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Yearbook of Intensive Care and Emergency Medicine 2010

Edited by J.-L. Vincent

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With 93 Figures and 59 Tables

Springer

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Common Abbreviations

AKI	Acute kidney injury
ALI	Acute lung injury
APACHE	Acute physiology and chronic health evaluation
ARDS	Acute respiratory distress syndrome
COPD	Chronic obstructive pulmonary disease
CPP	Cerebral perfusion pressure
CPR	Cardiopulmonary resuscitation
CT	Computed tomography
CVP	Central venous pressure
EEG	Electroencephalogram
EKG	Electrocardiogram
EVLW	Extravascular lung water
Hb	Hemoglobin
ICU	Intensive care unit
IFN	Interferon
IL	Interleukin
LPS	Lipopolysaccharide
MAP	Mean arterial pressure
MRI	Magnetic resonance imaging
NF-κB	Nuclear factor-kappa B
NO	Nitric oxide
NOS	Nitric oxide synthase
PAOP	Pulmonary artery occlusion pressure
PEEP	Positive end-expiratory pressure
$ScvO_2$	Central venous oxygen saturation
SIRS	Systemic inflammatory response syndrome
SOFA	Sequential organ failure assessment
SvO_2	Mixed venous oxygen saturation
SVR	Systemic vascular resistance
TBI	Traumatic brain injury
TNF	Tumor necrosis factor
VAP	Ventilator-associated pneumonia

I The Microcirculation

The Microcirculation and Oxidative Stress

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Introduction

Microvascular dysfunction appears to play a key role in the pathogenesis of many pathologies, such as hypertension, diabetes, ischemia-reperfusion or sepsis. One of the main players in microcirculatory regulation is the endothelium. Indeed, many studies outline the fundamental role of the endothelium in vascular tone regulation, vascular pro-anticoagulant balance, and vessel wall permeability modulation. Many stimuli are able to induce endothelial dysfunction, including pro-inflammatory cytokines, hypoxia, and oxidative stress. Among the causes of endothelial dysfunction, oxidative stress has been the most extensively investigated. The endothelium represents both a source and a target for reactive oxygen species (ROS) released into the microcirculation. Rather than contribute to oxidative stress, endogenous endothelial systems for ROS generation may have normal physiological signal functions, generating 'second messengers' that regulate endothelial cell growth/proliferation, endothelial cell barrier function, vasorelaxation, and vascular remodeling. However, in pathologies such as sepsis or hemorrhagic shock, the imbalance between the production of ROS and their effective removal by non-enzymatic and enzymatic antioxidant systems may induce endothelial dysfunction with alteration of vascular tone, increased cell adhesion properties (leukocyte and platelet adhesion), and increased vascular wall permeability, leading to a pro-coagulant state.

Oxidative stress is difficult to describe *in vivo* because of the short half-life of ROS. Involvement of ROS in the pathophysiology of the microcirculation is, hence, mainly reported in experimental studies. Correlation of these results with future studies in humans will surely provide a better understanding of microcirculatory disturbances during sepsis, thereby offering new perspectives for therapeutic interventions.

Reactive Oxygen Species

ROS are chemical products with a short half-life and a high reactivity conferred by their free unstable electrons. These properties highlight the importance of the place where the ROS are produced because they may influence the target with which they will react. Several enzymes are able to produce ROS in tissues. However, cells possess many antioxidant defenses that counterbalance this production. As a consequence, the oxidative stress level results from the balance between the rate of ROS production by oxidases and the effectiveness of antioxidant enzymes or scavengers. The cytotoxicity of ROS is always due to the association of two phenomena: An

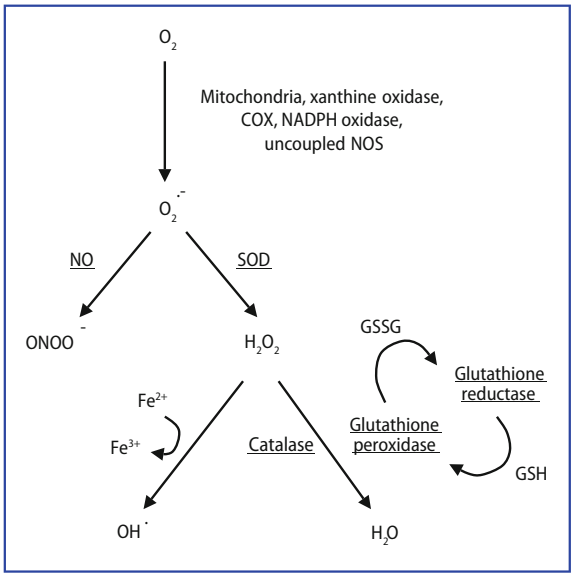

Fig. 1. Diagram of cellular reactive oxygen species (ROS) and their respective producing and detoxifying enzymes. O_2 is transformed into superoxide anion ($O_2^{\cdot-}$) by different intracellular enzymes (NOS: nitric oxide synthase, COX: cyclooxygenase). $O_2^{\cdot-}$ can then react with superoxide dismutase (SOD) to form hydrogen peroxide (H_2O_2). H_2O_2 may then either react with free iron to form $OH^{\cdot}$ (Fenton reaction) or be detoxified into water by catalase or glutathione peroxidase in the presence of GSH. OH: hydroxyl; GSSG: oxidized glutathione; GSH: reduced glutathione.

increase in ROS production and a decrease in antioxidants. During sepsis or ischemia-reperfusion, ROS can be produced by leukocytes, endothelial cells and smooth muscle cells. ROS production in endothelial cells has been reported to be by leukocytes interacting with the endothelial cell membrane. However, our group found that plasma from patients treated for septic shock was able to induce ROS formation in naïve endothelial cells [1, 2]. This ROS formation induced by plasma can lead to endothelial cell mortality. Moreover, the extent of ROS production was higher in non-survivors than in survivors and was correlated with mortality and with criteria of the severity of septic shock, such as the sequential organ failure assessment (SOFA) and the simplified acute physiology score (SAPS) II [1]. This finding might be clinically relevant because during septic shock, infection and the inflammatory response are initially spatially limited. Subsequently, however, a systemic inflammatory response and organ dysfunction can occur at a distance from the initial infection site, events in which endothelial cell activation with consequent ROS production could be a key element.

