While it is not possible to go into detail in this manuscript, readers are encouraged to explore further [31].

The stress of transportation can impair decision-making, such that some 'freeze' with indecision and others make rash choices. Using a decision-making

guideline can increase consistency [34, 35]. This creates a goal-directed structure that is useful both to control stress and to provide familiarity for team members unfamiliar with each other's style. It is also intended to improve efficiency as routine decisions can be made automatically (e.g., have we confirmed that suction is available). Using a decision-making guideline also reduces cognitive overload by freeing the brain to focus on more complex decisions (e.g., what advanced interventions will this patient require upon arrival). In short, all of these strategies are intended to make the patient safer by making the transport team work better.

Conclusion

Transportation of critically ill patients is time-consuming, resource-dependent, and potentially dangerous. It is an integral part of modern critical care medicine, and therefore needs to be 'done right'. Many national critical care programs require experience and proficiency in transportation medicine, but training is often ad-hoc. Furthermore, knowledge of, and adherence to, guidelines is insufficient. For these reasons, transportation is a substantial patient-safety concern. It is also a significant educational opportunity.

The goal of a transport curriculum is to encourage structured assessment and preparation based upon the specifics of the patient, the location, and the resources (**Table 2**). Education should also focus upon teamwork, communication, and decision-making, or what has been called 'Crisis Resource Management'. In

Table 2. Example of a standardized transport training algorithm

A	Assessment	Consideration of patient's condition and needs Rationale for transport Capabilities of transport team Who is involved
C	Control	Identify a team leader Identify tasks Allocate tasks
C	Communication	With own team With receiving center (department) With patient/relatives With ambulance control
E	Evaluation	Risk: benefit of transport Patient reassessment Urgency of transport Appropriate mode of transport
P	Preparation and packaging	Prepare patient Prepare equipment Prepare personnel
T	Transportation	Transport the patient

Based upon the "Mid Trent Critical Care Network Transfer Training Course" used with the permission of Dr A. Norton, Lead for Transfer Training

these ways, critical care medicine can show that its commitment to safe patient care goes beyond the walls of the ICU.

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References

1. Intensive Care Society (2002) Guidelines for the transport of the critically ill adult. Available at: http://www.ics.ac.uk/intensive_care_professional/standards_and_guidelines/transport_of_the_critically_ill_2002 Accessed Nov 24, 2010
2. Warren J, Fromm RE Jr, Orr RA, Rotello LC, Horst HM (2004) Guidelines for the inter- and intrahospital transport of critically ill patients. Crit Care Med 32: 256 – 262
3. Australian and New Zealand College of Anaesthetists (2003) Minimum standards for transport of critically ill patients. Emerg Med (Fremantle) 15: 202 – 204
4. Waddell G, Scott PD, Lees NW, Ledingham IM (1975) Effects of ambulance transport in critically ill patients. Br Med J 1: 386 – 389
5. Waddell G (1975) Movement of critically ill patients within hospital. Br Med J 2: 417 – 419
6. Voigt LP, Pastores SM, Raoof ND, Thaler HT, Halpern NA (2009) Review of a large clinical series: intrahospital transport of critically ill patients: outcomes, timing, and patterns. J Intensive Care Med 24: 108 – 115
7. Waydhas C (1999) Intrahospital transport of critically ill patients. Crit Care 3: R83 – 89
8. NHS Modernisation Agency (2004) The Neurosurgical Care Report. Available at: http://www.sehd.scot.nhs.uk/nationalframework/Documents/neuro/key%20docs/DOH-NeuroscienceCriticialCareReport.pdf Accessed Nov 24, 2010
9. Brindley PG (2010) Patient safety and acute care medicine: Lessons for the future, insights from the past. Crit Care 14: 217 – 222
10. Singh JM, MacDonald RD, Bronskill SE, Schull MJ (2009) Incidence and predictors of critical events during urgent air-medical transport. Can Med Assoc J 181: 579 – 584
11. Seymour CW, Kahn JM, Schwab CW, Fuchs BD (2008) Adverse events during rotary-wing transport of mechanically ventilated patients: a retrospective cohort study. Crit Care 12: R71
12. Doring BL, Kerr ME, Lovasik DA, Thayer T (1999) Factors that contribute to complications during intrahospital transport of the critically ill. J Neurosci Nurs 31: 80 – 86
13. Dryden CM, Morton NS (1995) A survey of interhospital transport of the critically ill child in the United Kingdom. Paediatr Anaesth 5: 157 – 160
14. Barry PW, Ralston C (1994) Adverse events occurring during interhospital transfer of the critically ill. Arch Dis Child 71: 8 – 11
15. Kanter RK, Boeing NM, Hannan WP, Kanter DL (1992) Excess morbidity associated with interhospital transport. Pediatrics 90: 893 – 898
16. Beckmann U, Gillies DM, Berenholtz SM, Wu AW, Pronovost P (2004) Incidents relating to the intra-hospital transfer of critically ill patients. An analysis of the reports submitted to the Australian Incident Monitoring Study in Intensive Care. Intensive Care Med 30: 1579 – 1585
17. Fan E, MacDonald RD, Adhikari NK, et al (2006) Outcomes of interfacility critical care adult patient transport: a systematic review. Crit Care 10: R6
18. Szem JW, Hydo LJ, Fischer E, Kapur S, Klemperer J, Barie PS (1995) High-risk intrahospital transport of critically ill patients: safety and outcome of the necessary "road trip". Crit Care Med 23: 1660 – 1666
19. Waydhas C, Schneck G, Duswald KH (1995) Deterioration of respiratory function after intra-hospital transport of critically ill surgical patients. Intensive Care Med 21: 784 – 789
20. Bercault N, Wolf M, Runge I, Fleury JC, Boulain T (2005) Intrahospital transport of critically ill ventilated patients: a risk factor for ventilator-associated pneumonia-a matched cohort study. Crit Care Med 33: 2471 – 2478
21. Essebag V, Halabi AR, Churchill-Smith M, Lutchmedial S (2003) Air medical transport of cardiac patients. Chest 124: 1937 – 1945

22. Wang HE, Callaway CW, Peitzman AB, Tisherman SA (2005) Admission hypothermia and outcome after major trauma, Crit Care Med 33: 1296 – 1301
23. Lenhardt R, Marker E, Goll V, et al (1997) Mild intraoperative hypothermia prolongs postanesthetic recovery, Anesthesiology 87: 1318 – 1323
24. Swanson EW, Mascitelli J, Stiefel M, et al (2010) Patient transport and brain oxygen in comatose patients. Neurosurgery 66: 925 – 931
25. Svenson JE, O'Connor JE, Lindsay MB (2006) Is air transport faster? A comparison of air versus ground transport times for interfacility transfers in a regional referral system Air Med J 25: 170 – 172
26. Diaz MA, Hendey GW, Bivins HG (2005) When is the helicopter faster? A comparison of helicopter and ground ambulance transport times. J Trauma 58: 148 – 153
27. Gray A, Bush S, Whiteley S (2004) Secondary transport of the critically ill and injured adult. Emerg Med J 21: 281 – 285
28. Bellingan G, Olivier T, Batson S, Webb A (2000) Comparison of a specialist retrieval team with current United Kingdom practice for the transport of critically ill patients, Intensive Care Med 26: 740 – 744
29. Hallas P, Folkestad L, Brabrand M (2009) Level of training and experience in physicians performing interhospital transfers of adult patients in the internal medicine department. Emerg Med J 26: 743 – 744
30. Cook C, Allan C (2008) Are trainees equipped to transfer critically ill patients? Journal of the Intensive Care Society 9: 145 – 147
31. Brindley PG, Reynolds SF (2010) Improving verbal communication in critical care medicine. J Crit Care (in press)
32. Gaba DM, Fish KJ, Howard SK (1994) Crisis Management in Anesthesiology. Churchill Livingstone, New York
33. St Pierre M, Hofinger G, Buerschaper C (2008) Crisis Management in Acute Care Settings: Human Factors and Team Psychology in a High Stakes Environment. Springer, New York
34. van Lieshout EJ, de Vos R, Binnekade JM, de Haan R, Schultz MJ, Vroom MB (2008) Decision making in interhospital transport of critically ill patients: national questionnaire survey among critical care physicians. Intensive Care Med 34: 1269 – 1273
35. Esmail R, Banack D, Cummings C, et al (2006) Is your patient ready for transport? Developing an ICU patient transport decision scorecard. Healthc Q 9: 80 – 86

Should We Still Order Chest X-rays in the ICU?

V. Ioos, A. Galbois, and B. Guidet

Introduction

Among the investigations performed daily in the intensive care unit (ICU), bedside chest x-rays (CXRs) are trivialized. However, they are a source of discomfort and irradiation for the patients, and carry a potential risk of accidental removal of devices (catheters, tubes) and microbial dissemination, all resulting in additional cost for the community. It is, therefore, essential to assess current practices in order to establish recommendations for prescription of CXRs and to determine whether it is possible to reduce the number of CXRs performed during an ICU stay without impairing quality of care. We will discuss alternatives to CXRs in specific situations (such as placement of feeding tubes and central venous lines). We will also consider bedside CXR prescription strategies, without considering medico-economic aspects such as the possible savings resulting from a reduction in the number of CXRs performed in the ICU. Indeed, the real cost of performing a bedside CXR is unknown because it integrates multiple parameters, such as cost of consumables, depreciation of equipment, working time of the x-ray technician and logistical costs.

Heterogeneity of Prescription Practices

In a preliminary, retrospective study (unpublished data), we compared the number of CXRs ordered in 19 medical ICUs of the Assistance Publique–Hôpitaux de Paris (APHP) group of hospitals during the year 2004. Two databases were used: RADOS, which collects the records of all medical imaging investigations (including bedside CXRs) performed in each hospital, and the medico-administrative database (Disease Related Groups database, DRG), which describes hospital stays in terms of length of stay, dates of admission and discharge, and diagnosis using the ICD-10. The RADOS and DRG databases were matched and each bedside CXR performed in the ICU was retrieved.

Differences among the ICUs were measured through direct standardization. The ratio comparing the number of bedside CXRs per day and per ICU stay in a given ICU to the mean number of bedside CXRs in all the 19 ICUs was called the "Radiology Performance Index" (RPI). We adjusted this RPI for several variables including case-mix, mechanical ventilation and ICU length of stay. The main characteristics of the 8975 analyzed ICU stays were: Mean length of stay 6.6 days (95 % confidence interval [CI] 3.9 – 12.8); percentage of mechanically ventilated patients 51.4 % (95 % CI 30.9 – 66.9) of the ICU stays; mean number of bedside

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CXRs performed per day 1.1 (95 % CI 0.4 – 2). The distribution of RPI showed great variability in the number of CXR prescriptions. There was still considerable heterogeneity after adjustment for case-mix (0.31 to 1.54), mechanical ventilation (0.31 to 1.53) and length of stay (0.41 to 1.58). One explanation for these variations could have been differences in indications according to medical teams and patient diagnoses. To explore this possibility, we designed a study to interview senior ICU physicians on their opinion about whether a systematic CXR should be ordered in a set of usual ICU clinical situations.

Searching for a Consensus on Indications for CXRs in ICUs

Indications for ordering CXRs in ICUs have been poorly studied in a systematic way. Research has mainly focused on prescribing strategies (routine versus on-demand) [1 – 8], rather than the precise clinical context, excluding invasive procedures [9 – 11] which are easier to study.

Taking into account the heterogeneity of the constraints of each hospital in terms of logistics (human resources, physical structure of the hospital, technology of equipments) and practices (prescription habits), we asked ICU physicians of the Cub-Réa network (34 medical, surgical or mixed ICUs in teaching and non-teaching hospitals in the Paris area) to participate in a search for a consensus about indications for CXR prescription using the Delphi method [12]. We used a structured questionnaire to which 95 ICU physicians (rate of answer = 50 %) agreed to answer (82 completed the full study). Their opinion on the systematic prescription of CXRs in various clinical scenarios was collected during iterative sequences of interrogation using a dedicated Web application. The questionnaire included 29 questions relative to the placement of medical devices and their surveillance, as well as various clinical situations (**Table 1**). During each round of interrogation, the respondent was asked to answer each item using a 9-point scale, in which 1 point indicated that routine CXR was considered to be always unnecessary and 9 points indicated that routine CXR was considered to be always necessary. Each doctor received detailed feedback of the answers (of all the participants) from the previous phase and could change his/her opinion in later rounds. The process of interrogation was interrupted when there was a stability in the answers. The distributions of answers observed for each question were analyzed in terms of convergence of opinion and strength of the consensus obtained.

We observed a strong consensus – that is a low variability in the answers – for 10 questions which represented widely accepted reasonable attitudes (**Table 2**). However, concerning whether or not to perform daily routine CXRs in patients on mechanical ventilation, a consensus was not reached. In certain very specific clinical situations (acute asthma, acute respiratory distress syndrome [ARDS]), systematic daily prescription was widely recommended, while in others (neurological or toxic coma with healthy lungs, for example) the answers of the doctors did not converge. These results demonstrate the importance of the clinical context in the decision of prescription and the difficulty in making general recommendations that do not take into account the heterogeneity of the clinical scenarios.

Table 1. Item wording of the Delphi survey [12]

item	Question
01*	After an intubation?
02*	After tracheotomy?
03*	After placement of a sub-clavian central venous catheter?
04*	After placement of an internal jugular central venous catheter?
05*	After placement of a pulmonary artery catheter?
06*	After placement of temporary transvenous pacing leads?
07*	After placement of a nasogastric tube for enteral nutrition?
08*	After placement of a nasogastric tube (for another reason than enteral nutrition), through which gastric secretions could be aspirated?
09*	After placement of a ballasted nasogastric tube (risk of pneumothorax)?
10*	After placement of a chest tube?
11#	Presence of an endotracheal tube?
12#	Non-invasive ventilation with $PaO_2/FiO_2 < 220$ mmHg?
13#	Non-invasive ventilation with $PaO_2/FiO_2 > 220$ mmHg?
14#	Presence of a nasogastric tube?
15#	Pulmonary artery catheter?
16#	Presence of a catheter in the superior vena cava system?
17#	Presence of a chest tube?
18#	Presence of temporary transvenous pacing leads?
19#	Invasive mechanical ventilation for ARDS?
20#	Invasive mechanical ventilation for hemodynamic pulmonary edema (cardiogenic, kidney failure)?
21#	Non-invasive ventilation for hemodynamic pulmonary edema (cardiogenic, kidney failure)?
22#	Hemodynamic instability in a patient under invasive mechanical ventilation?
23#	Invasive mechanical ventilation for status asthmaticus?
24#	Invasive mechanical ventilation for acute respiratory failure in a severely immunocompromised patient?
25#	Non-invasive ventilation for acute respiratory failure in a severely immunocompromised patient?
26#	Invasive mechanical ventilation for acute-on-chronic respiratory failure?
27#	Non-invasive ventilation for acute-on-chronic respiratory?
28#	Invasive mechanical ventilation for neurologic or toxic coma with normal respiratory function?
29	Is it justified to systematically realize a CXR before extubation?

* item began with "Should a routine CXR be obtained (within 1h) ....."
\# item began with "Should a routine CXR be obtained daily for ...."

Reduction in the Number of CXRs Ordered in Patients on Mechanical Ventilation

The American College of Radiology recommends routine daily CXRs for mechanically ventilated patients, and use of additional CXRs if necessary [13]. This strategy is, however, controversial [1, 6, 7, 12, 14, 15]: Some clinicians support it, whereas others advocate on-demand prescription of CXRs only when warranted by the patient's clinical status. Our Delphi study revealed that the recommendations for ordering CXRs in the ICU were not followed and that indications for prescription varied from one department to another, in particular for ICU patients on mechanical ventilation.

Routine CXR has two main advantages. First, some potentially life-threatening situations that might otherwise be missed can be discovered and treated. Second,

Table 2. Description of the 80 % central answers (n = 66) of the Delphi survey (the 10 % of the answers located at each end of the range were eliminated) for the situations listed in **Table 1** [12]

Question	Summary of answers				Indication for systematic prescription of radiography	Strength of the consensus
	mean	median	min	max		
1	8.64	9	7	9	YES	HIGH
2	7.64	8	5	9	YES	MODERATE
3	8.97	9	8	9	YES	HIGH
4	8.67	9	8	9	YES	HIGH
5	8.91	9	8	9	YES	HIGH
6	8.65	9	7	9	YES	HIGH
7	6.65	6	3	9	UNCERTAINTY	LOW
8	3.02	3	1	5	NO	MODERATE
9	8.05	8	5	9	YES	MODERATE
10	8.95	9	8	9	YES	HIGH
11	5.33	5	2	8	UNCERTAINTY	LOW
12	7.26	7	5	9	YES	MODERATE
13	4.82	5	3	7	UNCERTAINTY	MODERATE
14	1.79	2	1	3	NO	HIGH
15	6.36	6	3	9	UNCERTAINTY	LOW
16	1.53	2	1	2	NO	HIGH
17	6.65	7	4	9	YES	MODERATE
18	4.79	5	2	7	YES	MODERATE
19	8.73	9	8	9	YES	HIGH
20	7.38	7	5	9	YES	MODERATE
21	6.30	6	4	8	YES	MODERATE
22	8.14	8	6	9	YES	MODERATE
23	8.83	9	8	9	YES	HIGH
24	8.42	9	6	9	YES	MODERATE
25	7.74	8	6	9	YES	MODERATE
26	6.09	6	3	9	YES	LOW
27	4.80	5	2	7	UNCERTAINTY	MODERATE
28	4.77	5	2	9	UNCERTAINTY	LOW
29	2.67	3	1	6	NO	MODERATE

scheduling CXRs during morning rounds might be more efficient from a logistical point of view. In contrast, the on-demand strategy might avoid unnecessary radiation exposure and provides substantial cost savings [16] but an increased number of CXRs may be needed during the rest of the day to compensate for those not done in the morning.

In a randomized study, patients managed with an on-demand strategy had fewer CXRs during the ICU stay (4.4 vs 6.8) [6]. Compared with routine imaging, on-demand CXRs had more images with new findings (53 % vs 33 %) and with new findings requiring intervention (27 % vs 13 %). Another prospective controlled study showed that abandoning the routine strategy decreased the volume of CXRs ordered by 35 % [3]. Routine CXRs identified new or progressive major findings in only 4.4 % and changed management in only 1.9 %. In a single center randomized study, delayed diagnoses occurred in only 0.7 % of the on-demand group and all findings were minor [1]. In another study, after an on-demand strategy was implemented, the number of CXRs per patient-day decreased from 1.1 to 0.6 [4]. None of these studies identified complications associated with the

on-demand approach, such as increased duration of mechanical ventilation, length of stay, or mortality [1, 3, 4, 6]. Finally, a meta-analysis selected eight studies comparing on demand and daily routine strategies, including a total of 7078 patients [17]. In a pooled analysis, no difference in ICU mortality, ICU length of stay or duration of mechanical ventilation was found between the on-demand and daily routine groups. However, this meta-analysis included only two small size randomized controlled trials, both single center studies. No study has, therefore, had sufficient power to totally convince ICU physicians to abandon daily routine CXRs.

In the RARE study [18], we evaluated two strategies for prescribing morning CXRs in ICU patients on mechanical ventilation using a cluster-randomized, open-label crossover design. In the 'routine strategy', CXRs were performed daily in patients on mechanical ventilation, irrespective of their clinical status. In the 'on-demand strategy', CXRs were performed in the morning if warranted by the clinical examination and the analysis of biological parameters. We randomly assigned 21 ICUs (medical, surgical or medico-surgical) in 18 hospitals (teaching and non-teaching) to use the 'routine' or 'on-demand' strategy during the first of two treatment periods. ICUs used the alternative strategy in the second period. The primary outcome measure was the mean number of CXRs per patient-day of mechanical ventilation. Secondary outcome measures where related to the quality and safety of care (days of mechanical ventilation, ICU length of stay and ICU mortality, number of unscheduled CXRs performed) as well as diagnostic and therapeutic value of the CXRs performed within each strategy. Finally, disturbances in the organization of the ICU and medical imaging departments were also analyzed.

During the study period, 424 patients had 4607 routine CXRs (mean per patient-day of mechanical ventilation 1.09, 95 % CI 1.05 – 1.14), and 425 had 3148 on-demand chest radiographs (mean 0.75, 95 % CI 0.67 – 0.83), which corresponded to a reduction of 32 % (95 % CI 25 – 38) with the on-demand strategy ($p < 0.0001$). Duration of mechanical ventilation as well as ICU length of stay and 28-day mortality did not differ between the groups (**Table 3**). The difference in the total number of routine and on-demand chest radiographs was not significant

Table 3. Numbers of CXRs, length of stay, duration of mechanical ventilation, and mortality rates in the RARE study [18]

	Strategy of CXR prescription	
	Routine (424 patients)	On-demand (425 patients)
CXRs performed		
Total number	4607	3148
With new finding	688	618
With new finding leading to therapeutic intervention		
Mean number per patient and per day	728 1.11	729 0.77
Length of mechanical ventilation (days)		
Total number of days	4172	4226
LOS: mean, median [5th and 95th percentile]	9.82, 7 [2;30]	9.94, 7 [2;30]
Mortality in ICU (dead/alive, %)	131/293, 30.9 %	136/289, 32.0 %

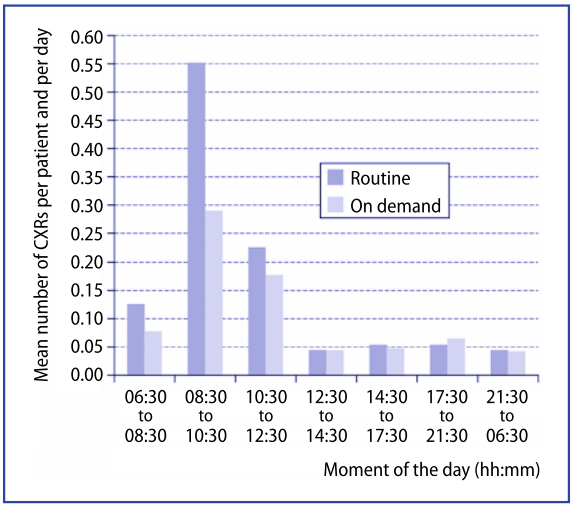

Fig. 1. Distribution of the CXRs performed during the day in the RARE study [18]. The morning reduction in the number of CXRs was not compensated for by a concomitant increase in CXRs ordered during the rest of the day.

when the analysis was restricted to CXRs with new findings that led or contributed to diagnostic procedures or therapeutic interventions. Finally, there was no increase in the number of unscheduled CXRs performed in the afternoon and in the night in the on-demand strategy, and, therefore, no disruption in the organization of the medical imaging department (**Fig. 1**).

This study strongly suggests that routine daily CXRs in the ICU patient on mechanical ventilation should be abandoned [19]. This restrictive strategy is in line with previous studies that had some methodological flaws [17]. The main limit to its broad application lies in the fact that French ICUs are closed units and the results may not be applicable to open ICUs, an organizational model which is found in other countries [20].

Alternatives to CXR

Alternatives to CXR to Ensure Correct Placement of Enteral Feeding Tube

Accidental placement of the enteral feeding tube in the tracheobronchial tract can lead to potentially lethal complications. Tracheal intubation does not always prevent this misplacement [21]. Ensuring correct enteral feeding tube position is therefore of paramount importance for patients in ICU. Confirmation of the adequate placement of an enteral feeding tube by epigastric auscultation after air injection through the feeding tube is not a reliable test when used alone [22–24]. Some studies have suggested testing the pH of an aspirate obtained from the enteral feeding tube to ensure proper placement, but this test can be inconclusive in patients with small bore feeding tubes or in those receiving acid suppression therapies [22]. Therefore, most of the guidelines recommend confirmation of enteral feeding tube placement by CXR before starting enteral nutrition [24, 25]. We studied two interesting alternatives to CXR.