The production of the superoxide anion ($O_2^{\cdot-}$) is often the first step in the production of most ROS. Indeed, after its production, $O_2^{\cdot-}$ may be either spontaneously dismutated into hydrogen peroxide (H_2O_2) or enzymatically catalyzed by superoxide dismutase (SOD), the first detoxifying enzyme, in a faster reaction (Fig. 1). H_2O_2 does not have singular electrons, but does have oxidative properties that allow it to react with several signaling pathway components. The H_2O_2 level depends on its rate of formation by superoxide dismutation and its buffering rate by glutathione peroxidase (GPx) and catalase, which transform it into water. However, in the presence of free iron or copper, H_2O_2 may be transformed into the hydroxyl radical ($OH^{\cdot}$) by the Fenton reaction (Fig. 1). Interactions of nitric oxide (NO) with ROS are also important, as excess NO may react with $O_2^{\cdot-}$ to form peroxynitrite ($ONOO^-$), a very reactive radical that is able to nitrate tyrosine and, thereby, modify protein functions. This reaction occurs at a constant rate that is three times greater than the reaction

of superoxide with SOD, demonstrating the high level of reactivity between NO and superoxide. This privileged reaction has two main consequences: An excess of NO in the presence of superoxide may form $ONOO^-$ with its downstream signaling consequences and, conversely, an excess of superoxide may buffer NO and thereby decrease the bioavailability of NO in one of the key mechanisms of endothelial dysfunction [3].

Sources of ROS in the Microcirculation

Mitochondria

A continuous production of ROS by the mitochondrial respiratory chain is observed during physiological cellular respiration. Indeed, 0.4 to 4% of oxygen consumed by the mitochondria is reduced to $O_2^{\cdot -}$ by electrons that leak from complexes I and III of the mitochondrial electron transport chain [4]. This basal ROS production is counterbalanced by cell antioxidant defenses, and $O_2^{\cdot -}$ is, in turn, converted to H_2O_2 by mitochondria-specific, manganese-dependent SOD without any deleterious effects. During hypoxia, ROS formation induced by mitochondria was found to lead to stabilization of hypoxia inducible factor-1 alpha (HIF1-α) and the removal of the repression of genes encoding for proteins involved in adaptation to hypoxia [5]. Moreover, the rapid onset of ROS production under hypoxic conditions could be implicated in vascular tone adaptation to hypoxia and has been described as such with respect to pulmonary hypoxic vasoconstriction [6]. Mitochondria can then be considered in this context as potential oxygen sensors, though other enzymatic complexes, such as NADPH oxidase, have efficient oxygen sensing properties under some conditions. During sepsis or ischemia-reperfusion, mitochondrial ROS production may also be exacerbated with several implications: ROS may have direct toxic effects by reacting with cell membranes, thereby creating lipid peroxidation or signaling effects by interfering with the apoptotic pathway, intracellular calcium concentration and adhesive protein expression [7], particularly in endothelial cells.

NADPH Oxidase

NADPH oxidase was first described in the membrane of polynuclear cells where its activation leads to formation of ROS that participate in defense against pathogens. Several isoforms of this enzyme, which are situated in the membrane of endothelial and smooth muscle cells, have now been described. NADPH oxidase is composed of two parts. The first part contains cytochrome b558, which has two subunits (gp91phox and p22phox). gp91phox enables NADPH oxidase to transfer an electron from NADPH to O_2 and is located with p22phox in the cell membrane. The second part is composed of three subunits (p40phox, p47phox and p67phox) and protein G (rac1) that together form the regulatory subunit of NADPH oxidase, which is located in the cytoplasm. p47phox phosphorylation or rac1 activation (which is sensitive to GTP binding) stimulate migration of the regulatory subunit from the cytoplasm to the oxidizing membrane complex and enhance $O_2^{\cdot -}$ formation. NADPH oxidase is a major source of oxidative stress because the extent of the cell pathways in which it is implicated is vast [8]. $O_2^{\cdot -}$ production by NADPH oxidase may be triggered by several stimuli including hypoxia, shear stress, or pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α).

NO Synthase

NO is produced by NO synthase (NOS). The substrate L-arginine is oxidized in the presence of the cofactor tetrahydrobiopterin (BH_4), which is necessary for the catalysis of the transfer of an electron from NADH to the terminal guanidine of L-arginine to form NO. NOS does not produce ROS under physiological conditions. However, a decrease in the bioavailability of BH_4 may impair the ability of NOS to produce NO without altering its oxidase capacity [9]. In this context, NOS is uncoupled and leads to the production of $O_2^{\cdot -}$. Thus, when the production of $O_2^{\cdot -}$ is not controlled by SOD, $O_2^{\cdot -}$ may react with NO to generate $ONOO^-$. Not only does $O_2^{\cdot -}$ alter endothelium-dependent vascular relaxation through its interaction with NO, but the resultant formation of $ONOO^-$ can also oxidize BH_4 and promote NOS uncoupling. Uncoupling of NOS may also be triggered by endogenous NOS inhibitor activity, namely by asymmetric dimethylarginine (ADMA), or by a decrease in L-arginine biodisponibility. NOS uncoupling results in loss of endothelial vasodilation properties due to a decrease in NO availability and an increase in oxidative stress.

ROS production by uncoupled NOS was principally described in experiments involving cardiovascular disease and remains to be explored in the context of inflammatory pathologies. However, in a clinical study, supplementation of L-arginine in hypercholesterolemic patients restored endothelium-dependent vasodilation [8], one of the first elements that suffers in endothelial dysfunction.