Bedside ultrasonography is a non-invasive procedure that is increasingly used in the ICU by non-radiologist physicians who can obtain reliable results after a short period of training [26, 27]. Using a probe of 2 to 5 MHz, we showed that

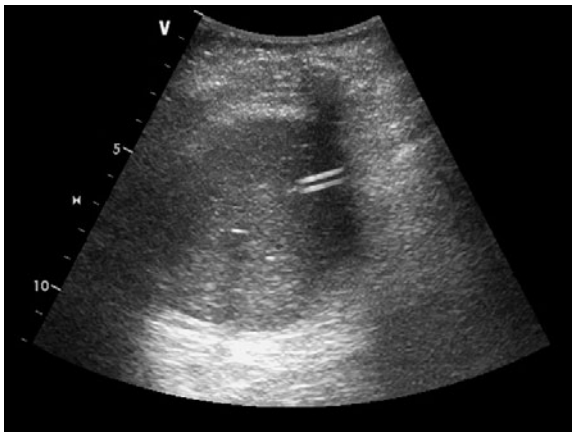

Fig. 2. Assessment of intragastric position of a small bore enteral feeding tube by ultrasonography. The probe is placed in the middle epigastric area and oriented towards the left upper abdominal quadrant to visualize the gastric area. The small bore feeding tube appears as two parallel hyperechogenic lines.

ultrasonography enables small-bore enteral feeding tubes to be visualized in the digestive tract with a sensitivity of 97 % and to assess whether it is properly placed in the stomach within 5 minutes (**Fig. 2**) [28]. If the enteral feeding tube is not immediately visible by ultrasound, injection of 5 ml normal saline mixed with 5 ml air into the tube increases the sensitivity. This technique is more rapid than conventional radiography, is radiation free, and can be taught to ICU physicians during a short training period [28]. Radiography could then be performed only in the rare cases of ultrasonography failure, due to gas interposition, for example.

Capnography is often used to assess expiratory CO_2. However, it is possible to connect the capnography device to the enteral feeding tube via the tip of an endotracheal tube and to assess the correct placement of the enteral feeding tube by the absence of CO_2. The feeding tube must be inserted to a depth of 30 cm from the nostril and should not get coiled in the pharynx. When the enteral feeding tube is accidentally inserted in the respiratory tract, the capnograph displays a normal capnogram. When the enteral feeding tube is inserted in the esophagus, the capnograph displays a "purging warning" [29]. It has to be noted that enteral feeding tube permeability is essential for CO_2 detection. In our ICU, we ensure this permeability by removing the guidewire, insufflating then exsufflating with air using a 50 ml syringe, before connecting the capnography device. We use a colorimetric capnography device after 30 cm insertion and then we complete the insertion until 50 cm from the nostril. Finally, in order to check that the enteral feeding tube is not coiled in the esophagus after its complete insertion, nurses perform epigastric auscultation. Radiography is required only in cases of inconclusive epigastric auscultation (10.1 % of cases). We showed that this local protocol combining colorimetric capnography and epigastric auscultation had perfect specificity for confirming enteral feeding tube placement in stomach, improved nurse organization of care, saved time, and decreased costs [30, 31]. Another advantage of this procedure is that accidental tracheobronchial insertion is detected after 30 cm insertion, which prevents any risk of pneumothorax or hydrothorax, which are rare but potentially fatal complications of feeding tube misplacement that are detected but not prevented by post-procedural radiography.

Alternative to CXR to Diagnose and Monitor Pneumothorax

Chest computed tomography (CT-scan) is the gold standard for diagnosing pneumothorax. Conversely, CXRs miss 30 % to 72 % of pneumothoraces due to their anterior location [32], of which half can be tension pneumothoraces. Pleural ultrasonography has greater sensitivity than CXR for pneumothorax diagnosis in patients in ICUs [33] or trauma centers [32, 34] and after pleural biopsy [35, 36]. Lichtenstein et al. reported that ultrasonography detected all pneumothoraces in ICU patients, including those not identified by CXR [33]. Ultrasound diagnosis of pneumothorax relies on three signs: Abolition of lung sliding, the A-line sign, and the lung point. The sensitivity and specificity of the abolition of lung sliding for the diagnosis of pneumothorax are 100 % and 91 % respectively (**Figs. 3–5**) [37]. The presence of horizontal linear artefacts at regular intervals below the pleural line (A-lines) is part of the ultrasound semiology of normal lungs and pneumothoraces (**Fig. 3**). In contrast, vertical linear artefacts arising from the pleural line, i.e., B-lines or comet-tail artefacts, are observed when alveolar-interstitial syndrome is present, as well as in the last two intercostal spaces in 27 % of healthy subjects (**Fig. 6**) [38]. The A-line sign is defined as the presence of A-lines without B-lines (**Fig. 3**) and has a sensitivity of 100 % and a specificity of 60 % for the diagnosis of pneumothorax. The presence of B-lines rules out a diagnosis of pneumothorax [39]. The lung point is detected while the probe is stationary: There is lung sliding during inspiration (when the lung contacts the wall), which disappears during expiration (when the lung is not in contact with the wall). The sensitivity of this sign for diagnosis of pneumothorax is 66 % while its specificity is 100 % [40]. After drainage, ultrasonography is better than CXR for detecting residual pneumothoraces, with 39 % not identified by CXR [27]. After drainage of primary spontaneous pneumothoraces, performance of ultrasonography is excellent [27]. After drainage of non-primary spontaneous pneumothorax, the predictive positive value of ultrasonography was 100 % if a lung point was present. However, it decreased to 90 % in the absence of a lung point. Many factors have been reported to be responsible for lung sliding abolition, including atelectasis, ARDS, selective intubation, and pleural symphysis, among others [37, 38, 41].

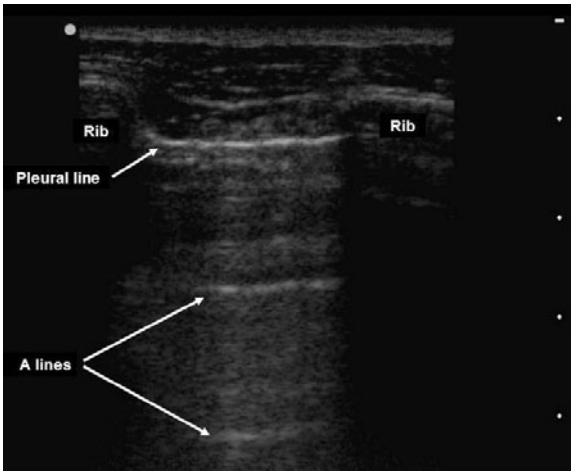

Fig. 3. Pleural ultrasonography in two-dimensional mode. The pleural line is seen between two ribs. Lung sliding is abolished when both the parietal and visceral pleura do not slide while the patient is breathing. The A-line sign is the presence of linear horizontal artefacts at regular intervals below the pleural line (A-lines) without B-lines. The A-line sign is part of the ultrasound semiology of the normal lung and of pneumothorax. From [27] with permission

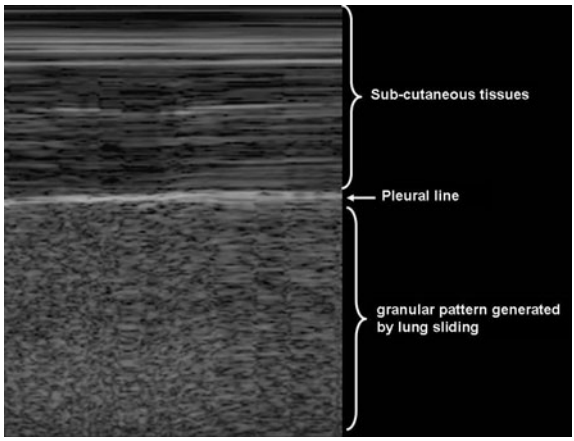

Fig. 4. Assessment of lung sliding on pleural ultrasonography in time-motion mode in a patient without pneumothorax. Lung sliding generates a granular pattern under the pleural line. Subcutaneous tissue over the pleural line does not move while the patient is breathing, generating horizontal lines. From [27] with permission

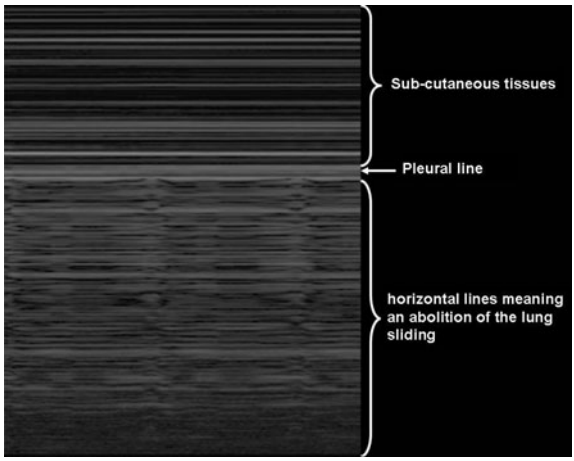

Fig. 5. Detection of abolition of lung sliding on pleural ultrasonography in time-motion mode in a patient with pneumothorax. While the patient is breathing, the (normal) granular pattern under the pleural line is replaced by horizontal lines, indicating abolition of lung sliding. From [27] with permission

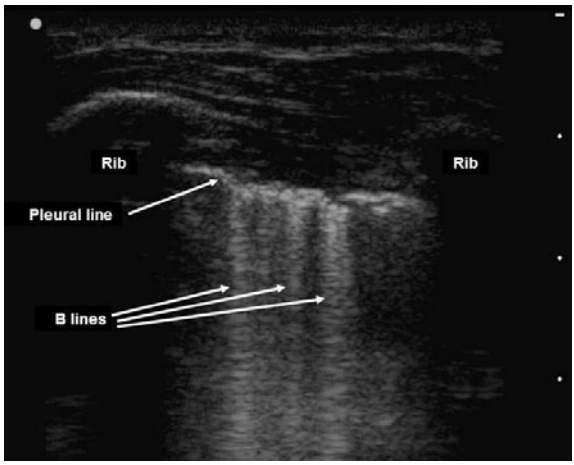

Fig. 6. Detection of B-lines on pleural ultrasonography in two-dimensional mode. The presence of vertical linear artefacts arising from the pleural line (B-lines or comet-tail artefacts) rules out pneumothorax in this patient with interstitial syndrome. From [27] with permission

Exclusive use of ultrasonography for follow-up of non-primary spontaneous pneumothorax seems possible, but the physician must be aware that in the absence of a lung point, a diagnosis of pneumothorax should not be made if other causes of lung sliding abolition have not been ruled out. We recommend performing a CT-scan if doubt persists, especially if new chest tube insertion is being considered.

These excellent performances make pleural ultrasonography more than an alternative to CXR and it should be considered as the 'bedside gold-standard' to diagnose and monitor pneumothorax. Moreover, ultrasonography gives faster results than CXR and can be performed competently by naïve physicians after a brief training session [27, 42].

Alternative to CXR after Central Venous Catheter (CVC) Insertion

Radiography is usually performed after CVC insertion in the superior vena caval system to assess the correct placement of the CVC tip and to ensure the absence of pneumothorax. CVC tip misplacement occurs in 5–6 % of cases after catheterization of the subclavian or internal jugular vein, and pneumothorax occurs in 1.5–3.1 % and 0.1–0.2 %, respectively [43].

Clinical evaluation of the patient to predict the absence of complications after CVC insertion via the subclavian vein or internal jugular vein was very accurate in a study by Gray et al. [44]. However, Gladwin et al. showed that the clinical impression of the operator (based on the number of needle passes, difficulty establishing access, operator experience, poor anatomical landmarks, number of previous catheter placements, resistance to wire or catheter advancement, resistance to aspiration of blood or flushing of the catheter ports, sensations in the ear, chest, or arm, and development of signs or symptoms suggestive of pneumothorax) had poor sensitivity and specificity for predicting a complication (44 % and 55 %, respectively) [45]. Gladwin and colleagues concluded that post-procedural CXR remains necessary because clinical factors alone cannot reliably identify tip misplacement.

However, as detailed above, numerous pneumothoraces can be missed by bedside CXR whereas ultrasonography showed excellent sensitivity and specificity for the diagnosis of pneumothorax within a few minutes. We compared post-procedural ultrasonography to CXR after insertion of 85 central venous catheters (70 subclavian and 15 internal jugular) [46]. Ten misplacements and one pneumothorax occurred. Ultrasonic examination feasibility was 99.6 %. The only pneumothorax and all misplacements except one were diagnosed by ultrasound. Taking into consideration signs of misplacement and pneumothorax, ultrasonic examination did not give any false positive results. Moreover, ultrasound guidance increased the success rate of CVC insertion, saved time and decreased the complication rate [47]. Considering these results, it seems logical to use the same ultrasonographic device to assess both the adequate position of the CVC and the absence of pneumothorax after the procedure. The only limit of ultrasonography in this indication is the lack of visualization of the azygos, internal thoracic and cardiophrenic veins and an inconstant visualization of the superior vena cava. Thus, it may be proposed that the absence of misplacement and pneumothorax could be assessed using ultrasonography and CXR limited to patients in whom ultrasonographic analysis is incomplete.

Conclusion

We have convincingly showed that bedside CXR could be avoided in most circumstances. This is true for mechanically ventilated patients and to insure proper placement of devices, such as feeding tubes and central venous catheters. This new restrictive policy for ordering bedside CXRs implies that the patient's clinical status is assessed at least once a day before ordering a CXR; CXRs should never replace clinical evaluation of the patient but should rather be prescribed on the basis of a clinical suspicion. As a consequence, ICU organization may have to be modified in order to allow implementation of such a prescribing strategy and a reduction in the number of CXRs ordered.

Ultrasonography is a very good alternative to CXR. For example, ultrasonography is more accurate than CXR for detecting pneumothorax. However, short training courses must be organized in order to achieve a basic level of competency for every physician working in the ICU.

A policy of reducing the number of CXRs has many advantages (patient comfort, better organization of the radiology department, cost reduction) and should be widely implemented in the ICU.

References

1. Clec'h C, Simon P, Hamdi A, et al (2008) Are daily routine chest radiographs useful in critically ill, mechanically ventilated patients? A randomized study. Intensive Care Med.34: 264 – 270
2. Kappert U, Stehr SN, Matschke K (2008) Effect of eliminating daily routine chest radiographs on on-demand radiograph practice in post-cardiothoracic surgery patients. J Thorac Cardiovasc Surg 135: 467 – 468
3. Hendrikse KA, Gratama JW, Hove W, Rommes JH, Schultz MJ, Spronk PE (2007) Low value of routine chest radiographs in a mixed medical-surgical ICU. Chest 132: 823 – 828
4. Graat ME, Kroner A, Spronk PE, et al (2007) Elimination of daily routine chest radiographs in a mixed medical-surgical intensive care unit. Intensive Care Med 33: 639 – 644
5. Bhagwanjee S, Muckart DJ (1996) Routine daily chest radiography is not indicated for ventilated patients in a surgical ICU. Intensive Care Med 22: 1335 – 1338
6. Krivopal M, Shlobin OA, Schwartzstein RM (2003) Utility of daily routine portable chest radiographs in mechanically ventilated patients in the medical ICU. Chest 123: 1607 – 1614
7. Silverstein DS, Livingston DH, Elcavage J, Kovar L, Kelly KM (1993) The utility of routine daily chest radiography in the surgical intensive care unit. J Trauma 35: 643 – 646
8. Hall JB, White SR, Karrison T (1991) Efficacy of daily routine chest radiographs in intubated, mechanically ventilated patients. Crit Care Med 19: 689 – 693
9. Rao PS, Abid Q, Khan KJ, et al (1997) Evaluation of routine postoperative chest X-rays in the management of the cardiac surgical patient. Eur J Cardiothorac Surg 12: 724 – 729
10. Houghton D, Cohn S, Schell V, Cohn K, Varon A (2002) Routine daily chest radiography in patients with pulmonary artery catheters. Am J Crit Care 11: 261 – 265
11. Haddad SH, Aldawood AS, Arabi YM (2007) The diagnostic yield and clinical impact of a chest X-ray after percutaneous dilatational tracheostomy: a prospective cohort study. Anaesth Intensive Care 35: 393 – 397
12. Hejblum G, Ioos V, Vibert JF, et al (2008) A web-based Delphi study on the indications of chest radiographs for patients in ICUs. Chest 133: 1107 – 1112
13. American College of Radiology (2006) Appropriateness criteria: routine chest radiograph. Available at: http://www.acr.org/SecondaryMainMenuCategories/quality_safety/app_criteria/pdf/ExpertPanelonThoracicImaging/RoutineChestRadiographDoc7.aspx, accessed Oct 11, 2010
14. Graat ME, Hendrikse KA, Spronk PE, Korevaar JC, Stoker J, Schultz MJ (2006) Chest radi-

ography practice in critically ill patients: a postal survey in the Netherlands. BMC Med Imaging 6: 8
15. Graat ME, Stoker J, Vroom MB, Schultz MJ (2005) Can we abandon daily routine chest radiography in intensive care patients? J Intensive Care Med 20: 238 – 246
16. Price MB, Grant MJ, Welkie K (1999) Financial impact of elimination of routine chest radiographs in a pediatric intensive care unit. Crit Care Med 27: 1588 – 1593
17. Oba Y, Zaza T (2010) Abandoning daily routine chest radiography in the intensive care unit: meta-analysis. Radiology 255: 386 – 395
18. Hejblum G, Chalumeau-Lemoine L, Ioos V, et al (2009) Comparison of routine and on-demand prescription of chest radiographs in mechanically ventilated adults: a multicentre, cluster-randomised, two-period crossover study. Lancet 374: 1687 – 1693
19. Hejblum G, Guidet B (2010) Evidence-based data for abandoning unselective daily chest radiographs in Intensive Care Units. Radiology 256: 1013 – 1014
20. Siegel MD, Rubinowitz AN (2009) Routine daily vs on-demand chest radiographs in intensive care. Lancet 374: 1656 – 1658
21. Woodall BH, Winfield DF, Bisset GS 3rd (1987) Inadvertent tracheobronchial placement of feeding tubes. Radiology 165: 727 – 729
22. Kunis K (2007) Confirmation of nasogastric tube placement. Am J Crit Care 16: 19
23. Stroud M, Duncan H, Nightingale J (2003) Guidelines for enteral feeding in adult hospital patients. Gut 52 Suppl 7: vii1-vii12
24. Metheny NA (2006) Preventing respiratory complications of tube feedings: evidence-based practice. Am J Crit Care 15: 360 – 369
25. Jolliet P, Pichard C, Biolo G, et al (1998) Enteral nutrition in intensive care patients: a practical approach. Working Group on Nutrition and Metabolism, ESICM. European Society of Intensive Care Medicine. Intensive Care Med 24: 848 – 859
26. Chalumeau-Lemoine L, Baudel JL, Das V, et al (2009) Results of short-term training of naive physicians in focused general ultrasonography in an intensive-care unit. Intensive Care Med 35: 1767 – 1771
27. Galbois A, Ait-Oufella H, Baudel JL, et al (2010) Pleural ultrasound compared with chest radiographic detection of pneumothorax resolution after drainage. Chest 138: 648 – 655
28. Vigneau C, Baudel JL, Guidet B, Offenstadt G, Maury E (2005) Sonography as an alternative to radiography for nasogastric feeding tube location. Intensive Care Med 31: 1570 – 1572
29. Burns SM, Carpenter R, Truwit JD (2001) Report on the development of a procedure to prevent placement of feeding tubes into the lungs using end-tidal CO2 measurements. Crit Care Med 29: 936 – 939
30. Meyer P, Henry M, Maury E, Baudel JL, Guidet B, Offenstadt G (2009) Colorimetric capnography to ensure correct nasogastric tube position. J Crit Care 24: 231 – 235
31. Galbois A, Vitry P, Ait-Oufella H, et al (2011) Colorimetric capnography, a new procedure to ensure correct feeding tube placement in the intensive care unit: An evaluation of a local protocol. J Crit Care (in press)
32. Soldati G, Testa A, Pignataro G, et al (2006) The ultrasonographic deep sulcus sign in traumatic pneumothorax. Ultrasound Med Biol 32: 1157 – 1163
33. Lichtenstein DA, Meziere G, Lascols N, et al (2005) Ultrasound diagnosis of occult pneumothorax. Crit Care Med 33: 1231 – 1238
34. Soldati G, Testa A, Sher S, Pignataro G, La Sala M, Silveri NG (2008) Occult traumatic pneumothorax: diagnostic accuracy of lung ultrasonography in the emergency department. Chest 133: 204 – 211
35. Chung MJ, Goo JM, Im JG, Cho JM, Cho SB, Kim SJ (2005) Value of high-resolution ultrasound in detecting a pneumothorax. Eur Radiol 15: 930 – 935
36. Sartori S, Tombesi P, Trevisani L, Nielsen I, Tassinari D, Abbasciano V (2007) Accuracy of transthoracic sonography in detection of pneumothorax after sonographically guided lung biopsy: prospective comparison with chest radiography. AJR Am J Roentgenol 188: 37 – 41
37. Lichtenstein DA, Menu Y (1995) A bedside ultrasound sign ruling out pneumothorax in the critically ill. Lung sliding. Chest 108: 1345 – 1348
38. Lichtenstein D, Meziere G, Biderman P, Gepner A, Barre O (1997) The comet-tail artifact.

An ultrasound sign of alveolar-interstitial syndrome. Am J Respir Crit Care Med 156: 1640 – 1646
39. Lichtenstein D, Meziere G, Biderman P, Gepner A (1999) The comet-tail artifact: an ultrasound sign ruling out pneumothorax. Intensive Care Med 25: 383 – 388
40. Lichtenstein D, Meziere G, Biderman P, Gepner A (2000) The "lung point": an ultrasound sign specific to pneumothorax. Intensive Care Med 26: 1434 – 1440
41. Blaivas M, Tsung JW (2008) Point-of-care sonographic detection of left endobronchial main stem intubation and obstruction versus endotracheal intubation. J Ultrasound Med 27: 785 – 789
42. Noble VE, Lamhaut L, Capp R, et al (2009) Evaluation of a thoracic ultrasound training module for the detection of pneumothorax and pulmonary edema by prehospital physician care providers. BMC Med Educ 9: 3
43. McGee WT, Ackerman BL, Rouben LR, Prasad VM, Bandi V, Mallory DL (1993) Accurate placement of central venous catheters: a prospective, randomized, multicenter trial. Crit Care Med 21: 1118 – 1123
44. Gray P, Sullivan G, Ostryzniuk P, McEwen TA, Rigby M, Roberts DE (1992) Value of postprocedural chest radiographs in the adult intensive care unit. Crit Care Med 20: 1513 – 1518
45. Gladwin MT, Slonim A, Landucci DL, Gutierrez DC, Cunnion RE (1999) Cannulation of the internal jugular vein: is postprocedural chest radiography always necessary? Crit Care Med 27: 1819 – 1823
46. Maury E, Guglielminotti J, Alzieu M, Guidet B, Offenstadt G (2001) Ultrasonic examination: an alternative to chest radiography after central venous catheter insertion? Am J Respir Crit Care Med 164: 403 – 405
47. Hind D, Calvert N, McWilliams R, et al (2003) Ultrasonic locating devices for central venous cannulation: meta-analysis. BMJ 327: 361

The Effect of Light on Critical Illness

R. Castro, D.C. Angus, and M.R. Rosengart

"We shape our buildings, and afterwards our buildings shape us."
Winston Churchill

Introduction

The research of this decade has yielded substantial improvements in the delivery of and technology with which to provide care for critically ill intensive care unit (ICU) patients. Garnering less attention from the medical and scientific community is the environment in which that care is provided, which remains impersonal, noisy, and over illuminated. Noticeably, the nursing and business literature is replete with studies on the matter [1, 2].

This discussion will focus on the available evidence regarding associations between the ICU environment, specifically light, and patient outcome. Definitions of light and the biology, including neural, hormonal, and immunologic mechanisms, by which it affects the body will be initially emphasized. An integrative commentary will be presented at the conclusion. Because of constraints, the focus is upon the critically ill patient, recognizing that much of what will be discussed is equally applicable to the healthcare provider.

Light

Sunlight reaching the earth's surface is categorized by effective wavelength: ultraviolet B (UV-B, 280–315 nm), ultraviolet A (UV-A, 315–400 nm), visible light (400–760 nm), and infrared light (760 nm × 1.06 nm) [3]. Of these four categories, visible light is essential for vision and resetting of the circadian clock through photoreceptors in the retina [4]. Exposure to UV-B radiation induces biological changes in the integument, such as sunburn, skin cancers and, as will be discussed, immunosuppression [5]. UV-A is involved in carcinogenesis through the generation of highly reactive chemical intermediates and lipid peroxidation [6].

Light is measured using either radiometry (an analysis of the entire visible and non-visible wavelength spectra) or photometry [7]. Both methods provide valuable and distinct information that defines light. Photometry, a perception of brightness as seen by the human eye, is performed with a lux meter in units called lux. For comparison purposes, moonlight is 0.5 to 1 lux, a bright office is 400 lux, and a sunny day in spring is 32,000 to 60,000 lux [8]. Nocturnal light levels vary among ICUs with mean maximum levels ranging from 1 to 1,400 lux [8]. During the performance of procedures (e.g., catheter insertion), light devices can easily deliver > 10,000 lux.

Light affects the body by receptor stimulation through the eyes (retina) and through the skin. The classical visual sensory system is comprised of photorecep-

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tor cells of rods (low-level light) and cones (sharpness, detail, and color vision). The impact of a photon of light generates rhodopsin, thus creating electrical impulses in the optical nerve that converge within the visual cortex and are interpreted as 'vision' [4]. For more than 150 years, scientists considered rods and cones to be the sole photoreceptor cells in the eye. With the discovery of a novel, third type of retinal photoreceptor in mammals [9], a new retinohypothalamic pathway was described, providing evidence of a pathway mediating the biological but non-visual effects of light.

The Biological Perspective: Non-Visual Effects of Light

The health effects of light are realized through several biological processes additional to and independent of the ability of visually perceiving the external world [10]. Only recently have we acquired deeper insight into the biological mechanisms regulating these non-visual effects. Fundamental to this understanding is an appreciation of how light controls the biological clock and regulates important hormones through seasonal photoperiods (duration of an organism's daily exposure to light) and regular light-darkness rhythms.

Circadian Pathways

Circadian rhythms are cycles of physiologic processes and behaviors driven by an endogenous oscillator having a period of approximately (*circa*) one day (*diem*). The most evident circadian rhythm in humans is the sleep-wake cycle. Other circadian rhythms include body temperature, release of hormones (e.g., melatonin, cortisol), and gene expression. These rhythms persist with a near 24-h period even in the absence of time-of-day information [11]. Environmental stimuli can reset the phase of the circadian pacemaker, light being the ultimate entrainment signal [12]. A change in the timing of the light-dark cycle (e.g., nocturnal light exposure) will result in a shift in the phase of circadian rhythms that can only be detected in the next circadian cycle. However, the effects on circadian physiology (e.g., body temperature and melatonin suppression) can be observed during or immediately after the light exposure [13]. In the case of a disruption of the rhythm, exposure to bright light in the morning will help to restore it [14].

The suprachiasmatic nucleus in the anterior hypothalamus is the circadian pacemaker [15]. It contains cells that are able to express sustained periodicity, even *in vitro*. Functional neuroimaging studies have demonstrated that light quickly activates alertness-related subcortical structures in the suprachiasmatic nucleus and a sequence of intermediate connections terminating in the pineal gland that underlie the circadian-based synthesis and release of melatonin [16]. The thalamus functions as an interface between alertness, cognition, and the effects of light [17], anatomically connecting with the frontal, temporal and cerebral cortex (except for the olfactory system), cerebellum, and basal ganglia. It regulates the flow of information from the retina to the visual cortex or between cortical areas [18]. Light stimulates a retinal photoreceptor system expressing melanopsin, a photopigment produced in the human inner retina and directly activated by light [4]. Interestingly, even extensive degradation of the photoreceptor apparatus does not eliminate the synthesis of melanopsin [10]. Subsequent signals are channeled to the suprachiasmatic nucleus via the retinohypothalamic

pathway. Melanopsin plays a key role in mediating the non-visual effects of light and renders a small subset of retinal ganglion cells intrinsically photosensitive (ipRGC) with maximal sensitivity to blue light [11]. The efferent projections of the ipRGCs include multiple hypothalamic, thalamic, striatal, brainstem and limbic structures, which govern circadian cycles, body temperature, and alertness [17].

The ability of light to modulate cortical activity and circadian rhythm is defined, in part, by the duration, intensity and wavelength of the lighted stimulus [17, 19]. Biological processes dictate that non-visual responses are maximally sensitive to blue light (459–483 nm), in contrast to the green (~550 nm) spectral sensitivity of classical visual photoreceptors [11, 13]. Blue light most powerfully changes the rhythm of melatonin and cortisol secretion, acutely suppressing melatonin. It also elevates body temperature and heart rate, reduces subjective sleepiness and improves alertness [17, 20, 21]. In one study, office workers were exposed to two new lighting conditions for 4 weeks: A blue-enriched white light or a white light that did not compromise visual performance. Blue-enriched white light significantly heightened subjective measures of alertness, positive mood, performance, and concentration while reducing evening fatigue, irritability, and eye discomfort. Daytime sleepiness was reduced and the quality of subjective nocturnal sleep was improved [21]. Thus, evidence confirms that for the human brain, the absence of blue light, at least from a circadian point of view, is effectively darkness [22].

Melatonin

Most of the effects of the photoperiod are mediated by melatonin, the hormone secreted by the pineal gland in response to darkness. This hormone is synthesized within the pineal gland from the essential amino acid tryptophan through enzymatic processes of 5-hydroxylation and decarboxylation that yield 5-hydroxytryptamine (5-HT or serotonin). During daylight, serotonin remains stored in pinealocytes and unavailable for conversion to melatonin. With darkness, postganglionic sympathetic outflow to the pineal gland releases serotonin and induces enzymatic conversion of serotonin to melatonin [23].

Melatonin plays an equally important role in the adaptive response of an organism to environmental challenges. Experimental studies have shown that binding of melatonin to specific receptors in antigen-activated Type 1 T-helper cells (Th-1) upregulates pro-inflammatory cytokine production (such as interferon [IFN]-γ and interleukin [IL]-2) [24] and enhances the production of IL-1, IL-6 and IL-12 in human monocytes [25–27]. It is believed that it may increase phagocytosis and antigen presentation [28]. Animal models have demonstrated that melatonin has a protective effect in mice against lethal viral encephalitis [29], infectious hepatitis [30], and hemorrhagic [31] or septic [32] shock. In this context, melatonin has been shown to prevent endotoxin-induced circulatory failure in rats through inhibition of tumor necrosis factor (TNF)-α, and to reduce post-shock levels of IL-6, superoxide production in the aorta, and inducible nitric oxide synthase (iNOS) in the liver [32] (**Box 1**).

These data suggest that the winter immunoenhancement paradigm [38] could explain photoimmunomodulatory processes in animals and be applicable to patients contending with severe illnesses. This theory was developed in the context of lower mammals and proposes that in environments that undergo seasonal

Box 1. Examples of immune effects associated with photoperiods

Tumorigenesis was reduced and basal lymphocyte proliferation or mitogen-induced splenocyte proliferation were promoted with shorter days (rodents) [33, 34]
Seasonal attenuation of the immune response to Gram-negative infections was observed when shortening the length of days in a rodent model [35]
Measures of immune cell counts, lymphoid organ weights or T cell-dependent antibody responses to xenogeneic antigens were generally enhanced by short photoperiod of winter [36]
Exposure to short days increased mass of the spleen and enhanced the total number of leukocytes and lymphocytes when only photoperiod was manipulated [20]
Circulating numbers of leukocytes, neutrophils, and lymphocyte proliferation in response to mitogens were higher in winter than in the summer in a primate model [37]
Seasonal changes in immune parameters were observed, with enhancement of specific immune responses during autumn and winter compared with spring and summer, in animal models (rodents, rabbits, dogs and primates) [20]

changes in energy availability, selection should favor individuals that support enhanced immune function during the winter (shorter days). Photoperiodic information is used to bolster immune function in anticipation of winter [38]. Redirecting metabolic energy stores toward improved immune function should enable animals to contend better with the stressors (e.g., decreased temperature and food availability) of winter, a time of the year when reproductive efforts are less likely to succeed. Conversely, during the breeding season (longer days), energetic trade-offs favor reproduction, and immune function is relatively impaired [34].

A critically ill patient lies in a winter-like condition because energy resources are severely compromised. Moreover, immunity is impaired as the body is contending with many severe insults. The physiological regulation of melatonin secretion by darkness and light is probably abolished due to loss of the circadian rhythm, a consequence of the altered patterns of illumination in most ICUs [39]. Thus, this pathway is directly linked to the inflammatory response and, ultimately, a patient's outcome. It would be highly desirable to direct resources toward enhancing the immune system so as to enable the patient with a better chance to overcome this biological 'severe weather'. This might be accomplished by restoring a circadian light/darkness cycle, by providing longer periods of darkness and less hours of light in the ICU. The use of 'virtual darkness' by providing amber lenses to filter the impact of electrical light, particularly ubiquitous blue light, could attain the objective [22]. Beyond its antioxidant properties, the role of melatonin as a systemic immunoregulatory agent sensitive to exogenous regulation is an exciting idea to be tested in controlled trials of human sepsis [40].

Cortisol

Cortisol is a steroid hormone that influences metabolic, immunologic, muscle and brain functions. Its secretion is regulated primarily by the hypothalamic-pituitary-adrenal (HPA) axis through release of corticotrophin releasing hormone (CRH) from the hypothalamus and adrenocorticotrophic hormone (ACTH) from the anterior pituitary gland [41]. Cortisol negatively feeds back to the hippocam-

pus, hypothalamus, and the anterior pituitary, inhibiting CRH and ACTH. The suprachiasmatic nucleus regulates the circadian rhythm of corticosteroids [42]. Thus, cortisol decreases across the habitual waking day to attain a nadir near bedtime. Concentrations subsequently increase during the darkness of night and peak near arousal, regardless of continuous wakefulness or sleep [43]. Superimposed on this rhythm are fluctuations associated with the pulsatile or acute release of cortisol by diverse factors such as anxiety, stress, immune challenge, blood glucose levels, sleep onset, sleep loss, and exposure to light [44].

In sepsis, the HPA axis affects inflammation by modulating leukocytes, cytokines and NO synthesis [45]. Through negative feedback, inflammatory cytokines may suppress sensitivity to ACTH [46], resulting in adrenal insufficiency [47], or compete with intracellular glucocorticoid receptor function, thereby causing peripheral tissue glucocorticoid resistance [48].

The relationship between light and plasma levels of cortisol is complex. Inconsistent results have been attributed to differences in light intensity and wavelength, and the timing of application as it relates to the circadian cycle [44]. More recent studies, however, provide compelling evidence that light is a strong determinant of cortisol concentration. Bright light exposure (up to 10,0000 lux) elicited a significant suppressive effect when applied either on the rise or descent phase of cortisol rhythm. Lower intensities (less than ~5,000 lux) failed to induce significant changes [44]. These results would be consistent with the findings of light-intensity response curves for melatonin suppression [49]. In contrast to melatonin's responses, both blue and red lights increased cortisol plasma levels at night [50].

A multisynaptic neural pathway (retina-suprachiasmatic nucleus-adrenal gland) that bypasses the HPA axis is considered responsible for the acute influence of light on corticosteroid concentrations. These conclusions stem, in part, from the observation that cortisol variations are reported to be dependent upon an intact suprachiasmatic nucleus and not related to changes in ACTH levels [51]. Thus, aspects of a lighted environment could be adjusted to elicit this HPA-independent response. In a critically ill patient, this approach could lessen a relative or overt adrenal insufficiency and constitutes an interesting idea worthy of future study.

Photo-immunomodulation

Seasonal rhythms and fluctuations in innate and acquired immune responses have been documented in many species [52, 53]. Profound but selective effects on immune function are associated with the prevailing photoperiod [36, 54]. T cell immunity is depressed in most species in the winter, even when natural light sources and exposure are kept constant [20, 54]. Experimental data, however, show that immune cell numbers and immunoglobulin concentrations vary with respect to the season or day length [34, 54] even during the winter. Higher leukocyte counts are noted with less hours of light [20, 54], demonstrating that the photoperiod may also influence the functional capabilities of immune cells. Short days selectively enhance natural killer (NK) basal proliferative capacity and cell activity [34]. In contrast, in the same rodent model, phagocytic and granulocyte oxidative burst activity are reduced during short, by comparison to long, days [20, 55]. Collectively, these results confirm reduced immune function in winter compared to summer, but with enhanced immune function in short winter-like

photoperiods compared to long summer-like day lengths [56] (**Box 1**). The net elevated immune function in short days is thought to counteract the suppressive effects of environmental stressors such as low ambient temperature on immune function [20]. These facts raise many questions for the management of critically ill patients. Is there a consistent seasonality on the outcomes of critically ill patients? Should we shorten the day length for the most seriously ill septic patients in the ICU to enhance their immunity? These concepts await further investigation.

Central Pathways: The Inflammatory Reflex

A recent major advance in our understanding of the immune response during severe sepsis came with the identification of the cholinergic anti-inflammatory pathway [57]. Cytokine release can be controlled at multiple levels, including the central nervous system (CNS). Endotoxin and products of inflammation stimulate afferent neural signals in the vagus nerve that induce acute-phase responses, fever, and the upregulation of IL-1β in the brain. Concomitantly, afferent vagus nerve signals are transmitted to the medullary reticular formation, locus ceruleus, hypothalamus, and dorsal vagal complex, leading to an increase in ACTH from the anterior pituitary gland [57]. This stimulates an increase in systemic glucocorticoid levels, thereby inhibiting pro-inflammatory cytokine release [58]. Alternatively, ascending sensory fibers of the vagus nerve that synapse in the nucleus tractus solitarius of the upper medulla can inhibit cytokine release. Like other reflex arcs, the inflammatory reflex is comprised of a sensory afferent arm (described above) and an efferent motor arm that controls a rapid and opposing reaction [57]. This cholinergic anti-inflammatory efferent pathway inhibits inflammation. Efferent vagus nerve signals release acetylcholine (ACh) in organs of the reticuloendothelial system, including the spleen, liver, and gastrointestinal tract [57]. ACh binds to the nicotinic receptor (α7nAChR) expressed on the surface of activated macrophages and other immune cells, which inhibits nuclear factor κB (NF-κB) and attenuates cytokine production. The biological relevance of this pathway was made manifest by murine endotoxemia studies demonstrating that stimulation of the efferent vagus nerve inhibited TNF-α release, prevented shock, and improved survival [59]. The vagal inflammatory reflex also regulates localized inflammation. In a murine model of arthritis, vagus nerve stimulation inhibited inflammation and suppressed the development of paw swelling [60]. In the lungs, pharmacological α7nAChR stimulation correlated with reduced lipopolysaccharide (LPS)-induced neutrophil recruitment [61]. Collectively, these studies suggest that either by electrical or chemical intervention, this inflammatory reflex pathway can be modified to modulate the inflammatory response to injury or infection [62].

Consistent evidence supporting a link between sunlight exposure and the inflammatory reflex is lacking, however. The efferent arm of the inflammatory reflex regulates TNF-α production in the spleen via two serially connected neurons: One preganglionic, originating in the dorsal motor nucleus of the vagus nerve (parasympathetic), and the second postganglionic, originating in the celiac-superior mesenteric plexus, and projecting in the catecholaminergic splenic (sympathetic) nerve [63]. Therefore, one of the most crucial components of the efferent inflammatory reflex is catecholaminergic in nature. As the suprachiasmatic nucleus balances sympathetic and parasympathetic output to periph-

eral organs [64], one might speculate that the efferent arm of the inflammatory reflex could be directly activated or inhibited by light exposure, thereby establishing a neural link between the retinohypothalamic pathway and the inflammatory reflex. As the non-visual retinohypothalamic pathway's net effect is to enhance immunity, this inflammatory reflex mechanism could constitute a counterregulatory mechanism (**Fig. 1**).

Skin Pathways: Immunosuppression by Ultraviolet B Radiation

The skin represents an important interface between the external environment and internal tissues and is constantly bathed in sunlight. Both direct (skin-mediated) and indirect immunomodulation have been described. Visible light (400–700 nm) can penetrate the epidermal and dermal layers and directly interact with circulating lymphocytes. UV-B and UV-A radiation alter normal human immune function predominantly via a skin-mediated response [20]. Epidermal Langerhans cells survey invading agents and transmit the information into immune cells. After engulfing exogenous antigen, these sentinels migrate to draining lymph nodes and present the processed antigen to T cells, thereby inducing specific T cell differentiation and T cell activation. Ionizing and non-ionizing UV radiation (below 400 nm) inhibit this antigen presentation via induction of suppressive keratinocyte-derived cytokines. This reduces effector T cell proliferation and activity and induces immunotolerance [65]. In addition, regulatory T cells (Treg) serve important immunoregulatory and immunosuppressive functions. Induced by UV radiation, Treg cells release IL-10, leading to immunosuppression. Thus, functional alterations of epidermal Langerhans cells and a systemic increase in Treg cells couple the epidermis to local and systemic immunosuppression [66]. The balance between the numbers and function of regulatory and effector T cells is crucial for the immune system. Although the molecular mechanisms underlying the expansion of regulatory T cells after UV exposure are largely unknown, vitamin D3 has been recently shown to upregulate the RANKL (receptor activator for NF-κB ligand) expression that activates Langerhans cells [65]. This should be carefully considered when managing critically ill patients in an ICU with windows with no UV protection. Although not subjected to rigorous evaluation, UV-induced immunosuppression could play an adverse role in a critically ill patient (**Fig. 1**).

Vitamin D3, 1,25(OH)D2, and Cathelicidin

Vitamin D belongs to the family of steroid hormones. Exposure to UV-B radiation of 290–315 nm converts 7-dehydrocholesterol to pre-vitamin D3. Pre-vitamin D rapidly undergoes a thermally induced isomerization to form vitamin D3. D3 enters the circulation where it undergoes hydroxylation in the liver by vitamin D-25-hydroxylase and in the kidney by the 25-hydroxyvitamin D-1-alpha-hydroxylase (1α-OHase), thus forming 1–25(OH)D2. The classic function of vitamin D is to enhance intestinal absorption of calcium by regulating several calcium transport proteins in the small intestine [67].

Cells of the immune system also possess 1α-OHase and the vitamin D receptor (VDR) and, thus, are able to produce the hormonally active form. Macrophages produce the antimicrobial peptide, cathelicidin LL-37, in response to endogenously produced 1,25(OH)D2 to enhance innate immunity [67]. The antimicro-

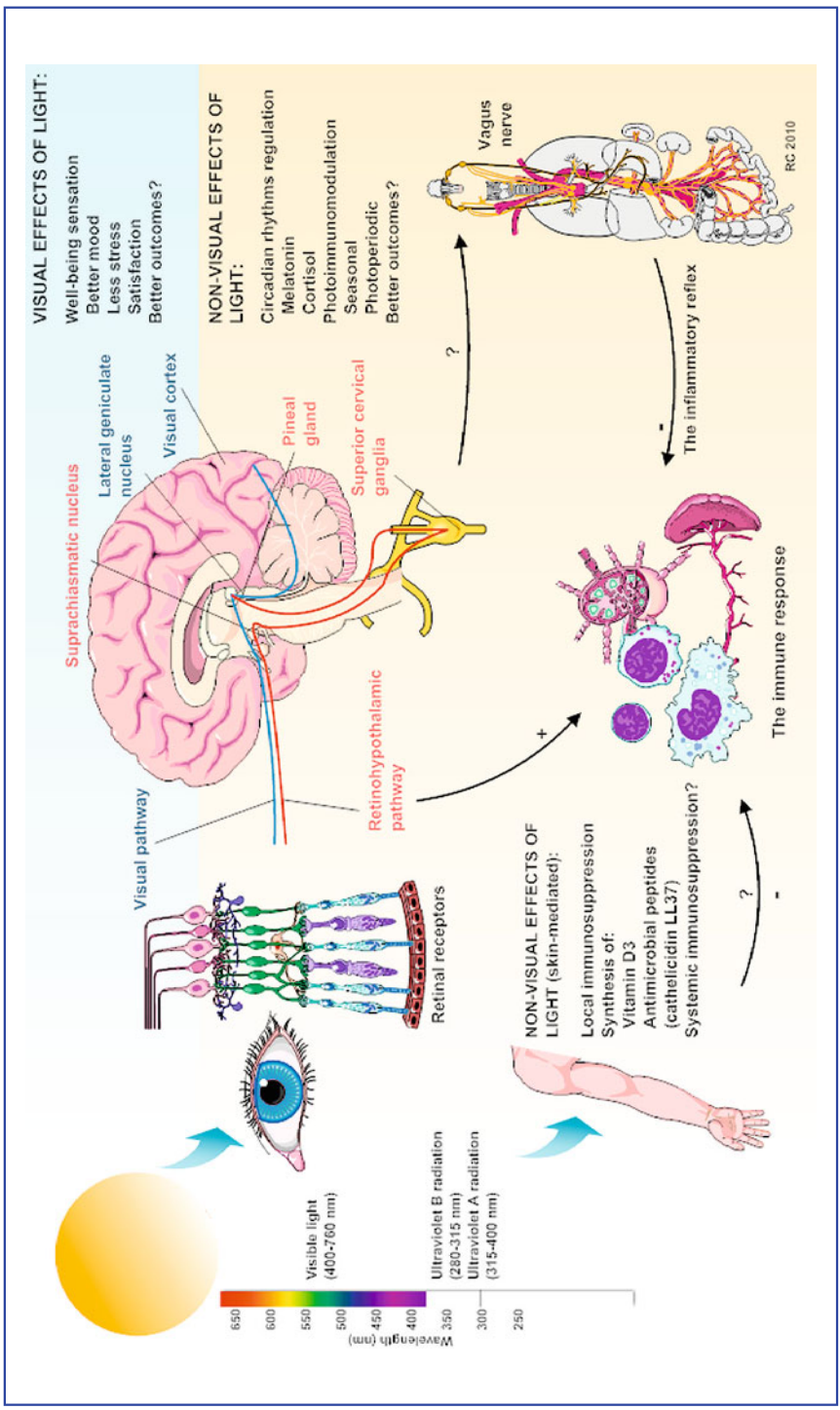

Fig. 1. Integrative diagram of the visual and non–visual pathways that mediate the biological and behavioral effects of sunlight exposure in a critically ill patient.

bial peptide, LL-37, is the only known member of the cathelicidin family expressed in humans. It is a multifunctional host defense molecule essential for normal immune responses to infection and tissue injury. LL-37 peptide exhibits strong activity against common ICU bacterial strains, including *Escherichia Coli*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Staphylococcus aureus* (methicillin-resistant [MRSA] and non-MRSA), and *Neisseria gonorrhoeae*. It prevents the immunostimulatory effects of bacterial cell wall molecules such as LPS and can, therefore, protect against lethal endotoxemia [68]. Cellular production of LL-37 is affected by multiple factors, including bacterial products, host cytokines, availability of oxygen, and sun exposure through the activation of CAP-18 gene expression by vitamin D3 [68]. As sunlight within the UV-B spectrum induces immunosuppression and heightens vulnerability to infection, 1,25(OH)D2 potentially balances this effect by stimulating the synthesis of LL-37 in the skin and circulating phagocytic cells [69]. Recently, lower circulating levels of 25(OH)D and vitamin D binding protein have been observed in critically ill patients compared to healthy controls [70]. Thus, it might be concluded that optimal function of our innate immune system requires some necessary amount of vitamin D and, accordingly, of sunlight (**Fig. 1**). This is a strong reason for providing septic patients with controlled exposure to direct sunlight.

The Biological Perspective: Visual Effects of Light

From the Greek Asclepieia[1] to the monastic Middle Age infirmaries[2], traditions of complementary medicine and holistic healing have been rooted in the provision of medical care. Pleasant views were obligatory characteristics of places designed to give shelter and provide care for diseased people. It is now appreciated that the visual environment can powerfully influence the atmosphere and visual impression of the workplace. Properly designed, the overall working environment can have a stimulating effect on the people working within it [71]. Interior daylight contributes substantially to the perceived quality of the working environment. Light is mood enhancing and fosters visual and general health [71]. An important benchmark in the history of integrating nature into the care of patients was made by Roger Ulrich in 1984 [72]. Post-surgical patients with a view of nature suffered fewer complications, used less pain medication, and were discharged sooner than those with a view of a brick wall. This pioneering study provided the first formal scientific evidence that 'healing environments' beneficially alter health. In the following years, many other groups from across the world have reported the health benefits associated with views of nature, daylight exposure and related elements [73] (**Box 2**). Based on these findings, many have proposed that exposure to daylight be considered as a medical intervention for critical care patients. Nevertheless, such studies have not been yet performed though the concept warrants further study.

1 Temples dedicated to the healing of the people, mostly erected in valleys near hot or cold springs, with an open entry facing to the south. So, patients could sleep and dream in a well-ventilated room warmed by sunlight.

2 Infirmaries were deliberately located adjacent to a central courtyard or garden so that patients could contemplate the scenery and 'make a connection with God'.

Box 2. Some beneficial health effects of light exposure reported in the literature

Light can alleviate seasonal depression [74]
Sunlight exposure improves cognitive function among depressed people in a dose-response relationship [75]
Light regulates melatonin, which has paramount immunomodulatory effects and has been shown to reduce breast cancer growth [20]
Female patients with a first cardiac attack treated in sunny rooms had a shorter stay than female patients treated in dull rooms and mortality in both sexes was consistently higher in dull rooms than in sunny rooms [76].
Absence of visible daylight in the room is significantly associated with delirium and higher risk of dementia in intensive care patients [77]

The Behavioral Perspective

People prefer daylight to electric lighting as their primary source of illumination [78]. Most prefer to work and live in buildings illuminated by daylight as it provides psychological comfort, increased satisfaction in the work environment, and visual and general health [79]. A window providing a beautiful view of the surrounding landscape or of the sky and mountains might bolster psychological coping and thereby facilitate healing [71], all through a sensation of well-being. Well-being can be defined in terms of an individual's physical, mental, social, and environmental status. These aspects interact with each other and possess differing levels of importance specific to that individual (**Box 3**). Almost all of these components are present in the critically ill patient.