Xanthine Oxidase

The main function of xanthine oxidase consists of oxidizing hypoxanthine and xanthine into uric acid and, thereby, has an important role in purine metabolism. Two forms of this enzyme are present in cells and differ principally in their final electron acceptor, xanthine dehydrogenase and xanthine oxidase. Xanthine dehydrogenase is

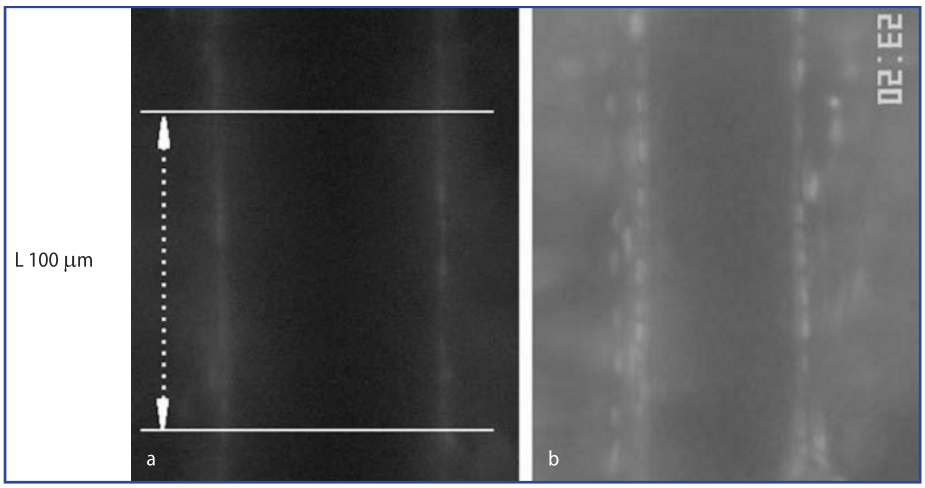

Fig. 2. Representative images of the dihydroethidium (a dye that fluoresces when oxidated by the superoxide anion) fluorescent signal in mice cremaster muscle arteriolar wall at baseline (a) and after 60 minutes of ischemia (b). In this experiment of muscle ischemia, reactive oxygen species (ROS) production involved both mitochondrial complex III and xanthine oxidase. Data from Baudry et al. [13].

the major enzyme form under physiological conditions and requires NAD^+ as an electron acceptor during the transformation of hypoxanthine/xanthine. Xanthine oxidase transfers an electron to O_2 to form $O_2^{\cdot-}$. Xanthine dehydrogenase is usually preponderant, but oxidase activity may become important in the context of ischemia in experimental animal studies and in endothelial cell experiments [10–12]. Our group observed the involvement of xanthine oxidase (as well as mitochondrial complex III) in ROS-induced production in the arteriolar wall of mice cremaster muscles submitted to ischemia (Fig. 2) [13]. It is then interesting to note that ROS produced by xanthine oxidase during ischemia-reperfusion may induce leukocyte adhesion at a venular level [12] while they may influence vascular tone regulation at the arteriolar level [13, 14].

Other Sources of Superoxide Anion Production

Cytochrome P450 and cyclooxygenase (COX) enzymes are also capable of producing $O_2^{\cdot-}$ under certain conditions. COX was demonstrated to produce $O_2^{\cdot-}$ simultaneously with prostaglandin in a model of endothelial cell activation [15]. Cytochrome P450 is known for its detoxification properties in hepatic tissues. However, vascular isoforms are particularly implicated in vascular tone regulation principally by interfering with arachidonic acid metabolism. During its enzymatic activity, the oxidizing capacity of the protein complex may induce $O_2^{\cdot-}$ production in the presence of O_2 and NADH. This phenomenon was observed in a model of cardiomyocytes submitted to ischemia-reperfusion injury [16] as well as in endothelial coronary artery cells [17].

Interactions of ROS with the Microcirculation

Endothelial cells situated at the interface between the vascular wall and blood components have an active and critical role in microcirculation homeostasis. During

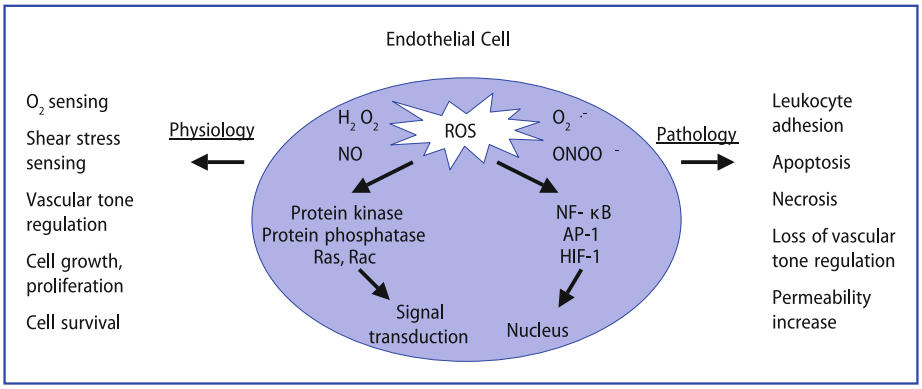

Fig. 3. Cell functions with which reactive oxygen species (ROS) have been reported to interact in physiological and pathological states. A non-exhaustive list of transcription factors and intracellular signaling proteins whose function may be modulated by ROS is represented in the schematic endothelial cell (activator protein-1 [AP-1], hypoxia inducible factor-1 [HIF-1], nuclear factor-kappa B [NF-κB]). Apoptosis is represented in the pathological column because it may be exacerbated by ischemia-reperfusion or sepsis. However, apoptosis may be, in many cases, a physiological process to renew cells in tissues.

pathological stimuli, such as in an inflammatory state with massive cytokine production, ischemia-reperfusion injury or shear stress variation, endothelial dysfunction may occur in which oxidative stress products play an important role (Fig. 3).

Leukocyte-endothelial Cell Adhesion

Adhesion of blood cells, such as white blood cells (WBCs) or platelets, to endothelial cells is a critical event associated with vascular inflammation mediated by oxidative stress. This adhesion is mediated by inducible proteins expressed on blood cell and endothelial cell membranes, allowing binding, rolling and transmigration of WBCs across the endothelium monolayer. Oxidative stress plays a key role in the interactions established between blood cells and the endothelium, as it triggers the expression of most adhesive proteins. Indeed, ROS production triggered by inflammation may enhance the migration of adhesive proteins from the intracellular space to the cell membrane, particularly P-selectin, which is the earliest adhesive protein expressed on endothelial cells [18]. In this way, endothelial cells submitted to hypoxia showed activation of mitogen activated protein kinase p38 (MAPK p38) via ROS-dependant phosphorylation, enabling endothelial cells to recruit intracellular P-selectin into the cell membrane and, thus, triggering WBC adhesion onto the endothelial surface [19]. Indeed, activated WBCs express P-selectin ligand-1 protein (PSGL-1), which binds P-selectin, on their surface. This first interaction slows leukocyte transit and initiates rolling on the vascular endothelium. ROS have also been reported to interact at a transcriptional level with the activation of genes encoding adhesive molecules, such as intercellular adhesion molecule-1 (ICAM-1), vascular adhesion molecule-1 (VCAM-1), and E-selectin in an endothelial cell model submitted to TNF-α activation [20]. E-selectin expression occurs later in comparison with P-selectin and reinforces the leukocyte rolling phase. Moreover, ROS-induced TNF-α production was able to activate monocyte chemoattractant protein-1 (MCP-1) production by endothelial cells with a specific role for $O_2^{\cdot-}$ and H_2O_2, but not for $ONOO^-$ [21]. This ROS production was mediated by NADPH oxidase, which was activated by Rac 1. Chemoattractants are important signaling proteins as they further activate rolling WBCs that may then initiate firm adhesion and transmigration. *In vivo* studies describe a similar central role for ROS in molecular adhesion signaling because mice intestine submitted to ischemia-reperfusion expressed E-selectin via nuclear factor kappa B (NF-κB) activation in an endothelial ROS-dependant manner [22]. Another important aspect concerns WBC ROS products that may also induce an endothelial adhesive phenotype in response to a pro-inflammatory challenge. Polymorphonuclear neutrophil (PMN) NADPH oxidase produces extracellular ROS in this context, which activates endothelial NF-κB, and then ICAM-1, expression [23]. In addition, Steiner et al. observed an important role for ROS produced by mastocytes during systemic hypoxia in rats, as they may enhance leukocyte-endothelium adhesion [24].

ROS, therefore, appear to be central signaling molecules in the leukocyte-endothelium interaction with a reciprocal activation between WBC and endothelial cells, leading to an organized 'molecular cross-talk' that allows WBC transmigration at the inflammatory site. If adhesive leukocytes have a protective role against pathogens in locally injured and inflamed tissue, the whole body generalization of this phenomena in the context of systemic inflammation, such as in sepsis, deeply perturbs microcirculatory behavior and contributes to organ failure. Adhesion of leukocytes on venules at the post-capillary level increases flux resistance and local secretion of

pro-inflammatory elements, ultimately leading to an increase in endothelial permeability [25] and tissue injury [26].

Moreover, it should be mentioned that interactions between blood cells and the endothelium may include additional players, such as platelets that adhere to endothelial cells, enhance recruitment of adhesive WBCs and can even aggregate with them. This phenomenon draws a link between adhesion and aggregation, which is usually balanced by functional endothelial cells [18].

Vascular Tone Regulation

Endothelial cells release several factors implicated in the regulation of vascular tone. Vasoconstriction can be achieved by thromboxane A2 (TXA2), endothelin 1, angiotensin II while vasodilation is mediated by NO, prostacyclin (PGI2) and epoxyeicosatrienoic acids (EETs). ROS are implicated in the physiological regulation of vascular tone at several levels, while H_2O_2 is implicated in experimental vasodilatation and vasoconstriction of bovine coronary and arterial pulmonary artery, respectively, in the context of hypoxia [27]. These fundamental vascular reactions are key functions in the adaptation of microcirculatory flux to meet the energetic needs of the myocardium and in the adequacy of the ventilation/perfusion ratio, respectively.

However, in some conditions, ROS production may interact with the physiological regulation of vascular tone. Indeed, when the ROS level becomes imbalanced, the rapid reaction of overproduced $O_2^{\cdot-}$ with NO may decrease bioavailability of NO and alter endothelium-dependent vasodilation. Additionally, the resulting formation of $ONOO^-$ (Fig. 1) is particularly important because $ONOO^-$ displays properties that other ROS do not. It may inactivate prostacyclin synthase in particular by nitrating its tyrosine residue [28], thereby modifying vascular tone. Moreover $ONOO^-$ interacts with antioxidant defenses, particularly mitochondrial SOD [29] and glutathione peroxidase [30], inhibition of which exacerbates ROS production.

In vivo, ROS level is a fundamental parameter that may induce a shift from dilator prostanoid (PGI2) synthesis to constrictor prostanoid (TXA2) synthesis by COX [14]. This vasoactive modulation induced by ROS is a unifying concept that may explain microvascular tone disturbances in the context of an increase in oxidative stress.

The Vast Spectrum of Intracellular Targets for ROS

The implication of ROS in cell transduction signaling of a wide range of stimuli (cytokines, growth factors, hormones) is well recognized. Oxidative stress is able to directly react with a vast panoply of intracellular targets (Fig. 3), such as the phosphatase/kinase couple (protein kinase A, G, C, Jun kinase, Akt), rho proteins (Ras), transcription factors (activator protein-1 [AP-1], NF-κB, P53) or metabolic enzymes [31]. ROS may induce small modifications on predefined protein regions, thereby affecting their function. For example, H_2O_2 may react with the cysteine thiol group and form a disulfide bond that modifies protein function. Thiols may also be modified by NO to form nitrosothiols that modulate protein activity. It is interesting to note that specific cellular proteins, like thioredoxin, glutaredoxin or glutathione, may reverse ROS-induced protein modification. In fact, these cellular reductants provide a strong argument in favor of the tightly controlled signaling role of ROS. Many transcription factors are sensitive to an oxidizing environment. NF-κB is one of these, and its complex activation may be triggered by successive pro-oxidant activities. Indeed, the inhibitory κB

kinase (IKK) is activated by ROS and enhances degradation of I-κB (usually by maintaining active NF-κB inhibition), allowing the translocation of NF-κB to the nucleus via its downstream transcription effects. It may be appealing to outline that changes in the gluthathione (GSH)/glutathione disulfide (GSSG) ratio (reflecting the pro-antioxidant balance) modulate AP-1 activity. Indeed AP-1 activation by lipopolysaccharide (LPS) is inhibited by N-acetylcysteine (a GSH precursor) [32]. The amount of AP-1 binding to DNA is decreased in transgenic mice that overexpress the glutathione peroxidase gene compared to control mice after ischemia-reperfusion [33].