Apart from the biological considerations previously discussed, the positive sensations elicited by a daylighted view might enable a patient to more appropriately cope with critical illness. Psychologists make an important distinction between short-term positive emotions (*hedonic* well-being) and psychological (*eudaimonic*) well-being. Eudaimonic well-being has to do with the realization of personal potential and purpose in life, and is mainly determined by childhood social circumstances and the development of loving and trusting relationships early in life [81]. Therefore, it is not subject to simple modifications through daily life experiences. Conversely, hedonic well-being is related to experiences of happi-

Box 3. Components of well-being [80]

Individual characteristics of people such as functional ability and physical and mental health
Physical environmental factors including facilities, amenities, and housing standards
Social factors such as family and social networks
Living environment including household status, household conditions, and neighborhood
Socioeconomic factors including income, standard of living, and ethnicity
Personal autonomy factors such as ability to make choices and control
Subjective satisfaction on the person's evaluation of their quality of life
Psychological health such as psychological well-being, morale, and happiness
Activities such as hobbies, leisure, and social participation
Life changes such as traumatic or disruptive events or lack of change
Care including expectations, amount, and kind of support

ness and satisfaction and is a short-term sensation. Several authors have described the short-term benefits of positive emotions and attitudes on reducing the cardiovascular response to stress [82], lowering pain ratings and sensitivity [83], and volunteers trained in meditation produced high levels of immunity to influenza [84]. Thus, the appreciation of sunlight may impact favorably upon the health of a critical patient through this shorter-term perspective (**Fig. 1**).

The Holistic Perspective

No single factor is responsible for any given health circumstance or condition. This common-sense statement was conceptually developed by Moos in 1976 [85] and is called the social-ecological framework. This model views a specific situation as the sum product of the interaction of many factors ordered in five levels: Individual, interpersonal, community-level, societal, and policy. Environment integrates into the third and fourth categories.

Humans can modify almost every aspect of their world to create hospitable places within which to work, play and live. They enjoy and seek the pleasant emotions that a beautiful landscape and a warm sunlight nourish. Over time, however, we have become extremely dependent upon a man-made environment. Artificial light constitutes an indispensable part of our modern lives. Consequently, seasons, daylight hours and healthy sleep-waking cycles are less a part of our existence. But physiology reminds us that maintaining a balanced sleep-wake cycle is essential to survive. It allows animals to enhance their immunity through light-mediated mechanisms even in adverse environmental conditions.

When a healthy individual suffers an acute serious illness, these ancient survival mechanisms reacquire relevance. The biologic environment becomes hostile and the patient starts to struggle with the most atavistic challenge he/she could face: The fight for survival. At this point, the provision of professional intensive care must include elements apart from standard medical care. It should consider the deliberate intention to modulate the patient's immune response via activation of visual and non-visual pathways. Modification of light settings and timing becomes a fundamental component in this approach, as well as prudent exposure to sunlight for some hours. We cannot assure that providing sunlight exposure to critically ill patients and shortening the daily time of exposition to light will result in improved survival. The final outcome will emerge from a dynamic ongoing process in which personal and environmental factors will exert influence upon each other according to the social-ecological framework. However, the systemic and local immunomodulatory effects and the positive emotions elicited by this sensorial experience give us a solid rationale to integrate them as key components in the delivery of care in the ICU.

Conclusion

XVII

Clearly light has the very real potential to alter the course of disease and the behavior of persons providing care. Although we have a deeper understanding of the biological mechanisms involved in the visual and non-visual effects of light, and the psychological and behavioral elements of the complex interaction between light exposure and health outcomes, it is far from complete. There are

still many nebulous aspects, and with each step of understanding, several new questions arise, particularly in the context of critical illness. How does illness alter the neural and endocrine pathways governing the biological effects of light? Do measures to engage the physiologic and neural feedback loops enhance, hinder, or fail to influence their actions? What are the effects of blue and green light wavelengths in a patient that is sedated and intubated? What happens to the biologic rhythms and immune responses if our critically ill patient rests in a room without windows, even though it is a greatly illuminated one? As artificial light sources in ICUs fail to account for retinal spectral sensitivity and the circadian clock, are our artificially lighted work environments leaving our patients and healthcare providers blue light 'deprived'? Hopefully, for these and many other questions, future studies will enlighten us as to the benefits of returning natural light and nature to the bedside.

References

1. Stichler JF (2001) Creating healing environments in critical care units. Crit Care Nurs Q 24: 1 – 20
2. Berry LL, Parker D, Coile RC Jr, Hamilton DK, O'Neill DD, Sadler BL (2004) The business case for better buildings. Healthc Financ Manage 58: 76 – 84
3. Commission International de l'Éclairage (1987) International Lighting Vocabulary, 4th edn. CIE, Paris
4. Barrett KE, Barman SM, Boitano S, Brooks H (2010) Vision. In: Barrett KE, Barman SM, Boitano S, Brooks H (eds) Vision. Ganong's Review of Medical Physiology, 23rd edn. McGraw Hill Companies, New York, pp 181 – 202
5. Soter NA (1990) Acute effects of ultraviolet radiation on the skin. Sem Dermatol 9: 11 – 15
6. Nishigori C (2006) Cellular aspects of photocarcinogenesis. Photochemical and Photobiological Sciences 5: 208 – 214
7. Patel M Chipman J, Carlin BW, Shade D (2008) Sleep in the intensive care unit setting. Crit Care Nurs Q 31: 309 – 318
8. Sabra AI (1981) Theories of Light, from Descartes to Newton. Cambridge University Press, New York
9. Brainard G, Hanifin J, Greeson J, et al (2001) Action spectrum for melatonin regulation in humans: evidence for a novel circadian photoreceptor. J Neurosci 21: 6405 – 6412
10. Terman M, Terman J (1985) A circadian pacemaker for visual sensitivity? Ann N Y Acad Sci 453: 147 – 161
11. Hankins MW, Peirson SN, Foster RG (2008) Melanopsin: an exciting photopigment. Trends Neurosci 31: 27 – 36
12. Lack L, Wright H (1993) The effect of evening bright light in delaying the circadian rhythms and lengthening the sleep of early morning awakening insomniacs. Sleep 16: 436 – 443
13. Brainard GC, Hanifin JP (2005) Photons, clocks, and consciousness. J Biol Rhythms 20: 314 – 325
14. Bechtold DA, Gibbs JE, Loudon ASI (2010) Circadian dysfunction in disease. Trends Pharmacol Sci 31: 191 – 198
15. Saper CB, Lu J, Chou TC, Gooley J (2005) The hypothalamic integrator for circadian rhythms. Trends Neurosci 28: 152 – 157
16. Dijk D-J, von Schantz M (2005) Timing and consolidation of human sleep, wakefulness, and performance by a symphony of oscillators. J Biol Rhythms 20: 279 – 290
17. Vandewalle G, Maquet P, Dijk D-J (2009) Light as a modulator of cognitive brain function. Trends Cogn Sci 13: 429 – 438
18. Shipp S (2004) The brain circuitry of attention. Trends Cogn Sci 8: 223 – 230
19. Rea MS, Figueiro MG, Bierman A, Bullough JD (2010) Circadian light. J Circadian Rhythms 8: 2 – 12
20. Haldar C, Ahmad R (2010) Photoimmunomodulation and melatonin. J Photochem Photobiol B. 98: 107 – 117

21. Viola AU, James LM, Schlangen LJ, Dijk DJ (2008) Blue-enriched white light in the workplace improves self-reported alertness, performance and sleep quality. Scand J Work Environ Health 34: 297–306
22. Phelps J (2008) Dark therapy for bipolar disorder using amber lenses for blue light blockade. Med Hypotheses 70: 224–229
23. Wurtman RJ, Axelrod J, Phillips LS (1963) Melatonin synthesis in the pineal gland: Control by light. Science 142: 1071–1073
24. Garcia-Maurino S, Gonzalez-Haba MG, Calvo JR, et al (1997) Melatonin enhances IL-2, IL-6, and IFN-gamma production by human circulating CD4+ cells: a possible nuclear receptor-mediated mechanism involving T helper type 1 lymphocytes and monocytes. J Immunol 159: 574–581
25. Garcia-Maurino S, Gonzalez-Haba MG, Calvo JR, Goberna R, Guerrero JM (1998) Involvement of nuclear binding sites for melatonin in the regulation of IL-2 and IL-6 production by human blood mononuclear cells. J Neuroimmunol 92: 76–84
26. Maestroni GJ (1999) Therapeutic potential of melatonin in immunodeficiency states, viral diseases, and cancer. Adv Exp Med Biol 467: 217–226
27. Cutolo M, Maestroni GJ (2005) The melatonin-cytokine connection in rheumatoid arthritis. Ann Rheum Dis 64: 1109–1111
28. Maestroni GJ (2001) The immunotherapeutic potential of melatonin. Expert Opin Investig Drugs 10: 467–476
29. Ben-Nathan D, Maestroni GJ, Lustig S, Conti A (1995) Protective effects of melatonin in mice infected with encephalitis viruses. Arch Virol 140: 223–230
30. Wang H, Wei W, Shen YX, et al (2004) Protective effect of melatonin against liver injury in mice induced by Bacillus Calmette-Guerin plus lipopolysaccharide. World J Gastroenterol 10: 2690–2696
31. Wichmann MW, Haisken JM, Ayala A, Chaudry IH (1996) Melatonin administration following hemorrhagic shock decreases mortality from subsequent septic challenge. J Surg Res 65: 109–114
32. Wu CC, Chiao CW, Hsiao G, Chen A, Yen MH (2001) Melatonin prevents endotoxin-induced circulatory failure in rats. J Pineal Res 30: 147–156
33. Hotchkiss AK, Nelson RJ (2002) Melatonin and immune function: hype or hypothesis? Crit Rev Immunol 22: 351–371
34. Nelson RJ (2002) Seasonal Patterns of Stress, Immune Function, and Disease. Cambridge University Press, New York
35. Baillie SR, Prendergast BJ (2008) Photoperiodic Regulation of Behavioral Responses to Bacterial and Viral Mimetics: A Test of the Winter Immunoenhancement Hypothesis. J Biol Rhythms 23: 81–90
36. Nelson RJ (2004) Seasonal immune function and sickness responses. Trends Immunol 25: 187–192
37. Mann DR, Akinbami MA, Lunn SF, Fraser HM, Gould KG, Ansari AA (2000) Endocrine-immune interaction: alteractions in immune function resulting from neonatal treatment with a GnRH antagonist and seasonality in male primates. Am J Reprod Immunol 44: 30–40
38. Nelson RJ, Demas GE (1996) Seasonal changes in immune function. Q Rev Biol 71: 511–548
39. Perras B, Meier M, Dodt C (2007) Light and darkness fail to regulate melatonin release in critically ill humans. Intensive Care Med 33: 1954–1958
40. Srinivasan V, Pandi-Perumal SR, Spence DW, Kato H, Cardinali DP (2010) Melatonin in septic shock: Some recent concepts. J Crit Care 25: 656
41. Barrett KE, Barman SM, Boitano S, Brooks H (2010) The adrenal medulla and adrenal cortex. In: Barrett KE, Barman SM, Boitano S, Brooks H (eds) Ganong's Review of Medical Physiology, 23rd edn. Mc-Graw Hill Companies, New York, pp 337–362
42. Kalsbeek A, van der Vliet J, Buijs RM (1996) Decrease of endogenous vasopressin release necessary for expression of the circadian rise in plasma corticosterone: a reverse microdialysis study. J Neuroendocrinol 8: 299–307
43. Weibel L, Follenius M, Spiegel K, Ehrhart J, Brandenberger G (1995) Comparative effect of night and daytime sleep on the 24-hour cortisol secretory profile. Sleep 18: 549–556

44. Jung CM, Khalsa SB, Scheer FA, et al (2010) Acute effects of bright light exposure on cortisol levels. J Biol Rhythms 25: 208 – 216
45. Chrousos GP (1995) The hypothalamic-pituitary-adrenal axis and immune-mediated inflammation. N Engl J Med 332: 1351 – 1362
46. Jäättelä M, Ilvesmäki V, Voutilainen R, Stenman UH, Saksela E (1991) Tumor necrosis factor as a potent inhibitor of adrenocorticotropin-induced cortisol production and steroidogenic p450 enzyme gene expression in cultured human fetal adrenal cells. Endocrinology 128: 623 – 629
47. Annane D, Sebille V, Troche G, Raphael JC, Gajdos P, Bellissant E (2000) A 3-level prognostic classification in septic shock based on cortisol levels and cortisol response to corticotropin. JAMA 283: 1038 – 1045
48. Molijn GJ, Koper JW, van Uffelen CJ, et al (1995) Temperature-induced down-regulation of the glucocorticoid receptor in peripheral blood mononuclear leucocyte in patients with sepsis or septic shock. Clin Endocrinol (Oxf) 43: 197 – 203
49. Zeitzer JM, Dijk DJ, Kronauer R, Brown E, Czeisler C (2000) Sensitivity of the human circadian pacemaker to nocturnal light: melatonin phase resetting and suppression. J Physiol 3: 695 – 702
50. Figueiro MG, Rea MS (2010) The effects of red and blue lights on circadian variations in cortisol, alpha amylase, and melatonin. Int J Endocrinol 2010: 829351
51. Ishida A, Mutoh T, Ueyama T, et al (2005) Light activates the adrenal gland: timing of gene expression and glucocorticoid release. Cell Metab 2: 297 – 307
52. Nelson RJ, Drazen DL (2000) Melatonin mediates seasonal changes in immune function. Ann N Y Acad Sci 917: 404 – 415
53. Martin LB, Weil ZM, Nelson RJ (2008) Seasonal changes in vertebrate immune activity: mediation by physiological trade-offs. Philos Trans R Soc Lond B Biol Sci 363: 321 – 339
54. Haldar C, Singh R, Guchhait P (2001) Relationship between the annual rhythms in melatonin and immune system status in the tropical palm squirrel, Funambulus pennanti. Chronobiol Int 18: 61 – 69
55. Nelson RJ, Demas GE, Klein SL, Kriegsfeld LJ (1995) The influence of season, photoperiod and pineal melatonin on immune function. J Pineal Res 19: 149 – 165
56. Blom JM, Gerber JM, Nelson RJ (1994) Day length affects immune cell numbers in deer mice: interactions with age, sex, and prenatal photoperiod. Am J Physiol 267: R596 – 601
57. Tracey KJ (2002) The inflammatory reflex. Nature 420: 853 – 859
58. Eskandari F, Sternberg EM (2002) Neural-immune interactions in health and disease. Ann NY Acad Sci 966: 20 – 27
59. Borovikova LV, Ivanova S, Zhang M, et al (2000) Vagus nerve stimulation attenuates the systemic inflammatory response to endotoxin. Nature 405: 458 – 462
60. Borovikova LV, Ivanova S, Nardi D, et al (2000) Role of vagus nerve signaling in CNI-1493-mediated suppression of acute inflammation. Auton Neurosci 85: 141 – 147
61. Giebelen IA, van Westerloo DJ, LaRosa GJ, de Vos AF, van der Poll T (2007) Local stimulation of alpha7 cholinergic receptors inhibits LPS-induced TNF-alpha release in the mouse lung. Shock 28: 700 – 703
62. van Westerloo DJ (2010) The vagal immune reflex: a blessing from above. Wien Med Wochenschr 160: 112 – 117
63. Rosas-Ballina M, Ochani M, Parrish WR, et al (2008) Splenic nerve is required for cholinergic antiinflammatory pathway control of TNF in endotoxemia. Proc Natl Acad Sci USA 105: 11008 – 11013
64. Buijs RM, la Fleur SE, Wortel J, et al (2003) The suprachiasmatic nucleus balances sympathetic and parasympathetic output to peripheral organs through separate preautonomic neurons. J Comp Neurol 464: 36 – 48
65. Loser K, Beissert S (2009) Regulation of cutaneous immunity by the environment: An important role for UV irradiation and vitamin D. Int Immunopharmacol 9: 587 – 589
66. Loser K, Mehling A, Loeser S, et al (2006) Epidermal RANKL controls regulatory T-cell numbers via activation of dendritic cells. Nat Med 12: 1372 – 1379
67. Kamen D, Tangpricha V (2010) Vitamin D and molecular actions on the immune system: modulation of innate and autoimmunity. J Mol Med 88: 441 – 450

68. Bucki R, Leszczyñska K, Namiot A, Soko³owski W (2010) Cathelicidin LL-37: A multitask antimicrobial peptide. Arch Immunol Ther Exp (Warsz) 58: 15–25
69. Zasloff M (2005) Sunlight, vitamin D, and the innate immune defenses of the human skin. J Invest Dermatol 125: 16–17
70. Jeng L, Yamshchikov AV, Judd SE, et al (2009) Alterations in vitamin D status and antimicrobial peptide levels in patients in the intensive care unit with sepsis. J Transl Med 7: 28
71. van den Berg A (2005) Health Impacts of Healing Environments. The Architecture of Hospitals. University Hospital Groningen, Groningen
72. Ulrich R (1984) View through a window may influence recovery from surgery. Science 224: 420–421
73. Rubin HR, Owens AJ, Golden G, Status report (1998) An investigation to determine whether the built environment affects patients' medical outcomes. The Center for Health Design, Martinez, CA
74. Lewy AJ, Kern HA, Rosenthal NE, Wehr TA (1982) Bright artificial light treatment of a manic-depressive patient with seasonal mood cycle. Am J Psychiatry 139: 1496–1498
75. Kent ST, McClure LA, Crosson WL, Arnett DK, Wadley VG, Sathiakumar N (2009) Effect of sunlight exposure on cognitive function among depressed and non-depressed participants: a REGARDS cross-sectional study. Environ Health 8: 34
76. Beauchemin KM, Hays P (1998) Dying in the dark: sunshine, gender and outcomes in myocardial infarction. J R Soc Med 91: 352–354
77. Van Rompaey B, Elseviers MM, Schuurmans MJ, Shortridge-Baggett LM, Truijen S, Bossaert L (2009) Risk factors for delirium in intensive care patients: a prospective cohort study. Crit Care 13: R77
78. Heerwagen JH, Heerwagen DR (1986) Lighting and psychological comfort. Lighting Design and Application 16: 47–51
79. Boyce P, Hunter C, Howlett O (2003) The Benefits Of Daylight Through Windows. Lighting Research Center, New York
80. Kiefer RA (2008) An integrative review of the concept of well-being. Holist Nurs Pract 22: 244–252
81. Huppert FA, Baylis N (2004) Well-being: towards an integration of psychology, neurobiology and social science. Philos Trans R Soc Lond B Biol Sci 359: 1447–1451
82. Fredrickson BL (2004) The broaden-and-build theory of positive emotions. Philos Trans R Soc Lond B Biol Sci 359: 1367–1378
83. Zeidan F, Johnson SK, Gordon NS, Goolkasian P (2010) Effects of brief and sham mindfulness meditation on mood and cardiovascular variables. J Altern Complement Med 16: 867–873
84. Davidson RJ, Kabat-Zinn J, Schumacher J, et al (2003) Alterations in brain and immune function produced by mindfulness meditation. Psychosom Med 65: 564–570
85. Moos RH (1976) The Human Context: Environmental Determinants Of Behavior. Wiley, New York

Context Information in Critical Care

G. Murias, B. Sales, and L. Blanch

Introduction

Medical decisions are based on information coming from two main sources: Patient information from medical records, physical examination, monitoring devices, medical images, laboratory results, etc.; and medical information from knowledge databases, medical papers, books, etc. The two kinds of information source have been largely unconnected: Usually, a medical problem detected at the bedside poses a question that impels physicians to search for information. Although this is a traditional, consolidated, and useful approach, it is also highly time consuming.

It would be extremely convenient if physicians could have access to the information they need in order to make decisions whenever and wherever they need it from a depository of pertinent answers for questions that have never even been asked. If you are used to using web mail servers or web search engines, you have probably noticed that advertisements closely related to your email or web search subject are displayed. These advertisements are produced by systems that analyze your virtual movements to make potentially useful information immediately available and thus increase the chance that you will actually access it.

What is Context Information?

Context information is any information that can be used to characterize the situation of any element (a person, place, problem or object) that is considered relevant in decision making. In a broad sense, we use context information almost continuously in everyday tasks. Even when not explicit, daily decisions are the final consequence of considering many issues that include who you are, what you have to do, where you will do it, and whom you will do it with. In the narrow sense, context information refers to explicitly including the items that influence decision making into a structured model.

Context Information in Critical Care Monitoring

Up to 77 % of admissions to medical intensive care units (ICU) take place, at least in part, for monitoring purposes, even though only 10 % of the patients monitored will subsequently have indications for major interventions [1]. As response time is a key issue, most monitoring devices are equipped with alarms that alert

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personnel to changes that could place patients at risk. Alarms, however, are a problem in and of themselves: As the signal-to-noise ratio from many devices is low and trigger thresholds are kept low to avoid false negatives, false alarms are very frequent. Only 3 % of the alarms that go off in the operating room [2], and less than 6 % in the ICU [3], are clinically significant. In this scenario, clinically important alarms are left unattended [4, 5] and noise levels surpass safe limits [6], disturbing patients' sleep [7, 8] and increasing personnel burnout [9] while increasing costs and wasting human resources [10].

Once alerted to a problem, personnel must solve it. This usually involves accessing other sources of patient information and medical information to reduce uncertainty and then using it to take decisions. Thus, as the final aim of monitoring is to shorten the time needed to solve the problems that may arise, the problem-solving process should be analyzed to improve the behavior of the entire system.

Figure 1 shows the traditional problem-solving process: When an event occurs, the personnel in charge must first determine whether it is clinically significant; second, they must seek to understand the causes; third, in most cases, they must solve the problem. For example, a mechanical ventilator's 'high airway pressure' alert is a false alarm in nearly 4 of 5 cases, so, the first step is to establish its clinical relevance. Once a false alarm has been ruled out, physicians will need to examine the ventilatory setup, ventilatory pattern, patient's status, flow and airway pressure tracings, etc., to determine what might be causing the rise in peak airway pressure. This additional information coupled with the physician's medical knowledge may suffice to solve the problem. However, if they are unable to determine why the airway pressure is high or to correct the situation, physicians will have to seek additional information from other physicians or in the literature. Because it is so time consuming, this approach is useful in only a few cases.

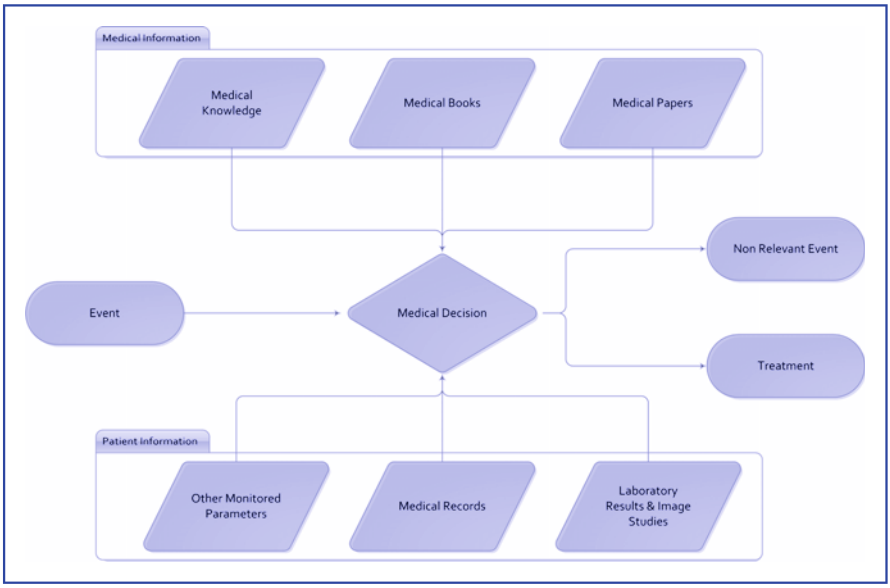

Fig. 1. Traditional medical problem solving process

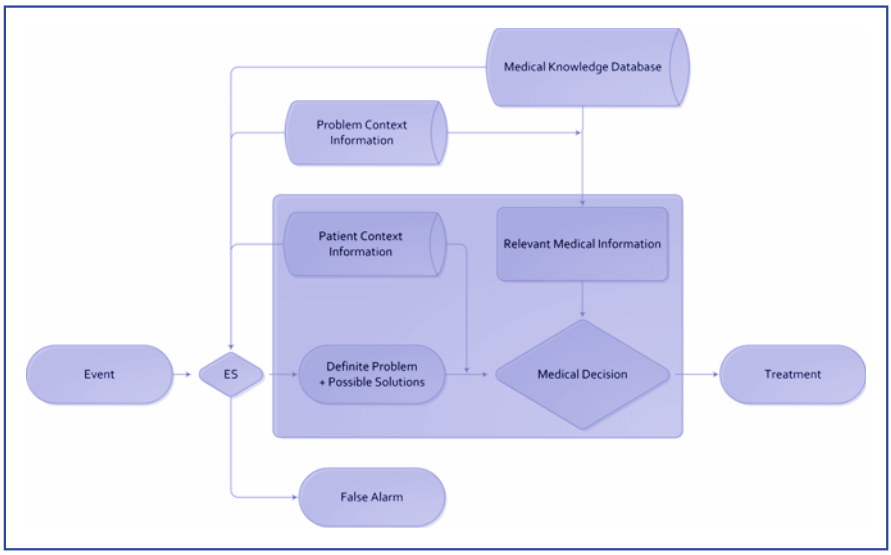

Fig. 2. Alternative medical problem solving process. ES: expert system

There is much room for improvement in the traditional model. **Figure 2** shows an alternative problem-solving process. In this model, an expert system analyzes the event in context and uses a well-defined (or a fuzzily defined) rule to decide to what extent it is clinically significant. Next, it analyzes the airway pressure and, finding a persistent expiratory flow, it checks the ventilatory setup and finds a tidal volume of 12 ml/kg and a 1:1 inspiratory/expiratory ratio. It replaces the low level 'high airway pressure' alarm with a high level 'Auto positive end-expiratory pressure (PEEP)' alarm and recommends that the attending personnel reduce tidal volume and lengthen expiratory time; additionally, the system provides links to some highly relevant articles.