The interaction of ROS with cellular proteins may have consequences on fundamental cell functions. For example, vascular endothelial growth factor (VEGF) stimulates cell growth in a ROS-dependent fashion [34] by activating extracellular signal regulated kinase (ERK). ROS may act in several steps of the apoptotic pathway, as they are able to directly or indirectly affect mitochondrial function by mitochondrial membrane alteration or by reacting with mitochondrial membrane protein thiols, respectively. Release of mitochondrial intermembrane space proteins, such as cytochrome c, may further activate caspase 9, which promotes DNA fragmentation and condensation and subsequent cell apoptosis. Apoptosis-induced factor (AIF) may also come from mitochondrial external membrane permeabilization and directly induce apoptosis at the nuclear level [35]. In some cases, mitochondrial dysfunction may lead to an increase in ROS production that causes so much damage to mitochondria that energetic failure may lead to necrotic cell death.

Role of Oxidative Stress in Microcirculatory Dysfunction

We will illustrate the key role of ROS in the physiopathology of two major situations encountered in critical care, namely ischemia-reperfusion and sepsis.

Ischemia-reperfusion

ROS production during ischemia-reperfusion occurs mainly during reperfusion and may contribute to direct tissue injury caused by energetic failure and cell death [36], a well described phenomenon with regard to myocardial infarction. In addition to the induction of cell death, ROS-induced production may alter microcirculatory behavior. Indeed, ischemia-reperfusion is associated with impaired endothelial-dependent vasodilation that can be triggered by NO buffering by excess $O_2^{\cdot -}$. Ischemia-reperfusion may also induce an increase in endothelial permeability at the capillary level, creating vascular wall edema that leads to ischemic lesions. A rise in endothelial permeability may be triggered by endothelial ROS production during reoxygenation as well as by WBC ROS that are recruited in the ischemic zone. The WBC may also release inflammatory cytokines during reperfusion that exacerbate capillary leaks. Finally, at the level of post-capillary venules, endothelial ROS production associated with the secretion of leukotriene B4 (LTB4) and platelet activating factor (PAF) activate WBCs, which become adhesive to the endothelium [37]. Neutrophil adhesion may then participate in tissue injury. It is important to note that adhesion after ischemia-reperfusion is a sustained reaction with recruitment of several types of WBC over time. While early PMN adhesion after ischemia-reperfusion is well described, the leukocyte population switches to mononuclear cells (T lymphocytes) in the days following stroke. Lymphocytes may then modulate inflammation and participate in late-stage tissue injury [38].

Sepsis

Sepsis induces disturbances at the level of both the macro- and the micro-circulation. As septic shock occurs, organ dysoxia may be observed due to hypovolemia that may be associated with septic cardiac failure. However, once macrohemodynamic parameters are stabilized in a sufficient range, the microcirculation may still be disturbed with capillary deperfusion as if dysfunction of microcirculatory regulation were present, independent of macrohemodynamics [39]. This microcirculatory dysfunction may be due to the release of mediators during sepsis including ROS, cytokines or LPS. Microcirculatory dysfunction occurs at several levels (Fig. 4):

- ROS production during sepsis may come from leukocytes by the so-called 'oxidative burst', which is triggered by inflammatory stimuli. The resulting WBC