In this model, only a fraction of the total number of events is presented to attending personnel. Using time delays and correlating alarms with clinical contexts can decrease the number of false alarms [11], and automatic detection of context-sensitive changes during surgery can improve tracking of dynamic physiologic systems [12]. Moreover, presenting events effectively converts them into well-defined problems. The patient's context information reduces uncertainty (considering bradycardia, hypertension, and increased intracranial pressure together provides much more information than the sum of the parts) and pertinent medical information is easily available in case physicians need it. As the focus of the physician's attention is narrowed considerably, response time and accuracy should improve markedly.

Context Information and Patient Safety

Patient safety (a key component of hospital performance) is receiving increasing attention at all levels of the healthcare system, most notably in the design of healthcare policies and hospital quality assurance programs. Recently, after care-

ful adjustment for severity of illness, Garrouste-Orgeas et al. [13] demonstrated that experiencing more than two adverse events was associated with a threefold increase in the risk of ICU death. The authors related the following factors to adverse events: Severity of illness, workload, teamwork climate, burnout, and possibly the lack of powerful information systems. The relation between the complex ICU environment, complexity of the patients, and occurrence of medical errors suggests that guidelines, education, and communication skills training might foster a culture of safety in the ICU, thereby decreasing medical error rates.

Many medical errors are not patient specific. Administering food through an enteral feeding tube without checking its position beforehand can lead to serious complications. Protocols are effective at reducing this kind of error. However, there are many situations in which errors derive from a lack of contextual information, such as delivering the standard dose of vancomycin to a patient who has renal dysfunction or ordering magnetic resonance imaging (MRI) for a patient who has a pacemaker made of magnetic metals. To prevent this kind of error, computer decision support systems (CDSS), functions of which vary from providing simple reminders to sophisticated help in diagnosis using artificial intelligence techniques, have become common in the last 30 years. Payne [14] identified the key features of successful CDSSs: They give patient-specific recommendations, they save time, and they are incorporated into the institution's workflow. To provide patient-specific recommendations, a CDSS has to be context aware; context information can be provided by the user, but it is preferable for the CDSS to collect these data directly from their sources (laboratory, pharmacy, monitors, and other systems).

Context Information and Telemedicine

Telemedicine has focused on the application of traditional physician-to-patient and physician-to-physician interactions through video and audio links. This professional interaction via a telemedicine link can dramatically extend a physician's or other caregiver's geographic range and availability. However, this telemedicine model is most often implemented on demand for a specified time-limited encounter. The remote ICU model described here similarly expands the geographic range of ICU physicians. However, it goes further, enabling a single specialist to simultaneously monitor multiple patients on a continuous basis by using an electronic medical record interface and computerized algorithms to detect potential risk situations [15]. Recent studies found that advanced networks can have an impact on telemedicine in several ways. Improved quality of service permits telemedicine to be used to support time-critical procedures such as surgery and critical care [16] or to assess the association of remote monitoring of ICU patients with mortality, complications, and length of stay. Along these lines, Thomas et al. [17] assessed the effects of a tele-ICU intervention on mortality, complications, and length of stay in six ICUs in a large healthcare system by measuring these outcomes before and after implementation of the tele-ICU. These authors found no reduction in overall hospital mortality after the implementation of the tele-ICU in these six ICUs. They did, however, find improved survival in sicker patients. The lack of apparent benefit may be attributable to low decisional authority granted to the tele-ICU as well as to varied effects across different types of patients or to the program's failure to extend the reach, scope, and availability

of intensivist specialty expertise sufficiently. Thus, it seems that telemedicine for critically ill patients would benefit from protocol-based care, computerized order entry, and intelligent alarms with contextual information to help bedside or remote clinicians.

Information and communication technologies have the potential to address many problems encountered in the ICU. Specifically, they make it possible to manage large amounts of patient and research data and to reduce medical errors. The ICU information system allows vital sign data capture, full access to laboratory tests, access to medical images, treatment control, and fluid balance, among others [15, 16]. Applications derived from ICU information systems include electronic clinical records and nursing registries as well as databases for demographic data. Once implemented, clinicians can take advantage of computerized medical prescriptions, full access to stored data, and the possibility of sharing this information among the heath community [18]. Information technology would be useful for managing the large amount of data generated by each patient, but few studies have formally evaluated the effects of introducing an information system into the ICU. Some studies have addressed the benefits of clinical information systems with automated data capture from ICU devices, demonstrating a reduction in nursing workload but this finding is certainly not uniform [19]. Others found the ward round team faced several difficulties when interacting with each other using the electronic record compared with the paper one. The physical setup of the technology may impede the consultant's ability to lead the ward round and may prevent other clinical staff from contributing to discussions [20]. Moreover, the problem of responding to alarms in potentially life-threatening events in the ICU is not solved. Advanced built-in alerts in sophisticated ICU information systems allow alarms to be customized to suit individual patients, and while this has brought about a reduction in common errors of omission or commission, these systems are not yet able to provide context information about all physiologic variables in a given patient [21, 22].

Beyond Patients and Problems

Human-to-human communication is successful thanks to a very rich language (both verbal and non-verbal) and a huge amount of shared general knowledge (from an implicit understanding of everyday situations to a common understanding of how the world works) that increases the communication channel bandwidth. Its main disadvantage is the uncertainty resulting from the way in which coded information at the source is decoded at the receptor. On the other hand, machine-to-machine communication can assure that information coding and decoding is perfect but no 'implicit' information is transmitted. In monitoring, machine-to-human communication offers the worst scenario: Coding-decoding accuracy is not guaranteed and the total lack of implicit information means the message has to be complete. As events in critical care monitoring can be life-threatening, this fragile scenario is of great concern.

Context information can help at this level by characterizing the user (receptor). User skills, for instance, could be critical in choosing the kind of information to be displayed. While some information might seem superfluous to expert users, it might be very useful for less trained ones. Even more, context information could take users' preferences into account (like preferred language, which will be more

important if telemedicine becomes as common as it seems it will in the very near future).

Moreover, context information could provide useful information about technological issues. Monitoring systems could benefit from pervasive and ubiquitous computing. There is no reason to limit critical care monitoring alerts to the bedside. In fact, as different kinds of alerts are intended to warn different staff members, many of them could be dispatched to portable devices. This is a profound change in paradigm (as was the change from 'calling a place' to 'calling a person' brought about by mobile phones). However, technological issues (from differences in display to bandwidth limitations) could make it difficult to show the same information in the same way in all cases. The way in which information is presented changes users' response time and their ability to solve a problem [23]. Thus, it is crucial for monitoring systems to be aware of the characteristics of the network and of the user's device.

Technical Requirements for Providing Context Information in a Monitoring System

Although it is relatively easy to integrate medical information into monitoring systems to provide caretakers with pertinent information, it is far more seductive to create a separate layer using information from different devices, including bedside monitors, clinical information systems, mechanical ventilators or infusion pumps, to analyze the patient's state. The integration of the information coming from these systems to a central hub requires a common language to ensure clear and unique interpretation of data.

For this purpose, a structured and standard model that provides a virtualized, unified view and a common means of access to information coming from multiple and heterogeneous data sources is necessary. A normalized data model should define the interface among heterogeneous systems to guarantee homogeneous data exchange. HL7 is the current standard by which various healthcare systems providing clinical and administrative data can communicate with each other. HL7 defines Conceptual Standards, Document Standards, Application Standards, and Messaging Standards, setting the language, structure, and data types required for seamless integration from one system to another. The version 3 standard (started around 1995) defines a Development Framework to document the processes, tools, actors, rules, and artifacts relevant to HL7 standard specifications, and it also introduces the Clinical Document Architecture (CDA), an XML-based markup standard intended to specify the encoding, structure, and semantics of clinical documents for exchange.

Extensible Markup Language (XML) seems to be a natural choice; it has become a standard for communication between applications and its flexibility and clear structure make it very suitable as a description language for context. **Figure 3** shows an example of context information in XML format.

```
<PATIENT_CONTEXT>
        <PATIENT_ID>234563</PATIENT_ID>
        <HEALTH_STATE>
                <heart_rate>97</heart_rate>
                <respiratory_rate>26</respiratory_rate>
                <oxygen_saturation>96</oxygen_saturation>
                <systolic_blood_pressure>107</systolic_blood_pressure>
                <dyastolic_blood_pressure>58</dyastolic_blood_pressure>
                <body_temperature>37.6</body_temperature>
                <end_tidal_co2>30</end_tidal_co2>
        </HEALTH_STATE>
        <MODS>
                <respiratory>1</respiratory>
                <cardiovascular>2</cardiovascular>
                <coagulation>3</coagulation>
                <glasgow>2</glasgow>
                <renal>1</renal>
        </MODS>
        <VENTILATORY_SUPPORT>
                <ventilatory_support_type>Mechanical Ventilation</ventilatory_support_type>
                <ventilatory_mode>CMV</ventilatory_mode>
                <tidal_volume>0.56</tidal_volume>
                <respiratory_rate>16</respiratory_rate>
                <inspiratory_flow>55</inspiratory_flow>
        </VENTILATORY_SUPPORT>
        <MEDICAL HISTORY>
                <COPD>Yes</COPD>
                <cardiac_failure>No</cardiac_failure>
        </MEDICAL HISTORY>
</PATIENT_CONTEXT>

<USER_CONTEXT>
        <USER_ID>324</USER_ID>
        <training_level>Internal Medicine Resident</training_level>
        <preferred_lenguage>English</preferred_lenguage>
</USER_CONTEXT>

<TECHNOLOGICAL_CONTEXT>
        <device_type>Mobile</device_type>
        <device_display>Color 16bits</device_display>
        <device_resolution>320×480</device_resolution>
        <network>WLAN</network>
</TECHNOLOGICAL_CONTEXT>
```

Fig. 3. XML file for context information exchange

Conclusion

The use of context information can improve many aspects of the critical care process, from medical decisions to alarms and telemedicine issues. The development of context-sensitive applications requires carefully designed interfaces to allow expert systems to interchange pertinent information. Furthermore, context information is by no means limited to characterizing patient-related or problem-related issues; on the contrary, it promises to be of great help in portraying physician-related or technology-related topics. As suggested in a Conference Summary of the Institute of Medicine [24], reaping the full benefits of innovation in diagnostics, therapeutics, and devices requires parallel innovations in the way health-

care is delivered. Context awareness systems could be of some help, but context aware applications will do a better job, providing clever advice, improving alarms, increasing the number of patients that can effectively be attended by a critical care specialist, reducing costs, and improving patients' safety.

References

1. Thibault GE, Mulley AG, Barnett GO, et al (1980) Medical intensive care: indications, interventions, and outcomes. N Engl J Med 302: 938–942
2. Kestin IG, Miller BR, Lockhart CH (1988) Auditory alarms during anesthesia monitoring. Anesthesiology 69: 106–109
3. Lawless ST (1994) Crying wolf: false alarms in a pediatric intensive care unit. Crit Care Med 22: 981–985
4. Koski EM, Makivirta A, Sukuvaara T, Kari A (1995) Clinicians' opinions on alarm limits and urgency of therapeutic responses. Int J Clin Monit Comput 12: 85–88
5. Joint Commission on Accreditation of Health Care Organizations (2002) Sentinel event alert. Preventing ventilator-related deaths and injuries. Washington, DC. Available at: http://www.jointcommission.org/SentinelEvents/SentinelEventAlert/sea_25.htm Accessed Nov 24, 2010
6. Balogh D, Kittinger E, Benzer A, Hackl JM (1993) Noise in the ICU. Intensive Care Med 19: 343–346
7. Aaron JN, Carlisle CC, Carskadon MA, et al (1996) Environmental noise as a cause of sleep disruption in an intermediate respiratory care unit. Sleep 19: 707–710
8. Freedman NS, Gazendam J, Levan L, Pack AI, Schwab RJ (2001) Abnormal sleep/wake cycles and the effect of environmental noise on sleep disruption in the intensive care unit. Am J Respir Crit Care Med 163: 451–457
9. Topf M, Dillon E (1988) Noise-induced stress as a predictor of burnout in critical care nurses. Heart Lung 17: 567–574
10. Noseworthy TW, Konopad E, Shustack A, Johnston R, Grace M (1996) Cost accounting of adult intensive care: methods and human and capital inputs. Crit Care Med 24: 1168–1172
11. Gorges M, Markewitz BA, Westenskow DR (2009) Improving alarm performance in the medical intensive care unit using delays and clinical context. Anesth Analg 108: 1546–1552
12. Dosani M, Lim J, Yang P, et al (2009) Clinical evaluation of algorithms for context-sensitive physiological monitoring in children. Br J Anaesth 102: 686–691
13. Garrouste-Orgeas M, Timsit JF, Vesin A, et al (2010) Selected medical errors in the intensive care unit: results of the IATROREF study: parts I and II. Am J Respir Crit Care Med 181: 134–142
14. Payne TH (2000) Computer decision support systems. Chest 118 (Suppl 2): 47S-52S
15. Murias G, Sales B, Garcia-Esquirol O, Blanch L (2009) Telemedicine in critical care. Open Respir Med J 3: 10–16
16. Wilson LS, Stevenson DR, Cregan P (2010) Telehealth on advanced networks. Telemed J E Health 16: 69–79
17. Thomas EJ, Lucke JF, Wueste L, Weavind L, Patel B (2009) Association of telemedicine for remote monitoring of intensive care patients with mortality, complications, and length of stay. JAMA 302: 2671–2678
18. Groves RH Jr, Holcomb BW Jr, Smith ML (2008) Intensive care telemedicine: evaluating a model for proactive remote monitoring and intervention in the critical care setting. Stud Health Technol Inform 131: 131–146
19. Lapinsky SE (2009) Clinical information systems in the intensive care unit: primum non nocere. Crit Care 13: 107
20. Morrison C, Jones M, Blackwell A, Vuylsteke A (2008) Electronic patient record use during ward rounds: a qualitative study of interaction between medical staff. Crit Care 12: R148
21. iMDsoft. MetaVision for ICUs Available at: http://www.imd-soft.com/metavision-for-icus. Accessed 24 November 2010

22. Philips Electronics N.V. VISICU. Available at: http://www.healthcare.philips.com/main/products/patient_monitoring/products/eicu/index.wpd. Accessed 24 November 2010
23. Uzawa Y, Yamada Y, Suzukawa M (2008) Evaluation of the user interface simplicity in the modern generation of mechanical ventilators. Respir Care 53: 329–337
24. Institute of Medicine of The National Academies (2002) Medical Innovation in the Changing Healthcare Marketplace: Conference Summary. National Academy Press, Washington DC

XVIII The Future

Ambient Intelligence in the Intensive Care Unit: Designing the Electronic Medical Record of the Future

B.W. Pickering, J.M. Litell, and O. Gajic

Introduction

Electronic medical record (EMR) systems have a lot to live up to. They have been proclaimed as the solution to many of the ills that afflict our health care systems, offering lower costs, fewer errors, increased efficiency, as well as clinical decision support for providers and patient empowerment. While the potential benefits are encouraging, in truth these claims are largely unsubstantiated. Where evidence does exist, the results are often conflicting or compromised by methodological limitations. As EMR systems become more prevalent, their impact on the quality and safety of health care delivery – good, bad or indifferent – will be amplified. In this chapter, we outline some of the key opportunities and challenges associated with the development and testing of integrated electronic environments and present a vision for the incorporation of smart EMR systems into acute care. With rigorous attention to development and testing, we contend that such systems will yield higher quality, safer care for our patients.

Intensive Care Can Be Costly and Error-Prone

Each year in the United States almost six million adults are admitted to the intensive care unit (ICU), and one in five Americans dies there [1]. The ICU is a costly place to receive care; estimates of the cost of providing intensive care services in the US approach 1 % of gross domestic product, or roughly 20 % of aggregate hospital budgets nationwide. At the same time, physicians, regulators, and the public have learned that preventable medical errors are a leading cause of death in the US, accounting for an estimated 44,000 to 98,000 deaths per year [2]. Although these numbers have been contested, the acute care community has identified the elimination of error in the ICU as a priority. In the recent declaration of Vienna, leaders of all major ICU societies described patient safety as being "of paramount importance to every practicing health professional and one of the major challenges of modern day medicine" [3]. One of the few studies to assess error rates in intensive care involved the observation of patient care in Israeli ICUs [4]. The authors reported an average of 178 observed processes of care per patient per day, 1.7 of which were associated with some error. Overall, this study identified more than 500 errors in a four month period, 200 of which were described as serious.

There are several likely contributors to these rates of both general and serious error. From a systems perspective, these include increasingly complex work envi-

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ronments, a lack of standard practices, provider fatigue, high workload, shift work effects, and inconsistent communication among team members. These factors converge to produce a hazardous environment in which preventable errors, poor outcomes, and high costs are common. Given these conditions, EMR systems that demonstrably enhance the quality and safety of care delivery will have a distinct advantage, but this requires a significant change in the way these EMR systems are developed and tested.

Medical Decision Making Takes Place in a Distributed Cognitive Network

Medical decision making is complex, especially in the ICU, where a high level of cognitive processing is required to manipulate multiple disparate types of data. Important information cues from human and artificial agents (physiologic monitors, medical records, radiographic images, patients and family members) must be processed and integrated by multiple providers in a variety of combinations (Fig. 1). The theory of distributed cognition suggests that intelligent behaviors, such as medical decision making, are built upon a network of interactions between such agents, and that the performance of the network can be altered by changes in their individual characteristics [5].

There are currently widespread calls for an acceleration in the "meaningful use" of EMR systems [6]. Under present conditions, this will challenge established

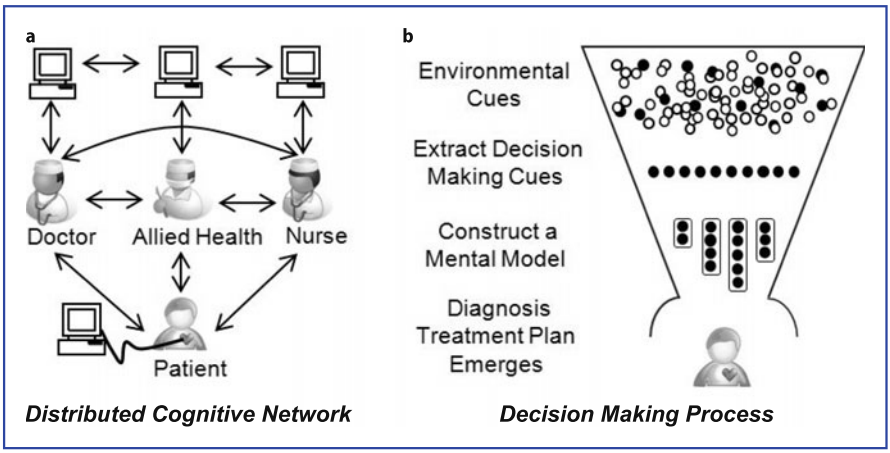

Fig. 1. **a** Representation of the distributed cognitive network. The ICU is a complex environment consisting of providers and patients (human agents), and technological and physical objects (artificial agents). The theory of distributed cognition suggests that complex behaviors such as medical decision making are built upon the interactions between human and artificial agents. Changes in any one of the elements in this type of a network can have an impact on the established cognitive behaviors. A deeper understanding of the distributed cognitive network in the ICU is necessary if we are to develop technologies that enhance, rather than disrupt network function. **b** Simple schematic of decision making in complex environments. The care of patients in the ICU generates large quantities of data. From this, the provider is challenged to extract relevant data and construct an accurate picture of the patient. Understanding information needs of providers will facilitate the development of smart, context specific displays which facilitate high quality care delivery.

cognitive networks, likely without a complete understanding of how these changes impact medical decision making and care delivery. Caution is essential here – the development of safe and effective electronic resources depends on a more complete understanding of the associated distributed cognitive networks. Opportunities exist for researchers to model cognitive networks and design system support tools that will lead to better patient outcomes. The complexity of the ICU and the vulnerability of critically ill patients make this an ideal clinical arena in which to develop that understanding.

Information Overload Impairs Timely and Rational Decision Making

The complexity of the ICU distributed cognitive network arises not only from the variety of data sources, but also the sheer quantity. Information overload represents one of the prime challenges of the informatics age, and its influence is profound, poorly understood, and likely accelerating [7]. A recent Canadian study estimated that the care of critically ill patients generates a median of 1348 individual data points per day [8]. This quantity has increased by approximately 26 % in the last five years, facilitated in part by the introduction of EMR systems. In their current iteration, these systems specialize primarily in the aggregation and storage of large quantities of minute-to-minute patient data. These elements are often scattered throughout the electronic environment, impairing pattern recognition and potentially delaying intervention [9]. Although the associated impact on providers is poorly understood, it is likely to be particularly relevant in the ICU, where severe illness and complex care delivery create an environment that can overwhelm providers' cognitive capacity [10]. Given the sophistication of modern computing technology, this interference with pattern recognition is an unnecessary side effect of the current approach to the design of EMR systems.

Parsing these vast repositories of data cues and defining the subset that is valuable to decision making is an essential first step in the development of a smarter electronic environment – one that eliminates information overload and allows a comprehensive clinical picture to emerge. EMR systems developed without knowledge of these cues will fail to manage data effectively, and will not fulfill their potential. Groups that invest time and energy to overcoming this challenge will be positioned to build tools that reliably extract important data from the electronic environment and present it clearly to bedside providers within the context of their workflow. This structured approach may yield tools that reduce cognitive errors and time to decision making, and may contribute to greater frontline acceptance of EMR systems [11].

EMR Systems may Facilitate Medical Error

While EMR technology is often lauded as a fundamental component of a new model of safer care delivery systems, widespread deployment of these systems without sufficient testing is potentially dangerous. Current knowledge gaps may complicate the construction of EMR systems that reliably meet our high expectations.

Generally speaking, the development of EMR systems has occurred with insufficient attention to the decision making environment in which they will be deployed [12]. Most current systems are essentially simple data repositories that

provide only basic layers of context (data, time, etc), and actionable information, such as physiologic trends, can be difficult to extract. By failing to distinguish between high value data and noise, the current generation of EMR systems places an unnecessary cognitive load on already overburdened decision makers. An incomplete understanding of provider workflow and information needs means that newly adopted EMR systems can complicate decision making by obscuring key data and disrupting cognitive processes [13]. This may produce unintended delays in time sensitive interventions, possibly increasing the very errors the system was intended to reduce. One graphic example of this occurred in a pediatric ICU where the introduction of a computerized physician order entry (CPOE) system was associated with a sustained doubling of mortality [14]. A subsequent review implicated a failure to adequately anticipate the impact of CPOE on care delivery, and called for alternative testing paradigms to identify potentially dangerous consequences of the electronic environment [15]. This example underscores the need to establish a baseline understanding of care processes and medical decision making as a prerequisite for EMR development. Furthermore, new EMR systems should undergo rigorous scrutiny of their impact on those processes prior to installation in the clinical setting.

Adoption of New Electronic Tools Must Be Preceded By Rigorous Testing

Currently only 1.5 % of American hospitals employ a comprehensive EMR, as defined by the presence of electronic functionality in all clinical units [16]. As accelerating political and social forces steer hospitals towards widespread implementation of EMR systems, it is essential for clinicians to consider how EMR systems can be tested against patient centered outcomes. To date, testing has primarily been conducted by groups responsible for the design and sale of EMR and CPOE systems, and has emphasized usability and technical issues. Although expanded testing standards have been proposed, they are by no means universal. For example, no currently available system has been subjected to the expanded standards proposed by the Healthcare Information and Management Systems Society (HIMSS) [17]. However, there is an increasing awareness among information technology experts that clinical systems operate in unique environments and that testing must reflect outcomes of relevance to providers and patients [18].

The underutilization of standardized testing procedures underlies some of the concerns of frontline providers confronted with the prospect of integrating EMR systems into their practice [19]. For these providers the primary outcome of interest is a good patient outcome delivered in a cost effective manner [20]. These broad concepts must be deconstructed into measurable components. Specifically, testing paradigms should include metrics that assess the impact of EMR systems on error frequency and omitted or wasteful steps in acute care delivery processes. Furthermore, both testing and development should ideally occur in high fidelity simulated environments that allow researchers to identify beneficial characteristics of EMR systems while insulating patients from potential harm [21]. The lack of such facilities and methods are key barriers to the development of EMR systems that reliably improve the outcomes of interest to frontline providers [22].

Potential Solutions

Simple Tools Can Improve System Performance and Patient Outcomes

Several simple systems-based tools have been successfully incorporated into ICU practice with measurable improvements in patient centered outcomes. Prominent examples include checklists for the placement of central venous catheters, daily patient care goal lists, and clinical practice guidelines [23]. While successful when used consistently, these static tools lack the responsiveness and oversight capability of applications developed for the electronic environment. For example, daily checklists can be reproduced in a 'smart' electronic form, taking advantage of the system's ability to retrieve relevant data and display only the items needing completion, with a direct CPOE link. Analogous non-medical examples include smartphone to-do list applications that take advantage of onboard global positioning system technology to restrict the list of displayed items to those that are relevant to the user's current location. The appeal of these applications is their relatively effortless integration into the end user's workflow, the lack of which is a key barrier to the widespread acceptance of clinical checklists and decision [24]. Miniaturization and mobile technology afford new opportunities to developers, but regardless of the hardware, EMR systems will remain fundamentally flawed unless resources are devoted to understanding clinical workflow. Once refined, accurate models of these processes will allow developers to more effectively integrate new tools into the clinical environment.

Ambient Intelligence Principles Can Guide the Development of a Smarter EMR

While we have characterized information overload as a threat, the repository function of comprehensive EMR platforms is also their potential saving grace. The vast quantity of data contained within the EMR represents an almost complete digital record of patient disease states, potential decision making cues, and associated provider actions, all of which can undergird the development of better data displays and decision support tools [25]. By applying rules to these databases, we can offer teams of providers comprehensive physiologic surveillance and feedback.

The concept of ambient intelligence describes an evolutionary step beyond standard data interfaces. It has been generically defined as interactive technology with the capacity to respond to changing contexts and to intelligently assist humans in the completion of tasks [26]. In the idealized ICU, this would take the form of an electronic environment that could recognize physiologic patterns and anticipate the information needs of providers, prompting them with 'smart' alerts and adaptive user interfaces. The incorporation of models of provider workflow could further facilitate the deployment of context-sensitive displays of patient data, resulting in an EMR that assists providers in completing tasks as proficiently and with as few errors as possible.

Many of the conditions for the development of ambient intelligence ICU applications currently exist. Multiple hardware interfaces, in the form of smart phones and gesture based user interfaces, have been developed and tested; databases of digital cues, including patient physiology and corresponding provider actions, are increasingly complete; financial and political incentives for the deployment of comprehensive EMR systems are in place; and increasingly sophisticated end users are driving demand for well designed electronic applications. However, this momentum must incorporate a clear-eyed understanding of current knowledge

gaps, such as the validation of existing digital cues, representative workflow models for health care delivery processes, an understanding of the most relevant information needs of the providers at each step of workflow, and patient centered outcome measures that facilitate reflect the impact of new systems.

Practical Examples from a Single Institution

In the following section, we describe a single center's initial experience in applying ambient intelligence principles to the ICU electronic environment – including the necessary infrastructure and determination of task-specific information needs – and provide examples of projects under development, such as CPOE forcing functions, smart alarms, and parsimonious data displays. In addition we provide a general framework for the development and testing of ambient intelligence applications in critical care.

The development of next generation EMR systems is beyond the scope of any group of individuals with a focused area of expertise. Rather, successful applications require close collaboration between software and systems engineers, informatics experts, clinicians, cognitive psychologists, and designers. Assuming the relevant expertise can be gathered, the development of ambient intelligence applications requires access to a preexisting high fidelity electronic environment, dense in real-time patient and provider data, and a clinical institution supportive of patient centered collaborative research and development. The involvement of end users at each phase of the development process greatly enhances the chances of success.

Building a Comprehensive Informatics Infrastructure

A fundamental requirement is the availability of comprehensive electronic cues that accurately represent patient physiology, provider actions, and care delivery processes. At Mayo Clinic's campus in Rochester, Minnesota, medical records for all new patients have been in electronic form since March 2005. This includes data from roughly 15,000 new ICU patients per year, divided among seven adult ICUs. The Clinic's custom system enables direct access to raw data sources facilitating sophisticated secondary data usage for multiple purposes. Mayo's Multidisciplinary Epidemiology and Translational Research in Intensive Care (METRIC) collaborative has developed and maintains a custom relational research database that contains a near-real time copy of the EMR of ICU patients. The so-called METRIC DataMart serves as the main data repository for the development and validation of tools for error prevention, decision support, reporting, and epidemiological investigations [27]. This provides the necessary data cues to which we can apply rules based on our assessment of provider information needs.

Defining Provider Information Needs

We prospectively examined more than 1200 physician-patient interactions by approaching providers shortly after ICU patient admission and asking them to identify data cues used in the management of that particular patient [28]. After ranking the resulting cues according to frequency of utilization, we analyzed the relative ranking of cues across various contexts (ICU type, provider role and level of experience, admission diagnosis). Using these data, we have extracted patterns of data cues

that are highly conserved across all contexts and are developing these into rules for data display, as well as other tools. These applications share an emphasis on patient safety and provider performance as important outcome metrics.

Developing Metrics for Work Load, Medical Error, Omissions, and Waste

The measurement of work load, defined as the subjective burden attributable to the performance of a standardized task, has long been essential to other high-tech, high-risk industries. In the US, astronaut training has for several years incorporated the NASA Task Load Index (TLX), an objective, validated metric of cognitive load [29]. This tool has increasingly found applications in health care, although its use in the comparison of electronic environments in the ICU setting is still uncommon [30]. We are evaluating this and other tools for their reliability and validity in the standardized evaluation of EMR systems. Errors in the ICU may profoundly impact a patient's clinical course and subsequent outcome. Any group intending to develop EMR systems, the primary functions of which include error reduction, faces the challenge of validating reliable metrics for error, omissions and waste in patient management. To date our attempts at developing such tools has involved a hybridization of clinical practice guidelines and a modified Delphi process to assess consensus expert opinion. The goal of this approach is to generate profiles of optimum actions for defined tasks, which will be validated against meaningful patient outcomes. Incorrect or delayed performance of these actions or their omission altogether, will be identified as error. Once validated, we anticipate that this methodology could be used to guide the development of clinical decision support tools as well as curricula and assessment modules.

Designing Progressively Complex EMR Applications for the ICU

Passive electronic oversight of transfusion orders

One of our institution's first efforts in electronic oversight was the introduction of a CPOE forcing function designed to reduce unnecessary patient exposure to the risks associated with red blood cell (RBC) transfusion. This simple decision support tool prompted providers to justify their transfusion order based on physiologic parameters (acute bleeding, ischemia, early septic shock) rather than specific hemoglobin concentrations. The implementation of this tool was associated with a reduction in transfusion of greater than 1,000 units of packed RBCs during a three month period, and a decrease in transfusion-related complications from 6.1 to 2.7 % [31]. Although this project has illustrated the potential impact of oversight embedded within the CPOE system, the additional step between providers and desired actions can disrupt workflow and is a relatively crude means to engineer patient safety.

Active oversight of mechanical ventilation (a "sniffer" for ventilator-induced lung injury)

At a somewhat more sophisticated level, the first true ambient intelligence tool developed and deployed in our ICUs was an automated alert for ventilator-induced lung injury (the "VILI sniffer") [32]. This application continuously surveys the electronic environment for predefined contextual cues suggestive of lung injury. These include a PaO_2/FiO_2 ratio below 300, certain biometric data, and free-text searches of radiology reports for "bilateral infiltrates" or "edema" on

recent chest radiographs. When detected, these trigger a secondary search for expected provider actions. If a patient with an electronic signature suggestive of lung injury is not receiving appropriate lung-protective ventilation, the sniffer alerts bedside providers via text pager to check ventilator settings. In contrast to the CPOE alert for transfusion decision support, which is activated by any provider's attempt to order RBC products in any patient, the VILI sniffer runs continuously and unobtrusively in the electronic environment, and only interrupts workflow when a pattern of predefined conditions are encountered. We have found that the VILI sniffer results in significantly less exposure to potentially injurious ventilator settings with minimal disruption to established workflow.

A parsimonious data display for the ICU

Based on these initial experiences, we have undertaken to develop a novel EMR platform designed using ambient intelligence principles and intended to more directly connect providers with decision making cues in the electronic environment. The impetus for the development of this tool has in part come from the input of clinical leaders in our practice, who have identified information overload as a growing threat to provider workflow and patient safety. The current intensivist workflow at Mayo Clinic involves the need to constantly access multiple applications in order to gather the patient data cues necessary to make informed decisions and to mentally filter data that are irrelevant to the task at hand. We believe that this exposes our patients to many of the risks discussed earlier in this chapter, and have begun a collaborative effort to remedy this daily clinical reality by designing a smarter EMR that we hope will serve as an example of the potential of ambient intelligence concepts.

Building from our efforts to identify highly conserved data utilization patterns for ICU providers, we have developed rules for the extraction of patient and provider data from the electronic environment, as well as a user interface that has been optimized to the tasks involved in managing newly admitted critically ill patients [11]. The resulting tool is a .NET based application that dynamically displays highly conserved patient data in real time on a single screen, grouped by organ system. Each grouping includes relevant data from multiple sources (physiologic monitors, laboratory results, past medical history, medications, investigations, provider actions) that have been identified in our research as being most relevant to the management of the patient.

Testing Novel Tools in a Safe, High-Fidelity Environment

A high-fidelity simulated clinical environment is an important component of any evaluation of novel ambient intelligence applications. EMR applications should not advance to clinical practice without satisfying the requirement to facilitate, rather than obstruct, safe task completion. Our expectation is that EMR interfaces constructed using ambient intelligence principles will outperform the standard available EMR, resulting in improved provider performance and reducing medical errors and associated workload. These expectations are consistent with those from other industries – parsimonious data displays, designed around specific tasks, reduce cognitive load and improve human performance. However, as with any intervention, these expectations must be subjected to rigorous and transparent testing so that we can ensure only the safest, most effective tools advance to the bedside.

Conclusion

The application of rules to data aggregated within a high fidelity EMR can transform the electronic environment from a passive repository into a smart member of the health care team. These tools will support providers in the error free completion of common patient management tasks, such as admission, rounding, resuscitation, handoff, and discharge. This type of smarter EMR could have substantial implications for patient safety and the effectiveness of intensive care.

The principal differences between ambient intelligence and traditional electronic environments include the processing and display of data and the nature and extent of integration into the workflow of the healthcare team. A tremendous amount of development time and refinement is necessary to ensure the unobtrusive and efficient deployment of this type of novel tool into the clinical environment. By carefully considering the proper place of ambient intelligence within the distributed cognitive network of the ICU, it is possible to transform even simple rule-based applications into effective tools for reducing medical error. The comparative effectiveness of one application over another to reduce error could be a powerful stimulus for the refinement and distribution of only those electronic tools that impact favorably on patient-centered outcomes.

Considerable effort is required to focus the development of EMR systems on these outcomes, in large part due to gaps in our understanding of issues relevant to the digitalization of the hospital environment, such as the definition of provider information needs, modeling of clinical workflow, and understanding established processes of care delivery. A unique opportunity exists for clinical researchers working in multidisciplinary teams to fill those knowledge gaps, and thereby participate in the construction of a safer model of high quality care delivery for our patients.

References

1. Angus DC, Barnato AE, Linde-Zwirble WT, et al (2004) Use of intensive care at the end of life in the United States: an epidemiologic study. Crit Care Med 32: 638–643
2. Institute of Medicine (1997) To Err Is Human. Building A Safer Health System. National Academy Press, Washintgon
3. Moreno RP, Rhodes A, Donchin Y (2009) Patient safety in intensive care medicine: the Declaration of Vienna. Intensive Care Med 35: 1667–1672
4. Donchin Y, Gopher D, Olin M, et al (1995) A look into the nature and causes of human errors in the intensive care unit. Crit Care Med 23: 294–300
5. Zhang J, Norman DA (1994) Representations in distributed cognitive tasks. Cognitive Science 18: 87–122
6. Blumenthal D (2009) Stimulating the adoption of health information technology. N Engl J Med 360: 1477–1479
7. McIntosh N (2002) Intensive care monitoring: past, present and future. Clin Med 2: 349–355
8. Manor-Shulman O, Beyene J, Frndova H, Parshuram CS (2008) Quantifying the volume of documented clinical information in critical illness. J Crit Care 23: 245–250
9. Zheng K, Padman R, Johnson MP, Diamond HS (2009) An Interface-driven Analysis of User Interactions with an Electronic Health Records System. J Am Med Inform Assoc 16: 228–237
10. Pickering BW, Hurley K, Marsh B (2009) Identification of patient information corruption in the intensive care unit: using a scoring tool to direct quality improvements in handover. Crit Care Med 37: 2905–2912
11. Pickering BW, Herasevich V, Ahmed A, Gajic O (2010) Novel representation of clinical

information in the icu: developing user interfaces which reduce information overload. Applied Clinical Informatics 1: 116 – 131
12. Southon G, Sauer C, Dampney K (1999) Lessons from a failed information systems initiative: issues for complex organisations. Int J Med Inform 55: 33 – 46
13. Ash JS, Berg M, Coiera E:(2004) Some Unintended Consequences of Information Technology in Health Care: The Nature of Patient Care Information System-related Errors. J Am Med Inform Assoc 11: 104 – 112
14. Han YY, Carcillo JA, Venkataraman ST, et al (2005) Unexpected increased mortality after implementation of a commercially sold computerized physician order entry system. Pediatrics 116: 1506 – 1512
15. Sittig DF, Ash JS, Zhang J, Osheroff JA, Shabot MM (2006) Lessons from "Unexpected increased mortality after implementation of a commercially sold computerized physician order entry system". Pediatrics 118: 797 – 801
16. Jha AK, DesRoches CM, Campbell EG, et al (2009) Use of electronic health records in U.S. hospitals. N Engl J Med 360: 1628 – 1638
17. Belden JL, Grayson R, Barnes J (2009) Defining and Testing EMR Usability: Principles and Proposed Methods of EMR Usability Evaluation and Rating. Available at http://www.himss.org/content/files/HIMSS_DefiningandTestingEMRUsability.pdf Accessed November 2010
18. Carroll C, Marsden P, Soden P, Naylor E, New J, Dornan T (2002) Involving users in the design and usability evaluation of a clinical decision support system. Comput Methods Programs Biomed 69: 123 – 135
19. Garg AX, Adhikari NKJ, McDonald H, et al (2005): Effects of computerized clinical decision support systems on practitioner performance and patient outcomes: A systematic review. JAMA 293: 1223 – 1238
20. Walsh SH (2004) The clinician's perspective on electronic health records and how they can affect patient care. BMJ 328: 1184 – 1187
21. Kushniruk AW, Patel VL (2004) Cognitive and usability engineering methods for the evaluation of clinical information systems. J Biomed Inform 37: 56 – 76
22. Kaushal R, Shojania KG, Bates DW (2003) Effects of computerized physician order entry and clinical decision support systems on medication safety: a systematic review. Arch Intern Med 163: 1409 – 1416
23. Pronovost P, Needham D, Berenholtz S, et al (2006) An intervention to decrease catheter-related bloodstream infections in the ICU. N Engl J Med 355: 2725 – 2732
24. Moxey A, Robertson J, Newby D, Hains I, Williamson M, Pearson SA (2010) Computerized clinical decision support for prescribing: provision does not guarantee uptake. J Am Med Inform Assoc 17: 25 – 33
25. Li M, Pickering BW, Smith VD, Hadzikadic M, Gajic O, Herasevich V (2009) Medical informatics: an essential tool for health sciences research in acute care. Bosn J Basic Med Sci 9 (Suppl 1): 34 – 39
26. Riva G: Ambient intelligence in health care. Cyberpsychol Behav 2003 6: 295 – 300
27. Herasevich V, Pickering BW, Dong Y, Peters SG, Gajic O (2009) Informatics infrastructure for syndrome surveillance, decision support, reporting, and modeling of critical illness. Mayo Clin Proc 85: 247 – 254
28. Pickering BW, Gajic O, Trillo Alvarez CA, Afessa B, Keegan MT (2008) Identification of data points which contribute to icu medical decision making. Crit Care Med 36 (12 Supplement): A83 (abst)
29. Cao A, Chintamani KK, Pandya AK, Ellis RD (2009) NASA TLX: Software for assessing subjective mental workload. Behav Res Methods 41: 113 – 117
30. Young G, Zavelina L, Hooper V (2008) Assessment of workload using NASA Task Load Index in perianesthesia nursing. J Perianesth Nurs 23: 102 – 110
31. Rana R, Afessa B, Keegan MT, et al (2006) Evidence-based red cell transfusion in the critically ill: quality improvement using computerized physician order entry. Crit Care Med 34: 1892 – 1897
32. Herasevich V, Yilmaz M, Khan H, Hubmayr RD, Gajic O (2009) Validation of an electronic surveillance system for acute lung injury. Intensive Care Med 35: 1018 – 1023

Simulation in Critical Care Medicine: The Next Ten Years

P.G. Brindley

Introduction

Simulation is a risk-free strategy to improve training, competence, and efficiency [1–9]. It also has the unique- but, as yet, not fully realized- potential to improve clinical outcome [1–4]. It has, therefore, already been identified by many professional societies as a prime means by which to improve patient safety [1, 2]. Some authors have also argued that, over the next decade, simulation will increasingly become a social justice imperative in order that those disadvantaged by income or illness do not also suffer disproportionately from inexperienced practitioners [9]. Others are increasingly endorsing simulation as essential to spur a badly needed "culture of safety" [2, 5]. For all of these reasons and more, simulation in critical care medicine needs to be prioritized and promoted. It is not a luxury, and we should not wait. However, as well as 'doing it right now' we need to 'do it right'. As well as arguing that we need 'more', we should understand exactly what we need 'more of'.

For the last decade, the case for simulation has been made repeatedly, eloquently and persuasively [1–9]. What has been comparatively lacking is a clear vision of just what critical care simulation programs should aspire to become (**Box 1**). In other words, the first step for simulation was to persuade and engage: The so-called 'why' of simulation. What will be increasingly needed in the next decade is the 'what' of simulation. Without a clear destination, simulation will not fully mature into a clear scientific discipline, nor will its potential be systematically leveraged towards better patient care.

Box 1. Ten developments for acute care simulation in the next ten years.

Facilitate the science of clinical performance
Facilitate the science of managing complexity
Incorporate 'process engineering' principles into curriculum development
Encourage competency-based, rather than time-based, criteria for training
Encourage a focus on the 'system' not just the individual
Encourage 'deliberate' education and training better matched to patient safety
Become the patient safety laboratory for the modern healthcare system
Become a vehicle for Crisis Resource Management
Become a key technique for team training
Foster a culture of safety

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The Danger of Complacency

Patient safety in developed countries is good...but it is certainly not good enough. It has been widely publicized that medical errors are the eighth leading cause of death, and as many as 100,000 people die annually from preventable medical errors in the United States alone [10]. Many more patients are damaged, and many exposed to errors, but lucky enough to suffer no obvious harm [11]. The first point to make is that simulation is more than just a novel educational strategy. Instead, over the next decade it should mature into a key tool for error mitigation.

Simulation programs will become increasingly commonplace in urban academic critical care programs. However, the goal of patient safety is to cover the entire health delivery system, not just its most specialized and technologically-dependant end. As such, the next phase of simulation's growth has to be to include simulation outside of traditional centers. This might be realized using electronic simulation, portable simulation, or by providing satellite services. Regardless, without a concerted effort, medical simulation may remain the purview of established medical ivory towers. This could perpetuate a primary focus on research publication over clinical change, intellectual property over sharing, patient through-put over patient safety, and in-hospital care instead of care across the continuum. This is not to denigrate the essential role of the academic center. In fact, if simulation truly is to become a "revolution in health care" [1, 2], then, as will be discussed below, we will need to grow the academic science of clinical performance. We also need to make a science of reducing healthcare's complexity.

Of course, securing dependable long-term funding will remain a priority. However, proponents need to understand that if the first stage of simulation was about engaging educators then the next decade also has to be about recruiting researchers. Without robust research data, simulation may remain little more than a 'faith-based initiative', with both zealous supporters and reactionary opponents – but little conclusive evidence to sway the agnostic majority. However, even with data, changing medicine's traditions will likely always be slow going. For example, despite the demonstrated benefits of preoperative briefings, and their recent endorsement by the World Health Organization, their use remains relatively low [12, 13]. Physicians and other health-care providers need to be convinced. They need to believe that incorporating new processes into their practice will have a significant enough positive impact in order to make change a priority.

Healthcare workers have developed norms of practice that- whether ideal or not- have served them faithfully. As a result, simply telling somebody that innovations are in the 'best interest of their patients', and then expecting immediate change is naïve. Instead, proponents need to commit to a long-term strategy of data, persistence, and pressure. Failure to do so will likely mean that simulation continues to be seen as a luxury, to be addressed after 'more pressing' concerns. Expressed another way, for simulation to achieve deliberate progress, it must commit to a more deliberate approach. Therefore, it is worth outlining what it will take to design a modern simulation curriculum, and a meaningful simulation research agenda.

Engineering a Better Simulation Experience

Unfortunately, in addition to lamentable patient safety figures, traditional medical curricula have been best described as 'accidental' [14]. Simulation must play a key role in making education and training more 'deliberate'. For example, currently, in pre-clinical years, we typically rely upon teachers to simply cover their favorite topics, with minimal attention to relevance. This is also despite knowledge that the didactic method is poorly translated to the clinical arena [15]. Meanwhile, during clinical training, education is still usually described in terms of time rather than competence, or what has been called 'input experience' [16]. For example, trainees are told that they will "spend two months attached to the ICU team". Once a clinician completes formal training, the requirements for continuing education are typically minimal and self-directed. The transformation over the next decade should be towards less focus on 'input experience' and more on 'outcomes-based education' [16]. For example, an 'outcomes based approach' would specify that: "by the end of your rotation you will safely perform the following activities....", or for the seasoned clinician "each five years you will demonstrate the following...". Simulation will have a key role to play in an outcomes-based evaluation. It should also fill in 'educational gaps' that are inevitable in a system that relies upon the random presentation of patients.

National educational organizations have recently summarized the skills expected of the modern trainee and practitioner. These include the Canadian CanMEDs model, the American Accreditation Council for Graduate Medical Education, and the United Kingdom's General Medical Council's Good Medical Practice [17–19]. These frameworks expand medical competencies from knowledge alone to- more difficult to define but no less important- competencies such as collaboration, communication, professionalism, and clinical judgment. It is hard to know how these can be realized, quantified, or evaluated, without simulation. In a similar vein, any simulation program would be wise to build future curricula around these modern educational domains.

A logical simulation curriculum should also be more deliberately matched to safety data [11]. After all, most of our clinical errors are predictable. Studies have repeatedly shown that poor communication, poor teamwork, procedural mishaps, drug errors, and postoperative complications (such as infections and thrombi) represent a majority of adverse outcomes [20–23]. In other words, if education really is about improving outcomes then we also know which problems warrant our finite attention [11, 25]. Routine audits could establish major problem areas (i.e., common shortfalls; steps that require particular precision; or processes that require the coordination of many people). These results should then be widely shared, rather than just the purview of a select few senior clinicians or administrators. A relevant curriculum can then be drafted (using all relevant experts and a modified-Delphi approach) and alpha-tested in order to produce a polished product. Next, wide-scale dissemination occurs using the optimized material (i.e., beta testing) [2, 11]. The process then begins again, *ad infinitum*. In this way, educators are not merely passing facts from one generation to another, but are in fact running the patient safety laboratory (or 'crash-test site') for modern healthcare [2, 11]. We are also applying principles of 'process engineering' to medical training and clinical care delivery. In this way, simulation educators become important agents of change, and as highly valued as good researchers or clinicians [11].