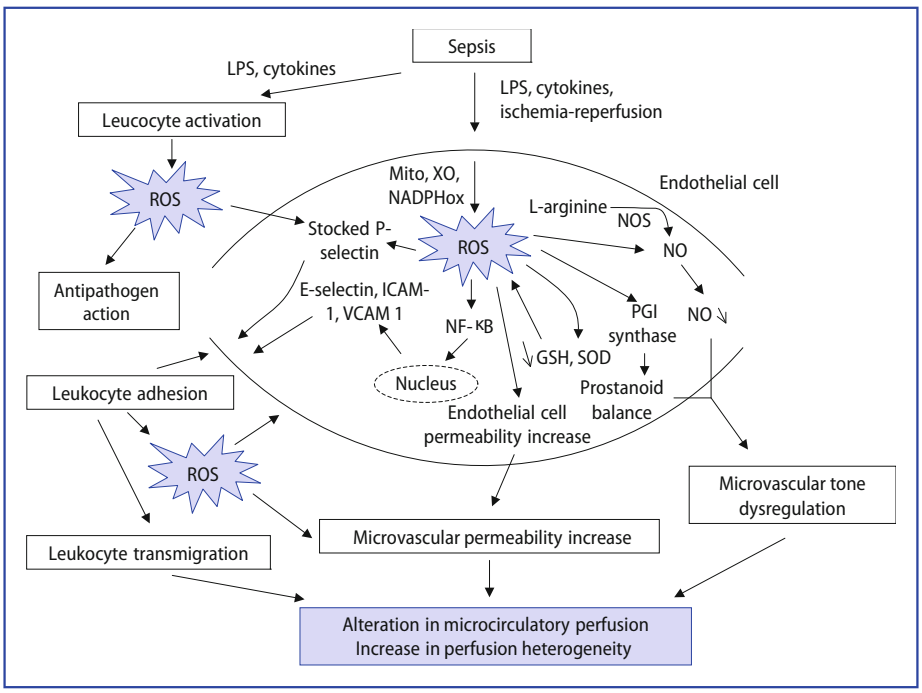

Fig. 4. Principal targets of reactive oxygen species (ROS) during sepsis. Sepsis induces systemic inflammation with leukocyte activation that produces ROS. ROS may help to defend against pathogens, but may also diffuse and activate endothelial cells, causing migration of P-selectin to the endothelial membrane. Pro-inflammatory cytokines may directly activate endothelial cells and trigger ROS production by mitochondria (Mito), xanthine oxidase (XO) and NADPH oxidase (NADPH ox). ROS may then directly stimulate migration of stocked P-selectin to the cell membrane or induce *de novo* production at the transcriptional level via nuclear factor-kappa B (NF-κB) activation. Adhesive protein expression (P and E-selectin, intercellular adhesion molecule-1 [ICAM-1] and vascular adhesion molecule-1 [VCAM-1]) permits leukocyte adhesion that produces ROS locally. Intracellular ROS production may buffer nitric oxide (NO) and decrease its availability, leading to vascular tone disturbances. Moreover, ROS may influence the balance between constrictor and vasodilator prostanoids by modifying cyclooxygenase activity. Glutathione (GSH) level decreases during sepsis, as does superoxide dismutase (SOD) function, leading to exacerbation of ROS levels due to a lack of detoxifying capacity. LPS: lipopolysaccharide

activation increases ROS production capacity, which, on the one hand, permits fighting of the pathogen responsible for the infection and, on the other hand, enhances the process of adhesion with endothelial cells (see above). Endothelial cells themselves are a source of ROS when they are in the presence of pro-inflammatory stimuli.

- Vascular tone modifications are observed in which NO may have a key role. NO is usually produced by endothelial NOS (eNOS) and participates in endothelium-dependent vasodilation. However, during sepsis, inducible NOS (iNOS) is expressed that increases total NO production. This induction is not uniform [40] and has important consequences with respect to ROS production. Indeed, as $O_2^{\cdot-}$ may react with NO to form $ONOO^-$, NO is consumed and no longer available, demonstrating that the heterogeneity of microcirculation perfusion depends on the balance of local NO and $O_2^{\cdot-}$ production. Moreover, the pathophysiology of microcirculatory deperfusion concerns additional vasoactive elements including PGI2, which is underproduced as ROS modulate the activity of PGI synthase by switching to vasoconstrictive prostaglandin production. Several studies have demonstrated the amelioration of microcirculation perfusion through the use of drugs that interact with microvascular tone regulation. Krejci et al. observed an amelioration in splanchnic microcirculation in pigs submitted to fecal peritonitis by using the endothelin receptor antagonist, bosentan [41]. Spronk et al. detected an amelioration of the sublingual microcirculation by using NO donors in septic shock patients [42]. However, this latter finding was not confirmed by a more recent, blinded, clinical randomized study that found no effect of systemic NO donor administration on microcirculatory dysfunction in septic shock patients [43].
- The microcirculation may be perturbed by capillary leak syndrome during sepsis because vascular edema decreases oxygen diffusion across the vascular wall and, thus, microcirculatory flow. The endothelial cell barrier is usually impermeable to fluids and macromolecules due to tight regulation of junction and adhesive protein expression, which confers a strong cohesion to the endothelium monolayer. During sepsis, an increase in endothelial permeability is observed along with massive fluid loss. Experimentally, the endothelial cell monolayer may become permeable when in contact with pro-inflammatory cytokines, such as TNF-α [44]. ROS seem to play a key role in this: Administration of antioxidant molecules may prevent this permeability increase [45] whereas direct endothelial contact with ROS increases permeability [46].

Another impact of oxidative stress during sepsis deals with cell metabolism. Mitochondrial dysfunction leads to a decrease in mitochondrial respiratory chain activity. Brealey et al. observed an inhibition of complex I in muscle biopsies from septic shock patients, which correlated with the severity of the condition [47]. Moreover, this mitochondrial dysfunction correlated with reduced glutathione concentrations and ATP levels. This finding is in phase with the oxidative stress activity on mitochondrial respiratory chain proteins; $ONOO^-$ has been demonstrated to interact with complex I and III, thereby decreasing their activity [48, 49]. However, this concept was recently discussed in the light of recent experimental studies that incriminated S-nitrosothiols, rather than $ONOO^-$, in the nitrosation of complex I [50].

Conclusion

As the microcirculation transports oxygen and nutrients to cells, its regulation is dynamic and very reactive according to environmental variation. Endothelial cells appear to be central in signal transduction from the blood compartment to the vessel wall in physiological and pathological conditions. Extensive research from the two last decades delineates a key role for oxidative stress in endothelial cell function and microvessel behavior. In certain settings, such as in ischemia-reperfusion and sepsis, ROS appear to contribute to microvascular injury. These observations raise the possibility that ROS will become a therapeutic target in various pathologies, including sepsis or ischemia-reperfusion injury. However, the involvement of ROS in cellular and microvascular homeostasis may complicate ROS-targeting therapeutics. A more precise knowledge of the role of ROS in microcirculatory injury is essential for the development of ROS-directed therapies.

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I Diagnosis and Treatment of the Septic Microcirculation

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Introduction

Shock has typically been classified into four types: Hypovolemic, cardiogenic, obstructive, and distributive. The first three categories are associated with a decrease in cardiac output, leading to tissue hypoxia. Distributive shock, such as septic shock, results from abnormal distribution of normal or increased cardiac output, secondary to microcirculatory dysfunction. Severe disruption of the microcirculation during sepsis results in a pathologic heterogeneity in microvascular blood flow that occurs as a consequence of the shutdown of weak microcirculatory units. This implies that oxygen transport is shunted from the arterial to the venous compartment, leaving the microcirculation hypoxic, and is the main pathogenic feature of distributive shock. Such a scenario results in maldistribution of microvascular blood flow and a mismatch between oxygen delivery and oxygen demand in different tissues that seems to be the first step in the progression to organ failure [1].