Too often, educational courses are designed and run, and only after their completion do investigators try and make sense of the data that has been generated [16]. As a result, the future of simulation will necessitate research questions that are predefined, but also more ambitious: "What features of medical simulation lead most to effective learning?" Over the next decade, simulation research must increasingly look at outcomes, and particularly those outcomes at the higher end of Kirkpatrick's hierarchy [26]. These are as follows: Level 1: participation in educational experiences; Level 2a: change of attitudes; Level 2b: change of knowledge and/or skills; Level 3: change in behavioral practice; Level 4a: change in professional practice; Level 4b: benefit to patients. Previously, the focus was on levels 1 and 2 or what had been described as "happy scores" [16]. For example, we can rate the first two levels of Kirkpatrick's hierarchy by simple questionnaires, given before and after a course. However, even the biggest simulation enthusiast should admit that the lower levels of evidence are unlikely to change behavior. Questionnaires may have been useful in the early days to demonstrate to skeptics that learners responded positively to simulation-based education. In the next decade, they may still provide useful teaching evaluations. However, they are no longer likely to garner publication.

Other high-risk professions did not wait for scientific proof before initiating simulation [25], and, as a result, nor should critical care medicine [11]. However, if simulation is really about a new approach to error reduction [2], then it must be open to unbiased examination followed by full disclosure. This means there is no choice but to push research, publication, and debate [16]. This also means that simulation programs of the future will require more than just enthusiasm and money. They also need to reach out to the widest possible talent-base. This will presumably include psychologists, human-factors experts, and educational theorists. It will also mean a continued 'charm offensive' with those that have, so far, remained unconvinced.

Updating our Understanding of Simulation

As outlined above, simulation already has both fervent apologists and vocal critics. These battle-lines are not only destructive; they are also increasingly outdated. For example, it must be admitted that medical simulation has yet to be shown to directly save lives. However, considerable evidence has now shown the unique ability of simulation to create safer patient environments [1–8]. Although research must continue, simulation has already shown that it can increase adherence to clinical guidelines, decrease time to competence, enhance team performance, and increase skill retention when compared to didactic instruction [1–8]. Therefore, another key future step will be to stop denigrating simulation for its supposed lack of proven benefit. Given deplorable adverse outcome data [10], despite decades of traditional research, even skeptics need to accept the need for alternatives such as simulation.

On the other hand, simulation's proponents must also acknowledge that it is far from perfect, and far from a panacea. For example, simulation is not realistic enough, sufficiently proven, or sufficiently resourced, to justify a wholesale rejection of bedside learning. It is, therefore, best understood as a supplement to, not a replacement for, traditional training and maintenance of competence. Simulation can shorten the learning curve, decrease knowledge decay, permit manual

skills development before any patient exposure, improve performance under stress, finesse teamwork, and even optimize communication [2–8]. However, it is also only one technique to improve safety. Moreover, it is not enough to simply spend time on a simulator [2], just as it is not enough simply to spend time on a clinical rotation. The focus should be on aiding long-term retention, and changing not just knowledge but also skills and behaviors [2–4, 16, 25]. Educational time, no matter in what form it takes, must be based upon sound principles of adult learning.

Simulation and Adult Education Theory

Good adult education means clear expectations of educators, just as it requires clear expectations of learners. Simulation is also better understood as a technique, and not just a technology [2, 11, 14, 25, 27]. As such, the mere purchase of simulation equipment will never be enough to facilitate behavioral change or to achieve patient safety. Previously, millions of dollars were wasted assuming otherwise. Simulation must also no longer be promoted merely because it is 'novel' or 'popular'. The future of simulation will be won or lost based upon its unique focus on an immersive, reflective, and emotionally engaging experience that leads to long-lasting behavioral change.

High fidelity simulation can be delivered with very low fidelity tools. However, in most cases, using realistic settings, believable cases, and real equipment will increase emotional engagement [1, 2]. As a result, in future, when a hospital purchases equipment it should include enough products so that the team can practice with the very same equipment that they are expected to use. This is in contrast to the early days of simulation, where programs improvised with broken or mothballed supplies. In addition, rather than excessive attention spent trying to make simulation enjoyable, we should accept that appropriate levels of performance anxiety can mimic the stress of clinical work, and thereby increase the likelihood of situational awareness and behavioral change [1]. At the same time as striving to make simulation ever more realistic, we should also stop being so apologetic for its current state. In a revealing letter-to-the-editor, a medical simulation proponent donated his house, scheduled for demolition, to the police force and fire brigade. He agreed to them simulating a hostage-taking, followed by a house fire, but on condition that he was included as a participant [28]. The unapologetically critical debrief that he witnessed made it clear to him that non-medical groups have accepted the validity- regardless of the reality- of simulation. [28]. It was clear that doing so had greatly improved the level of immersion, and, therefore, the usefulness of the exercise. In short, believing simulation was real made it more likely to be useful.

Adult education should be followed by reflection, which typically takes the form of a structured debrief by experts in feedback and formative evaluation [2, 14, 27]. Simulation experts have long incorporated this structure, but there is also no reason why bedside education cannot be similarly modernized. As a result, the question is not whether all teaching should take place in the simulation laboratory versus at the bedside. Instead, the challenge is how to harness the best learning opportunities from both. In other words, however novel or exciting the educational strategy, it is a means to an end (i.e., patient safety and skill development), rather than an end in itself.

Brief simulation exposures are unlikely to model the myriad behaviors required of a 'good doctor' [13, 25, 27]. These include the sense of 'patient ownership', the need to follow a patient through the entire arc of their illness, and even the need to soldier on even when fatigued. Occasional simulation exposures also fail to duplicate the myriad ways in which the same disease can present whether because of subtle differences in anatomy, physiology, genetics, age, or culture. As such, it is also not outdated to promote the apprentice model, the traditional gradual assumption of responsibility, or to demand expertise through volume. As a result, the next decade will be about achieving the best mix of both simulation and bedside experience. This will only be possible when we better understand the impact of finite instructional time, limited educational dollars, increasing clinical loads, the huge reduction in trainee work hours, decreased tolerance for trial and error with real patients, and even the attitudes of modern learners. In short, we need a more sophisticated understanding of the putative benefits and limitations of simulation as well as the traditional apprentice model [14].

As outlined above, current curricula typically focus on factual knowledge [2]. However, human performance errors, not knowledge errors, are the most common reason for errors in acute care [1–15]. It is, therefore, imperative that any simulation curricula in the next decade address human factors, such as leadership, teamwork, situational awareness and communication. These skills, known collectively as 'crisis resource management' (CRM) [2–5, 11–12, 16], can be taught through structured clinical exposure or via well-crafted simulation. The current trade off is that simulation is safer, but clinical practice is more realistic. Regardless, of all human errors, suboptimal communication is the number one cause of patient error [18–23]. This means that 'verbal dexterity' may be more important for the modern practitioner than a capacious brain or nimble hands. This is because strong verbal communication skills are key whether for establishing a shared mental model; coordinating tasks; centralizing the flow of information; refocusing attention; or even for stabilizing emotions [18–23]. When it comes to verbal communication, practical strategies can be readily borrowed from aviation. These include how to be appropriately assertive, how to manage interruptions, and how to confirm that instructions are not only heard but also understood and completed [13, 22–24]. CRM has been widely implemented in almost all high-risk professions. However, acute care medicine has been a comparative laggard. Perhaps this was because CRM did not readily lend itself to traditional didactic education. Simulation is ideally suited to fill this 'educational gap'.

Simulation and Error Mitigation

Many now accept the shocking patient safety numbers [13]. However, the next stage is to make it better understood that most errors are not because of inadequate knowledge (i.e., medical ignorance). Instead they are typically problems in transforming that knowledge into meaningful clinical action under the real-world conditions of patient care (i.e., medical implementation) [15]. Other high-risk professions, most notably aviation, faced similar challenges, but reconfigured how they train and maintain competence [15]. This was associated with a log-reduction in fatalities. In other words, practical strategies and modifiable curricula already exist, and we should 'beg, borrow and steal' wherever possible. The next

decade has to be about reaching out to expertise wherever it can be found. This will represent a substantial departure for an insular, self-regulating, profession such as medicine.

Addressing error also means training practitioners to avoid, capture, and mitigate errors, rather than assuming they result from mere arrogance, stupidity, or sloth [1–3, 11–16]. Applying engineering principles also explains the putative benefits from strategies such as checklists, standard operating procedures, redundancies, and fail-safes. Simulation will increasingly be used to practice and perfect these strategies [16]. In fact, this is one way in which to win over skeptics.

The traditional fear is that protocols and checklists will create mindless automatons: Slaves to a checklist and highly trained individuals no longer capable of using common sense, pattern recognition or judgment [12, 13]. However, as could be increasingly shown through simulation, a well-crafted checklist should encourage rather than discourage independent thought [1, 2]. A good checklist gets the 'easy', 'routine' or 'mundane' dealt with ("did the patient get antibiotics?"). This frees up the brain for more complex issues ("how can I best resuscitate this patient"). Simulation should also be used to show that checklists need to be practiced, and that often they need to be shortened in order to focus on what really matters, namely safety. For example, in the setting of a single pilot flight, the aviation safety list was shaved to only six items, of which the first is the most telling: "Remember to fly the airplane" [13]. While this may seem facetious, the point is that pilots may be so eager to fix the problem, or overly curious as to what went wrong, that cognitive overload makes them forget what really matters. The point is that simulation, now and in the future, must always be about making work easier for average clinicians and life safer for average patients. The next decade for simulation will also be about attempting to optimize the culture through which we deliver care [25, 27].

Simulation as an Agent of Culture Change

The term "disruptive innovation" [29, 30] refers to any change that alters a product or service in ways that were not expected. This is because this innovation promotes a different set of values and substantially upsets the status quo. Disruptive innovations in healthcare include the fact that we are opening the way to a new division of labor among health care providers. We are changing task allocation, flattening hierarchies, changing communication norms, and democratizing decision-making [16]. We have an increased focus on safety, at the same time as we have pressure to make the most efficient use of limited personal [11]. In short, we are modifying how, where, and by whom care is delivered. This means potentially jarring changes to personal identities, job descriptions, and team composition. These new roles and responsibilities need to be practiced. The unpredictable effects of change also need to be studied. Simulation is, of course, no panacea. However, it might increasingly become a 'rapid response system' for culture change, especially when compared to the protracted time line associated with traditional research.

If we accept that the history of medical simulation has pitted well-meaning enthusiasts against just as well meaning traditionalists, then we should also accept that something is required to break this impasse. This may well occur in the next decade as regulatory agencies finally mandate simulation as a condition

of employment or certification. Aviation clearly has many lessons for medical training [11]. It also offers a probable timeline for the transition from encouraging simulation to mandating it. The time from the first flight simulators to when they became mandated for all commercial pilots was approximately 30 years. Similarly in medicine, many clinical advances have followed a 30-year timeline from proposal, through acceptance, to expectation, and finally to a condition of accreditation. As a result, many proponents predict that simulation will be expected by regulatory boards, and given the 30-year timeline, this would occur within this decade. As a result, training programs have few options other than to lead, follow, or begrudgingly comply. In other words, the question is not can we afford to simulate, but rather can we afford not to – especially if we wish to attract and retain the best. However, as previously stated, the goal is to have good simulation not merely to simulate [25]. The challenge is, therefore, bigger than just obtaining one-time funds to establish simulation facilities. The challenge is actually whether we have the humility to learn from others, the insight to expunge the worst of our entrenched traditions, and the pride to unapologetically retain what is best.

We may be approaching simulation's 'tipping point'. However, the next decade should still employ both the 'carrot' and the 'stick'. For example, mandating simulation could rapidly increase its acceptance as routine and non-punitive in much the same way as mandating life support courses did. However, lowering malpractice for participants is probably equally beneficial. The concern is that health care workers are unlikely to be supportive if simulation becomes another demand on their time or wallet. This is where administrators and regulatory boards must step up. Equally, established clinicians need to show leadership with more than words. We must put aside our pride and participate, just as senior pilots participate in regular flight simulation. Only in this way will patient safety and self-improvement be seen as a shared goal [11].

To some these issues may seem self-evident or common sense. However, there are still many health-care organizations where tradition is valued over innovation, where errors are not reported for fear of repercussion, where subordinates are chastised for speaking-up, and where those in quality-control are viewed as adversaries Within the next decade we need a healthcare model which is optimized for safety and quality but balanced against the need for efficiency. The current data strongly argue that we have a long way to go [11, 13]. Simulation is only one strategy, but is one with enormous potential. If not, it will be not only a huge lost opportunity, it will also be patients that pay the price.

Conclusion

Within the next decade, simulation should play an integral role in what has been described as a "healthcare revolution" [1, 2]. To do so it must be central to how personnel are educated, trained, and sustained. Simulation proponents should promote a model where clinical personnel, teams, and even whole systems undergo continual training, rehearsal, and refinement. This vision is inspired by other high-reliability organizations, particularly aviation, but we must also appreciate healthcare's differences. Furthermore, optimizing patient safety is far more complex than merely adding simulation on top of the current system. The future of simulation will say a lot about our entire profession's attitude towards how

seriously we take the safety of our patients. When it comes to optimizing simulation in the next ten years, instead of asking "why?" or even "how?", the most appropriate question is "why on earth not?".

References

1. Brindley PG, Dunn W (2009) Simulation for clinical research trial: better by design. J Crit Care 24: 164 – 167
2. Dunn W, Murphy JG (2008) Simulation: About safety, not fantasy. Chest 133: 6 – 9
3. Gaba DM, Fish KJ, Howard SK (1994) Crisis Management in Anesthesiology. Churchill Livingstone, New York
4. Gaba DM (1992) Dynamic decision-making in anesthesiology: cognitive models and training approaches. In: Evans DA, Patel VI, (eds) Advanced Models of Cognition for Medical Training and Practice. Sprinter-Verlag, Berlin, pp 123 – 147
5. Devita MA, Schafer J, Lutz J Dongilli T, Wang H (2004) Improving medical crisis team performance. Crit Care Med 32: S61 – 65
6. Rall M, Gaba D (2005) Human performance and patient safety. In: Miller R (ed) Miller's Anesthesia. Elsevier Churchill Livingstone, Philadelphia, pp 3021 – 3072
7. Leonard M, Graham S, Bonacum D (2004) The Human Factor: The critical importance of effective teamwork and communication in providing safe care. Qual Saf Health Care 13: 185 – 190
8. Gaba DM (1992) Improving anesthesiologists'performance by simulating reality. Anesthesiology 76: 491 – 494
9. Ziv A, Wolpe P.R, Small SD, Glick S (2003) Simulation-based medical education: an ethical imperative. Acad Med 78: 783 – 788
10. Kohn LT, Corrigan J, Donaldson MS (2000) To Err Is Human: Building A Safer Health System. National Academy Press, Washington
11. Brindley PG (2010) Patient safety and acute care medicine: lessons for the future, insights from the past. Crit Care 14: 217 – 222
12. Haynes AB, Weiser TG, Berry WR, Lipsitz SR, Breizat AH and the Safe Surgery Saves Lives Study Group (2009) A surgical safety checklist to reduce morbidity and mortality in a global population. N Engl J Med 360: 491 – 499
13. Gawande A (2009) The checklist. In: Gawande A (ed) The Checklist Manifesto. Henry Holt and Company, New York, pp 32 – 48
14. Aron D, Headrick L (2002) Educating physicians prepared to improve care and safety is no accident: it requires a systematic approach. Qual Saf Health Care 11: 168 – 173
15. Davis D, O'Brien MA, Freemantle N, Haynes RB (1999) Impact of formal continuing medical education: Do conferences, workshops, rounds and other traditional education activities changes physician behavior or health care outcomes. JAMA 282: 867 – 874
16. Glavin RJ (2007) Simulation: agenda for the 21st century. Simul Healthc 2: 83 – 85
17. The CanMEDS 2005 Physician Competency Framework. Available at: http://rcpsc.medical.org/canmeds/CanMEDS2005/index.php. Accessed Nov 17, 2010
18. General Competencies. Available at: http://www.acgme.org/outcome/comp/compFull.asp. Accessed Sept 17, 2010
19. Good Medical Practice (2006) Available at: http://www.gmc-uk.org/guidance/good_medical_practice/index.asp. Accessed Sept 17, 2010
20. Sutcliffe K, Lewton E, Rosenthal M (2004) Communication failures: An insidious contributor to medical mishaps. Acad Med 79: 186 – 194
21. Gawande AA, Zinner MJ, Studdert DM, Brennan TA (2003) Analysis of errors reported by surgeons at three teaching hospitals. Surgery 133: 614 – 621
22. Knaus WA, Draper EA, Wagner DP, Zimmerman J (1986) An evaluation of outcomes from intensive care in major medical centers. Ann Intern Med 104: 410 – 418
23. Alvarez G, Coiera E (2006) Interdisciplinary communication: an uncharted source of medical error? J Crit Care 21: 236 – 242
24. Barry R, Murcko A, Brubaker C (2002) The six Sigma Book For Healthcare: Improving Outcomes By Reducing Errors. Health Administration Press, Chicago

25. Gaba DM (2007) The future vision of simulation in healthcare. Simul Healthc 2: 126–35
26. Kirkpatrick D (1967) Evaluation of training. In: Craig R, Bittle L (eds) Training and Development Handbook. McGraw-Hill, New York
27. Wiegmann DA, Dunn WF (2010) Changing culture: a new view of human error and patient safety. Chest 137: 250–252
28. Hudson D. Berry D (2006) comparison and contrast between police and medical simulation. Simul Healthc 1: 180
29. Brook RH (2009) Disruption and innovation in health care. JAMA 30: 1465–1456
30. CM Christensen, RMJ Bohmer, J Kenagy (2000) Will disruptive innovations cure health care? Harv Bus Rev 78: 102–111

Intensive Care Medicine: Where We Are and Where We Want To Go?

R.P. Moreno and A. Rhodes

Introduction

Intensive care medicine can be defined as the science and art of detecting and managing patients with impending or established critical illness, in order to prevent further deterioration and revert the disease process or its consequences, so as to achieve the best possible outcomes.

Evolution of Intensive Care

Florence Nightingale was best known as 'The Lady with the Lamp' for her habit of making rounds at night to tend to injured soldiers during the Crimean war (October 1853 – February 1856). She recognized that some patients needed more frequent and careful monitoring than others and as a consequence started to place these patients closer to the nursing station [1]. It could be argued that this was the beginnings of the specialty of intensive care.

Similar insights also began to emerge in other parts of the world [2]. As a consequence of the 1952 Copenhagen poliomyelitis epidemic [3, 4], hospitals started to create the first areas specifically designed and adapted to provide intense support for failing organ systems. The introduction of this new branch of medical science (both physiological and technological), quickly required the development of a new setting for these skills, and the subsequent creation of a designated area in the hospital, known today as the intensive care unit (ICU). Subsequent to this, many different individuals, including Vladimir Negovsky, Peter Safar, Max Harry Weil amongst others, created the science of reanimatology [5, 6]. These pioneers, together with subsequent generations of clinicians and nurses, have continued to develop new knowledge and skills as well as the technology required to transform this diverse series of competencies into an integrated package of care, now known as the art and science of intensive care medicine [7].

Why We Need Intensive Care Units

It is the concentration of the skills, expertise and resources (both human and technical) together in one designated area that makes an ICU. This concentration enables optimal care and management of patients to be provided. There is reasonable evidence now that demonstrates that the care of critically ill patients by intensivists and critical care trained nurses can improve many patient related out-

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comes as well as using the available resources more efficiently. These improved outcomes include a reduced rate of nosocomial infections, decreased complications, reduced length of ICU stays, and decreased mortality. If these resources are not concentrated, rather spread evenly throughout the hospital, with a couple of beds on each ward, then this 'improvement by quantity' is reduced with a less efficient use of resources and a decreased level of care being delivered to the patients.

The ICU of Today

The ICU is critically involved with many areas and specialties within the hospital. The location chosen for the ICU, however, commonly reflects the need for geographic proximity to the more acute areas, such as the emergency department and operating rooms. In addition, there needs to be some thought towards co-location with diagnostic facilities such as the availability of a computed tomography (CT) scanner and the availability of a 24-hour seven-day-a-week functioning laboratory. Most ICUs today have facilities and equipment located within the unit to perform the immediate analysis of arterial blood gas samples and some basic biochemistry and hematology tests. Since most situations in intensive care medicine are critically time-dependent, the successful provision of care is reliant on good relationships and communication between the ICU and the other services and departments of the hospital. This is also required to optimize the timing of admission and discharge of patients to, and from, the ICU.

The discharge process is especially important for a number of reasons [8]. A higher level of vigilance of recently discharged patients is necessary to identify and prevent any subsequent deterioration early. Failure to do so can compromise the patient and reverse any benefits that the ICU initially provided [9, 10]. Another risk to the recovering intensive care patient is inappropriate early discharge to the ward, due to lack of beds or time constraints [11], and although this is controversial [12, 13], it has been demonstrated that there is scope for improvement [14]. This need for an effective interface between the ICU and the other departments of the hospital has not only physical and architectural implications: it also has a crucial impact on human resource factors, both outside and inside the ICU. These include stress management, professionalism in facing and coping with rotating working patterns [15], and fatigue [16, 17].

Interfacing the ICU

Today, a significant number of ICUs in Europe (and also in Australia and New Zealand) are directed by a full-time, fully trained intensivist, leading a multi-professional team of experts in the field, able to provide all interventions potentially required by the patient 24 hours a day, 7 days a week. These professionals are also more and more involved in the management of unstable patients outside the ICU [18–21] in a movement called by Ken Hillman "critical care without walls" [21]. In the United States, the situation is slightly different, with a significant number of ICUs still using the so-called open model [22]. In this system, care and therapy are often supervised by nurses and younger physicians (with occasional mandatory or optional consultation with an intensive care professional), but under the

direction and orientation of a primary physician, paradoxically a system that the literature suggests provides less effective care [23].

This need for full-time, fully trained teams, with very intensive physician-to-patient and nurse-to-patient ratios, transformed the ICU into a very expensive and often scarce resource. The obvious implication of this is that it is vital to ensure that capacity is reserved for only those most likely to benefit from it. There is, therefore, a significant responsibility for the intensivist to triage patients appropriately so that those most likely to benefit are admitted, and those less likely to, are not. Often, however, the situation is more complex. ICU is but one part of the patient journey that takes in many differing parts of the hospital together with multiple professional consultations and interventions. ICU admission criteria must, therefore, be able to cope with not just the sick emergency patient but often also the elective patient whose admission has been planned even before hospital admission.

Triage of Admissions and Discharges

The development of admission (and discharge) criteria is a very complex issue, full of ethical implications, both to the patient and to society. Being a potentially life-saving asset, an ICU bed is also a scarce and costly resource that should be used in the most cost-effective way. Consequently, all possible expertise should be used when deciding whether a certain patient should, or should not, be admitted to an ICU, a decision that is notoriously difficult to get right with any precision [24]. Usually, several objective and subjective factors – both ICU related and patient-related – have an impact on this decision, such as the number of beds available, the admission diagnosis, the severity of illness, age and operative status [25]. Several proposals for standards for ICU admission have been proposed, with the most well-known being those from the Society of Critical Care Medicine [26] (**Box 1**).

In a recent multicenter study in France, Maité Garrouste-Orgeas et al. [27] demonstrated that the decision to deny ICU admission to a certain patient was common (23.8 %), explained by the patient being too well to benefit (55.4 %), too sick to benefit (37.2 %), the unit too busy (6.5 %), and/or refusal by the family

Box 1. Scheme of priorities to assess triage decisions [26]

- Priority 1 assigned to patients who are critically ill, unstable, in need of intensive treatment and monitoring that cannot be provided outside of the ICU. No limits are generally placed on the extent of the therapy that these patients can receive
- Priority 2 assigned to patients who require intensive monitoring, and may potentially need immediate intervention. This category includes patients who are at risk for intubation and invasive mechanical ventilation. No therapeutic limits are generally placed for these patients
- Priority 3 assigned to patients with underlying disease and/or acute illness with a reduced likelihood of recovery. Due to their long-term outcome, they may receive intensive treatment to relieve acute illness, but limits on therapeutic efforts may be set
- Priority 4 assigned to those who are generally not appropriate for ICU admission, either because they are 'too well to benefit' or 'too sick to benefit'. This level also includes those patients who have the capacity to make decisions and who decide to refuse aggressive interventions, although still require 'comfort' care at a level not deliverable on a normal ward setting.