In shock profiles other than sepsis, where the microcirculation is not affected to such an extent, optimization of systemic hemodynamic parameters would likely ensure adequate oxygenation of tissues. In severe sepsis, however, regional hypoperfusion can persist even after correction of global hemodynamic and oxygen-derived variables [2]. This disparity between systemic and regional tissue oxygenation makes it difficult to define monitoring and treatment endpoints.

The microcirculation can be assessed at the bedside using new imaging techniques, namely orthogonal polarization spectral (OPS) imaging and sidestream dark field (SDF) imaging. During resuscitation and treatment of septic shock, these techniques allow for evaluation and verification of whether the treatment strategies implemented really improve the microcirculation in an attempt to correct tissue dysoxia. In fact, some studies have been published recently that evaluate the effectiveness of different treatments on the microcirculation using these techniques.

The present chapter focuses on the pathophysiology of the distributive defect of septic shock at the microcirculatory level, as well as discussing new evidence regarding the effects of vasopressors and vasodilators on the microcirculation during septic shock.

Normal Microcirculation

Microcirculatory function is the main prerequisite for adequate tissue oxygenation and, thus, also organ function. The roles of the microcirculation include transporting oxygen and nutrients to tissue cells, ensuring adequate immunological function

and, in disease, delivering therapeutic drugs to target cells. The microcirculation network consists of the smallest blood vessels (< 100 μm diameter), where oxygen release to the tissues takes place, and includes arterioles, capillaries, and venules (microcirculatory units) [3]. This network accounts for 10 billion capillaries and the highest endothelial surface in the body (more than 0.5 km^2). The main cell types in the microcirculation are the endothelial cells, smooth muscle cells (mostly in arterioles), red blood cells (RBC), leukocytes, and platelets. The endothelial cells have a key role in microcirculatory functioning, participating in blood flow regulation, controlling coagulation and immune function, and releasing nitric oxide (NO) in response to shear stress and possibly also hypoxia [4]. NO is an important factor in maintaining the integrity of blood flow through the microcirculation by regulating resistance vessel diameter (relaxing smooth muscle cells in proximal arterioles), blood rheology (regulating RBC and leukocyte deformability), interactions between blood elements and the vascular wall (regulating leukocyte-endothelial adhesion and platelet adhesion and aggregation), and blood volume (increasing vascular permeability during endotoxemia) [5].

Microvascular oxygen delivery cannot be predicted from systemic or even regional oxygen delivery. First, microvascular hematocrit is lower than systemic hematocrit due to the Fahraeus effect (dynamic reduction of hematocrit due to axial migration of erythrocytes near the center of the vessel). Second, the distribution of hematocrit is nonlinear at vascular branch points. Third, microvascular PO_2 (partial oxygen pressure) is also lower than systemic PO_2 and is heterogeneously distributed. Hence, oxygen delivery is heterogeneously distributed throughout the microcirculation network [6].

The structure and function of the microcirculation is highly heterogeneous in different organs, and is closely related to the functional role played by a particular organ as a whole. The number of capillaries per unit mass of organ or tissue (capillary density) may be related to the organ's metabolic requirements (muscles, heart, brain) or to other functional requirements (skin, intestinal mucosa, kidney) [7]. This marked heterogeneity of the microcirculation leaves the network particularly vulnerable to hypoxic insult.

The microcirculation normally insures adequate oxygen delivery to meet the oxygen demands of every cell within an organ. A strict regulatory mechanism is in place to achieve this, with multiple signaling pathways interacting at different levels. In this way, oxygen transport to tissues with high oxygen need is augmented and oxygen transport to tissues with low metabolic activity is restricted [8]. This regulatory mechanism allows microcirculatory flow to occur independent of changes in systemic blood pressure, a mechanism called autoregulation [7]. In general, driving pressure, arteriolar tone, hemorheology, and capillary patency are the main determinants of microcirculatory blood flow.

Regional flow is determined by large vessels (medium-sized arterioles), which are mainly controlled by the sympathetic nervous system. In contrast, local distribution of blood flow to tissues is regulated by the microcirculation. When terminal arterioles are vasodilated, perfusion of the capillaries increases; when terminal arterioles are vasoconstricted, the number of recruited capillaries decreases. These vessels are primarily under local control, and the endothelial cells play a central role in this [4]. It has been proposed that these cells can regulate arteriolar smooth muscle tone upstream by sensing shear stress and different regulating substances (acetylcholine, catecholamines, prostaglandins, endothelin, bradykinin, thromboxane, adenosine, nitrosothiols and ATP) downstream in the capillary network. Endothelial cell-to-cell

signaling (via gap junctions) transmits upstream information about hemodynamic conditions downstream [5]. This cell-to-cell communication could involve ascending membrane hyperpolarization via activation of a K-ATP channel and electrical coupling with smooth muscle cells, with regulation of the vascular tone. RBCs also play an important role in the control of microcirculatory perfusion. These cells release ATP and S-nitrosothiol (SNO) in hypoxic conditions, both of which produce local vasodilation and increase blood flow [9]. Finally, other factors that affect blood flow in the capillary network are capillary resistance (determined by diameter and length) and hemorheologic factors (blood viscosity and RBC deformability) [5].

The Microcirculation in Sepsis

One of the primary functions of the microcirculation is to ensure adequate oxygen delivery to meet the oxygen demands of every cell. As long as the regulating mechanism is functional and capillary density is sufficient, the microvasculature will deliver all available oxygen to where it is needed within an organ. However, if the microvasculature is dysfunctional, as it is in sepsis, maldistribution of blood flow and tissue hypoxia can occur despite supranormal oxygen delivery values [10]. Microcirculation is the landscape where most of the pivotal events of sepsis pathogenesis take place [3].

Multiple mechanisms influence the microcirculatory network during sepsis [3, 11, 12]: Redistribution of blood flow from compliant vascular beds (skin and the splanchnic area) to more crucial body areas (brain, heart), with secondary microvascular derecruitment; endothelial activation and injury; loss of the glycocalyx (which covers the endothelium and forms an important barrier and transduction system); increased microvascular permeability (capillary leakage) with edema formation and hypovolemia; decreased RBC deformability, with concomitant capillary plugging; increased leukocyte adhesion and reduced deformability, with capillary and venular obstruction; leukocytes activated by septic inflammation that generate reactive oxygen species (ROS) that directly disrupt microcirculatory structures, cellular interactions, and coagulatory function; capillary obstruction by platelet/fibrin clots secondary to disseminated intravascular coagulation (DIC); and impaired arteriolar smooth muscle cell tone and response to vasoactive stimuli, secondary to excess NO production.