(0.7 %). The same authors demonstrated in multivariate analysis that the two patient-related factors more strongly associated with ICU refusal were dependency and metastatic cancer and that the most important organizational factors were the unit being full, the specific center, phone rather than face to face referral, and daytime admissions (odds ratio [OR] 0.52; 95 % confidence interval [CI] 0.32 – 0.84) [27].

Given the uncertainty of all these decisions, several authors in recent years have proposed that for patients with very severe disease, especially those with cancer, that a so-called 'ICU trial' should be offered; in other words, patients are admitted and fully treated for a limited period of time and then re-assessed for the continuation of life-sustaining therapy [28, 29]. If the patient is not benefiting from the ICU care, then appropriate decisions with regards end-of-life-care should be made, according to the state of the art, the law, and religious preferences, a process quite heterogeneous in different cultures [30 – 33].

For situations where the demand for intensive care could largely exceed supply in a short period of time, as happened during the epidemic of severe acute respiratory syndrome (SARS) in Hong-Kong [34] and in Toronto [35], or in certain places of the world during the recent influenza A (H1N1) virus pandemic [36, 37], contingency plans should exist in anticipation for both the need to increase the capacity of intensive care services and also for triage of patients who could benefit more from ICU admission, ideally based on objective and pre-defined criteria [38, 39].

As a consequence of all these factors, during their ICU stay all patients must be continuously evaluated for the need to remain in the ICU. According to consensus definitions, a discharge decision should be taken "when a patient's physiologic status has stabilized and the need for ICU monitoring and care is no longer necessary" [26]. However, this issue is more complex than it seems at first glance. Since the 1980s, many published outcome studies have presented data on vital status at ICU discharge and also at hospital discharge. Consequently, it has become clear that a significant number of patients either deteriorated or died following ICU discharge but before leaving the hospital (the so-called post-ICU mortality or occult mortality). Several published studies have raised attention to the magnitude of this phenomenon, which can be as high as 36.7 % of all deaths [40]. Some patients deteriorate and then need to be re-admitted to the ICU often soon after ICU discharge [41 – 44], again a common phenomenon carrying a large associated mortality [45].

Where are we Going and Where do we Want to Go?

Our speciality has sustained a continuous growth in recent years. In the early 2000s, it was estimated that intensive care beds represented 13.4 % of all hospital beds in the USA, costing upwards of $55.5 billion, accounting for 13.3 % of all hospital costs and 0.56 % of the gross domestic product (GDP). In the last few years, the panorama has changed [46], with the number of intensive care beds, days (as a percentage of the total hospital days) and occupancy rates continuing to increase. Also, the costs per day of intensive care medicine have increased by 30.4 % with a corresponding increase in the annual costs associated with this specialty of 44.2 %; in 2005, this represented 13.4 % of hospital costs, 4.1 % of national health expenditure, and 0.66 % of the GDP, If we add to this number

other costs incurred by caring for patients with critical illness the overall number accounts for 1 % of the GDP in the USA. In Europe, despite the fact that the heterogeneity is much greater across countries [47] or even inside the same country [48], the mean costs per intensive care bed per year could be as low as 30,990 euro or as high as between 225,000 to 471,330 euro in the UK (depending on the level of care) [48], similar to those in Germany [49]. Despite the fact that these numbers are consistently lower than the numbers presented in the USA, pressure on the economy remains an issue.

This panorama is likely to change, due to the increasing age of the population, with the increasing prevalence of comorbid diseases, together with significant advances in medical science. These factors when combined result in the application of more complex and costly procedures to an increasing fragile population, in which complications will have greater consequences due to the increasingly narrow cost-effective margin of a significant number of interventions. As a direct consequence of these changes, there has been a shift from the almost exclusive presentation in medical conferences and medical journals of new devices and drugs to an increasing discussion of topics that 15 years ago would not have been accepted in a large major conference, or would rarely have been heard. Examples are the increasing efforts put on patient safety [50–52], detection and prevention of adverse events [53–56], and cultural changes regarding patient safety and error management [57–61]. A major example of these changes in priorities and culture was the signature by more than 80 Scientific Societies, industry representatives and patient representatives of the Declaration of Vienna, during the last Annual Congress of the European Society of Intensive Care Medicine, a public call for attention and action to these issues [51]. This declaration was just a first step in an ongoing-process that includes the public presentation of a revised version of the structural norms for European ICUs [62] and the revision of mandatory indicators for ICU evaluation. Benchmarking and other methods of comparative evaluation of the effectiveness and the cost-effectiveness of ICUs will have a growing impact in the decisions made by purchasers of intensive care [63, 64]

In the future, maximization of the volume-outcome relationship will certainly lead to the fusion (or the closure) of small ICUs [65–69] and to the re-arrangement of existing ICUs and services into large networks, trained and evaluated for organizational performance and not just for clinical performance [70]. New drugs and devices will be subjected to ever greater scrutiny before utilization, with the quality of the trials in which they proved their efficacy (and cost-efficacy) being more highly scrutinized for adverse events than previously, and clearly separating practice guidelines and clinical orientations from industry campaigns [71, 72]. We will certainly have new tools and devices, new drugs and interventions [73], but we cannot just sit and wait for a magic bullet to appear, we must be proactive in applying existing (and new) interventions to decrease mortality [74], which translate evidence into practice [75].

This optimization in the use of resources will allow us to develop better and earlier triage criteria and a more extensive use of ICU trials [28]. As the utilization of critical care expands, we will need to be increasingly conscientious that our efforts are being applied only to those patients most likely to benefit from them. End-of-life practices must, therefore, be incorporated into the assessment of quality [30, 76]. For this to be fair, clear, honest and transparent these issues have to be better and more openly discussed with the patients and their families [77–79]. This debate must start before admission to intensive care with discus-

sion and re-education that resets the expectations, desires and perceptions of the general public to allow for more rationale decision making and an assurance that these therapies are directed only to those most likely to benefit.

The education and training of the next generation of intensivists [80–82], needs to be re-evaluated. In the USA, it is probable that the pendulum has already swung beyond the point where the equilibrium between the need for these specialists and the ability to provide them can be restored just by training alone. This will inevitably result in increased outsourcing of several medical interventions to other professional groups, for instance the increase in the use of physicians-assistants and nursing practitioners. New technologies such as tele-ICU [83] can help solve this problem but their effectiveness has not yet been demonstrated in a convincing fashion, as recently shown [84, 85].

Europe, the home country of the closed ICU model and of the fully trained, fully dedicated intensivist, will make an effort to meet the increasing demand with more intensivists, shifting education and training programs from time-based to competency-based curricula [86, 87], such the CoBaTrICE (Competency Based Training program in Intensive Care Medicine for Europe) collaboration [88], and by an increased use of simulation for critical situations [89, 90]. This will not be an easy process. It will need a change in our perception of teaching and the skills of our teachers [91, 92], but it can and should be done.

References

1. Nightingale F (1863) Notes on Hospitals, 3rd ed. Longman, Green, Longman, Roberts, and Green, London 1863
2. Takala J (2007) Organisation of intensive care. In: Kuhlen R, Moreno R, Ranieri M, Rhodes A (eds) 25 Years of Progress and Innovation in Intensive Care Medicine. Medizinisch Wissenschaftliche Verlagsgesellschaft, Berlin, pp 343–350
3. Lassen HCA (1953) A preliminary report on the 1952 epidemic of poliomyelitis in Copenhagen with special reference to the treatment of acute respiratory insufficiency. Lancet 1: 37–41
4. Ibsen B (1954) The anaesthetist's viewpoint on the treatment of respiratory complications in poliomyelitis during the epidemic in Copenhagen, 1952. Proc R Soc Med 47: 72–74
5. Negovsky VA (1961) Some physiopathologic regularities in the process of dying and resuscitation. Circ Metab Cerveau 23: 452–457
6. Negovsky VA (1986) Essays on Reanimatology. MIR Publishers, Moscow
7. Moreno RP, Rhodes A (2010) Intensive Care: a specialty coming to life 376: 1275–1276
8. Moreno R, Miranda DR, Matos R, Fevereiro T (2001) Mortality after discharge from intensive care: the impact of organ system failure and nursing workload use at discharge. Intensive Care Med 27: 999–1004
9. Moreno R, Agthé D (1999) ICU discharge decision-making: are we able to decrease post-ICU mortality? Intensive Care Med 25: 1035–1036
10. Iapichino G, Morabito A, Mistraletti G, Ferla L, Radrizzani D, Miranda RR (2003) Determinants of post-intensive care mortality in high-level treated critically ill patients. Intensive Care Med 29: 1751–1756
11. Goldfrad C, Rowan K (2000) Consequences of discharges from intensive care at night. Lancet 355: 1138–1142
12. Bell CM, Redelmaier DA (2001) Mortality among patients admitted to hospitals on weekends as compared with weekdays. N Engl J Med 345: 663–668
13. Arabi Y, Alshimemeri A, Taher S (2006) Weekend and weeknight admissions have the same outcome of weekday admissions to an intensive care unit with onsite intensivist coverage. Crit Care Med 34: 605–611
14. Perren A, Conte P, De Bitonti N, Limoni C, Merlani P (2008) From the ICU to the ward:

cross-checking of the physician's transfer report by intensive care nurses. Intensive Care Med 34: 2054 – 2061
15. Harrocks N, Pounder R (2006) Working the night shift: preparation, survival and recovery – a guide for junior doctors. Clin Med 6: 61 – 67
16. West CP, Tan AD, Habermann TM, Sloan JA, Shanafelt TD (2009) Association of Resident Fatigue and Distress With Perceived Medical Errors. JAMA 302: 1294 – 1300
17. Gaba DM, Howard SK (2002) Fatigue among clinicians and the safety of patients. N Engl J Med 347: 1249 – 1255
18. Hourihan F, Bishop GF, Hillman KM, Daffurn K, Lee AJ (1995) The medical emergency team: a new strategy to identify and intervene in high-risk patients. Clin Intensive Care 6: 269 – 272
19. Lee AJ, Bishop GF, Hillman KM, Daffurn K (1995) The medical emergency team. Anaesth Intensive Care Med 23: 183 – 186
20. Hillman K, Parr M, Flabouris A, Bishop G, Stewart A (2001) Redefining in-hospital resuscitation: the concept of the medical emergency team. Resuscitation 48: 105 – 110
21. Hillman K (2002) Critical care without walls. Curr Opin Crit Care 8: 594 – 599
22. Capuzzo M, Valentin A, Alvisi R (2009) Open versus closed units. In: Chice J-D, Moreno R, Putensen C, Rhodes A (eds) Patient Safety and Quality of Care In Intensive Care Medicine. Medizinisch Wissenschaftiche Verlagsgesellschaft, Berlin, pp 177 – 188
23. Pronovost P, Angus DC, Dorman T, Robinson KA, Dremsizov TT, Young TL (2002) Physician staffing patterns and clinical outcomes in critically ill patients. a systematic review. JAMA 288: 2151 – 2162
24. Joynt GM, Gomersall CD, Tan PSK, Lee A, Cheng CAY, Wong ELY (2001) Prospective evaluation of patients refused admission to an intensive care unit: triage, futility and outcome. Intensive Care Med 27: 1459 – 1465
25. Sprung CL, Geber D, Eidelman LA, et al (1999) Evaluation of triage decisions for intensive care admission. Crit Care Med 27: 1073 – 1079
26. Task Force on Guidelines, Society of Critical Care Medicine (1999) Recommendations for intensive care unit admission and discharge criteria. Crit Care Med 27: 633 – 638
27. Garrouste-Orgeas M, Montuclard L, Timsit J-F, et al (2005) Predictors of intensive care unit refusal in French intensive care units: A multiple-center study. Crit Care Med 33: 750 – 755
28. Lecuyer L, Chevret S, Thiery G, Darmon M, Schlemmer B, Azoulay E (2007) The ICU Trial: A new admission policy for cancer patients requiring mechanical ventilation. Crit Care Med 35: 808 – 814
29. Azoulay E, Bele N, Thiery G, Schlemmer B (2007) An alternative to refusing ICU admission of cancer patients. In: Kuhlen R, Moreno R, Ranieri M, Rhodes A (eds) 25 Years of Progress and Innovation in Intensive Care Medicine. Medizinisch Wissenschaftliche Verlagsgesellschaft, Berlin, pp 449 – 458
30. Azoulay E, Metnitz B, Sprung C-L, et al (2009) End-of-life practices in 282 intensive care units: data from the SAPS 3 database. Intensive Care Med 35: 623 – 630
31. Sprung CL, Woodcock T, Sjokvist P, et al (2008) Reasons, considerations, difficulties and documentation of end-of-life decisions in European intensive care units: the ETHICUS Study. Intensive Care Med 34: 271 – 277
32. Bülow H-H, Sprung C-L, Reinhart K, et al (2008) The world's major religions' points of view on end-of-life decisions in the intensive care unit. Intensive Care Med 34: 423 – 430
33. Randall Curtis J (2007) End-of-life care for patients in the intensive care unit. In: Kuhlen R, Moreno R, Ranieri M, Rhodes A (eds) 25 Years of Progress and Innovation in Intensive Care Medicine. Medizinisch Wissenschaftliche Verlagsgesellschaft, Berlin, pp 469 – 479
34. Tsang KW, Ho PL, Ooi GC, et al (2003) A cluster of cases of severe acute respiratory syndrome in Hong Kong. N Engl J Med 348: 1977 – 1985
35. Skowronski DM, Petric M, Daly P, et al (2006) Coordinated response to SARS, Vancouver, Canada. Emerg Infect Dis 12: 55 – 58
36. Rello J, Rodriguez A, Ibanez P, et al (2009) Intensive care adult patients with severe respiratory failure caused by Influenza A (H1N1) in Spain. Crit Care 13: R148
37. Webb SAR, Seppelt IM, for the ANZIC Influenza Investigators (2009) Pandemic (H1N1) 2009 influenza ("swine flu") in Australian and New Zealand intensive care. Crit Care Resusc 11: 170 – 172

38. Eastman N, Philips B, Rhodes A (2010) Triaging for adult critical care in the event of overwhelming need. Intensive Care Med 36: 1076–1082
39. Sprung CL, Zimmerman JL, Christian MD, et al (2010) Recommendations for intensive care unit and hospital preparations for an influenza epidemic or mass disaster: summary report of the European Society of Intensive Care Medicine's Task Force for intensive care unit triage during an influenza epidemic or mass disaster. Intensive Care Med 36: 428–443
40. Metnitz PG, Moreno RP, Almeida E, et al (2005) SAPS 3. From evaluation of the patient to evaluation of the intensive care unit. Part 1: Objectives, methods and cohort description. Intensive Care Med 31: 1336–1344
41. Rosenberg AL, Hofer TP, Hayward RA, Strachan C, Watts CM (2001) Who bounces back? Physiologic and other predictors of intensive care readmission. Crit Care Med 29: 511–518
42. Hasan M (2001) Readmission of patients to hospital: still ill defined and poorly understood. Int J Qual Health Care 13: 177–179
43. Rubins HB, Moskowitz MA (1988) Discharge decision-making in a medical intensive care unit. Identifying patients at high risk of unexpected death or unit readmission. Am J Med 84: 863–869
44. Bhatia N, Gombar S, Gombar KK, Thapa D (2010) Why patients are readmitted to ICU. J Anaesthesiol Clin Pharmacol 26: 91–93
45. Metnitz PG, Fieux F, Jordan B, Lang T, Moreno R, Le Gall JR (2003) Critically ill patients readmitted to intensive care units--lessons to learn? Intensive Care Med 29: 241–248
46. Halpern NA, Pastores SM (2010) Critical care medicine in the United States 2000–2005: An analysis of bed numbers, occupancy rates, payer mix, and costs. Crit Care Med 38: 65–71
47. Csomós A, Janecsko M, Edbrooke D (2005) Comparative costing analysis of intensive care services between Hungary and United Kingdom. Intensive Care Med 31: 1280–1283
48. Edbrooke DL, Ridley S, Hibbert CL, Corcoran M (2001) Variations in expenditure between adult general intensive care units in the UK. Anaesthesia 56: 208–216
49. Prien T, Groll O, Geldner G, et al (2002) Ist-Kosten Intensivmedizin deutscher Anasthesieabteilungen-Bezugsjahr 1999. Anasthesiol Intensivmed 43: 244–254
50. Haller G, Stoelwinder J, Myles PS, McNeil J (2009) Quality and safety indicators in anesthesia. A systematic review. Anesthesiology 110: 1158–1175
51. Moreno RP, Rhodes A, Donchin Y (2009) Patient safety in intensive care medicine: the Declaration of Vienna. Intensive Care Med 35: 1667–1672
52. Chakravarthy M (2010) Errors in cardiac anesthesia – A deterrent to patient safety. Ann Cardiac Anaesth 13: 87–88
53. Donchin Y, Gopher D, Olin M, et al (1995) A look into the nature and causes of human errors in the intensive care unit. Crit Care Med 23: 294–300
54. Valentin A, Capuzzo M, Guidet B, et al (2006) Patient safety in intensive care: results from the multinational Sentinel Events Evaluation (SEE) study. Intensive Care Med 32: 1591–1598
55. Valentin A, Capuzzo M, Guidet B, et al (2009) Errors in the administration of parenteral drugs – an urgent safety issue in intensive care units. Results from a multinational, prospective study. BMJ 338: b814
56. Beydon L, Ledenmat PY, Soltner C, et al (2010) Adverse events with medical devices in anesthesia and intensive care unit patients recorded in the French Safety Database in 2005–2006. Anesthesiology 112: 364–372
57. Zohar D, Livne Y, Tenne-Gazit O, Admi H, Donchin Y (2007) Healthcare climate: A framework for measuring and improving patient safety. Crit Care Med 35: 1312–1317
58. Wiegmann DA, Dunn WF (2010) Changing culture. A new view of human error and patient safety. Chest 137: 250–252
59. Livne Y, Donchin Y (2009) Building a safety culture within the ICU. In: Chiche J-D, Moreno R, Putensen C, Rhodes A (eds) Patient Safety and Quality of Care in Intensive Care Medicine. Medizinisch Wissenschaftiche Verlagsgesellschaft, Berlin, pp 39–46
60. O'Connor MF (2007) Safety culture: Easy to advocate, difficult to create. Crit Care Med 35: 1429

61. Sexton JB, Helmreich RL, Neilands TB, et al (2006) The Safety Attitudes Questionnaire: psychometric properties, benchmarking data, and emerging research. BMC Health Serv Res 6: 44
62. Ferdinande P, Members of the Task Force of the European Society of Intensive Care Medicine (1997) Recommendations on minimal requirements for intensive care departments. Intensive Care Med 23: 226 – 232
63. Poole D, Rossi C, Anghileri A, et al (2009) External validation of the Simplified Acute Physiology Score (SAPS) 3 in a cohort of 28,357 patients from 147 Italian intensive care units. Intensive Care Med 35: 1916 – 1924
64. Poole D, Bertolini G (2009) Outcome-based benchmarking in the ICU Part I: Use and limitations of severity scores in critical care. In: Chiche J-D, Moreno R, Putensen C, Rhodes A (eds) Patient Safety and Quality of Care in Intensive Care Medicine. Medizinisch Wissenschaftiche Verlagsgesellschaft, Berlin, pp 151 – 160
65. Aujesky D, Mor MK, Geng M, Fine MJ, Renaud B, Ibrahim SA (2008) Hospital volume and patient outcomes in pulmonary embolism. Can Med Assoc J 178: 27 – 33
66. Lindenauer PK, Behal R, Murray CK, Nsa W, Houck PM, Bratzler DW (2006) Volume, quality of care, and outcome in pneumonia. Ann Intern Med 144: 262 – 269
67. Glance LG, Dick AW, Osler TM, Mukamel DB (2005) The relation between surgeon volume and outcome following off-pump vs on-pump coronary artery bypass graft surgery. Chest 128: 829 – 837
68. Kahn JM (2009) Volume and outcome in intensive care. In: Chice J-D, Moreno R, Putensen C, Rhodes A (eds) Patient Safety and Quality of Care In Intensive Care Medicine. Medizinisch Wissenschaftiche Verlagsgesellschaft, Berlin, pp 161 – 170
69. Matti R, Sari K, Tero V, et al (2009) Are small hospitals with small intensive care units able to treat patients with severe sepsis? Intensive Care Med 36: 673 – 679
70. Minvielle E, Aegerter P, Dervaux B, et al (2008) Assessing organizational performance in intensive care units: A French experience. J Crit Care 23: 236 – 244
71. Eichacker PQ, Natanson C, Danner RL (2007) Separating practice guidelines from pharmaceutical marketing. Crit Care Med 35: 2877 – 2878
72. Eichacker PQ, Natanson C, Danner RL (2006) Surviving Sepsis – Practice Guidelines, Marketing Campaigns, and Eli Lilly. N Engl J Med 355: 1640 – 1642
73. Vincent JL, Singer M, Marini JJ, et al (2010) Thirty years of critical care medicine. Crit Care 14: 311
74. Pronovost PJ, Berenholtz SM, Goeschel C, et al (2008) Improving patient safety in intensive care units in Michigan. J Crit Care 23: 207 – 221
75. Winters BD, Gurses AP, Lehmann H, Sexton JB, Rampersad CJ, Pronovost PJ (2009) Clinical review: Checklists – translating evidence into practice. Crit Care 13: 210
76. Bertolini G, Boffelli, Malacarne S, et al (2010) End-of-life decision-making and quality of ICU performance: an observational study in 84 Italian units. Intensive Care Med 36: 1495 – 1504
77. Fassier T, Darmon M, Laplace C, et al (2007) One-day quantitative cross-sectional study of family information time in 90 intensive care units in France. Crit Care Med 35: 177 – 183
78. Siegel MD (2009) Lost in translation: Family conferences for families that do not speak English. Crit Care Med 37: 340 – 341
79. Azoulay E, Pochard F, Chevret S, et al (2001) Meeting the Needs of Intensive Care Unit Patient Families. A Multicenter Study. Am J Respir Crit Care Med 163: 135 – 139
80. Goodman DC, Fisher ES (2008) Physician Workforce Crisis? Wrong Diagnosis, Wrong Prescription. N Engl J Med 358: 1658 – 1661
81. Samb B, Celletti F, Holloway J, Van Damme W, De Cock KM, Dybul M (2007) Rapid expansion of the health workforce in response to the HIV epidemic. N Engl J Med 357: 2510 – 2514
82. Angus DC, Kelley MA, Schmitz RJ, White A, Popovich J, for the Committee in Manpower for Pulmonary and Critical Care Societies (COMPACCS) (2000) Caring for the critically ill patient. Current and projected workforce requirements for care of the critically ill and patients with pulmonary disease: can we meet the requirements of an aging population? JAMA 284: 2762 – 2770

83. Sapirstein A, Lone N, Latif A, Fackler J, Pronovost PJ (2009) Tele ICU: paradox or panacea? Best Pract Res Clin Anaesthesiol 23: 115 – 126
84. Yoo EJ, Dedley RA (2009) Evaluating telemedicine in the ICU. JAMA 302: 2705 – 2706
85. Thomas EJ, Lucke JF, Wueste L, Weavind L, Patel B (2009) Association of telemedicine for remote monitoring of intensive care patients with mortality, complications, and length of stay. JAMA 302: 2671 – 2678
86. Bion J, Reay H, Bullock A (2007) Training in intensive care medicine. In: Kuhlen R, Moreno R, Ranieri M, Rhodes A (eds) 25 Years of Progress and Innovation in Intensive Care Medicine. Medizinisch Wissenschaftliche Verlagsgesellschaft, Berlin, pp 351 – 358
87. Perkins GD, Barrett H, Bullock I, et al (2005) The Acute Care Undergraduate TEaching (ACUTE) Initiative: consensus development of core competencies in acute care for undergraduates in the United Kingdom. Intensive Care Med 31: 1627 – 1633
88. The CoBaTrICE Collaboration (2009) The educational environment for training in intensive care medicine: structures, processes, outcomes and challenges in the European region. Intensive Care Med 35: 1575 – 1583
89. Park CS, Rochlen LR, Yaghmour E, et al (2010) Acquisition of critical intraoperative event management skills in novice anesthesiology residents by using high-fidelity simulation-based training. Anesthesiology 112: 202 – 211
90. Cooper JB, Murray D (2010) Simulation training and assessment. a more efficient method to develop expertise than apprenticeship. Anesthesiology 112: 8 – 9
91. Pardo M Jr (2010) Anesthesia: How to organize and train our teachers. Anesthesiology 112: 773 – 774
92. McMahon GT, Katz JT, Thorndike ME, Levy BD, Loscalzo J (2010) Evaluation of a redesign initiative in an internal-medicine residency. N Engl J Med 362: 1304 – 1311

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