The combination of these mechanisms contributes to a reduction in perfused capillaries (decreased functional capillary density), the development of heterogeneous abnormalities in microcirculatory blood flow, and the loss of intrinsic vasoregulation in almost all vascular beds [13]. Decreased capillary density implies that the diffusion distance for oxygen is increased [7]. The increased heterogeneity of the microcirculation, in which some vascular beds exhibit preserved functional capillary density, whereas others have sluggish blood flow and still others have no flow at all, generates areas of hypoxia and impairs oxygen extraction in both mathematical and animal models of septic shock [10]. These alterations generate an impaired ability to regulate local oxygen delivery, which translates to rapid onset of tissue hypoxia [9]. If this state of hypoperfusion is not reversed in a timely manner, tissue injury and multiple organ failure can occur.

It is important to consider that many of the clinical manifestations of severe sepsis are secondary to alterations in the microcirculation, such as hypotension, low vascular resistance, low filling pressure, and hypovolemia. Therefore, basic elements

of the septic hemodynamic profile, typically thought to be macrovascular derangements in nature, are actually rooted in the microcirculation [2].

Bedside Study of the Microcirculation

Expedient detection and correction of tissue dysoxia may limit organ dysfunction and improve outcomes in septic patients. However, tissue dysoxia is very difficult to detect at the bedside because there are no specific clinical signs or simple laboratory tests to assess it. On the other hand, measurements of hemodynamic and oxygen-derived parameters fail to assess the microcirculatory network, where oxygen delivery to cells really occurs, so are not sensitive enough to detect regional hypoxia [13].

Hence, one of the most important advances in the study of sepsis in recent years has been the development of imaging techniques that allow for direct visualization of microcirculation at the bedside. These techniques include OPS and SDF imaging. The OPS technique consists of a handheld device that illuminates the area of interest with polarized green light while imaging the remitted light through a second polarizer (analyzer) oriented in a plane precisely orthogonal to the plane of illumination. The green light has a wavelength within the hemoglobin absorption spectrum (548 nm), so RBCs appear as dark moving bodies and leukocytes may be visible as refringent bodies [14]. SDF imaging is the successor of OPS and is based on essentially the same physical principles, but has higher resolution and picture quality than OPS [15].

Because of direct *in vivo* observation of the microcirculation in septic patients, microcirculatory abnormalities, particularly heterogeneity of flow, are now being recognized as key characteristics in the pathogenesis of organ dysfunction during sepsis, corroborating previous experimental data. The presence and persistence of such abnormalities has been found to be associated with prognosis of morbidity and mortality. De Backer et al. [16] reported a significant decrease in vessel density and in the proportion of small perfused vessels in septic patients compared to healthy volunteers; this impairment of the microcirculation was more severe in non-survivors. These results were later confirmed by Trzeciak and colleagues [17], who also found that alterations in the microcirculation were related to the severity of organ failure, as assessed by the Sequential Organ Failure Assessment (SOFA) score. Sakr et al. [18] characterized the time course of microcirculatory alterations in patients with septic shock and its relation to outcomes. Although similar at baseline, the microcirculation improved rapidly in survivors as compared to non-survivors, even though global hemodynamic variables did not differ. More importantly, capillary perfusion when shock ended was related to the severity of organ failure.

Finally, as microcirculatory failure can occur in the presence of normal or supranormal systemic hemodynamic and oxygen-derived variables, monitoring the microcirculation with OPS and SDF during the resuscitation of septic shock could, in theory, allow for evaluation and verification of whether the treatment strategies implemented do really improve the microcirculation in an attempt to correct tissue dysoxia [3].

The Microcirculation in Distributive Shock

Shock is a condition that occurs when there is insufficient transport of blood carrying oxygen to meet the metabolic demands of the tissue cells. Many years ago, Weil

and Shubin [19] classified four states of shock: Hypovolemic, cardiogenic, obstructive and distributive. The first three categories predictably result in a decrease in cardiac output, leading to tissue hypoxia. However, distributive shock, such as septic shock, has been more difficult to characterize. This difficulty is primarily because this type of shock results from distributive alterations in tissue perfusion caused by microvascular dysfunction, resulting in abnormal distribution of normal or increased cardiac output [1]. Shunting of oxygen transport is the main pathogenic feature of distributive shock and is secondary to microcirculatory dysfunction. This leads to a maldistribution of microvascular blood flow and a mismatch between oxygen delivery and oxygen demand in different tissues, which seems to be the first step in the progression to organ failure [13]. Hence, in shock profiles other than sepsis, where the microcirculation is not affected to such an extent, correction of global hemodynamic parameters would likely ensure adequate oxygenation of the tissues. However, in severe sepsis, regional hypoperfusion can persist even after global optimization of conventional hemodynamic and oxygen-derived parameters [2]. This disparity between systemic and regional tissue oxygenation makes it difficult to define monitoring and treatment endpoints.

Septic shock is characterized by shunted microcirculatory units, resulting in regional dysoxia. Global hemodynamic and oxygen-derived variables can seem quite normal, while regional microcirculatory areas could be hypoxic secondary to the shutdown of weak microcirculatory units [20]. This implies that oxygen transport is shunted from the arterial to the venous compartment, leaving the microcirculation hypoxic [12]. Weak microcirculatory units have unfavorable rheological and/or resistive properties, such that they are the first to become hypoxic during ischemia, shock, and sepsis, and the last to recover during reperfusion [8]. In addition, during sepsis, alterations in different components of the microcirculation, disturbed microvascular autoregulation, and heterogeneous inducible NO synthase (iNOS) expression between different vascular networks, all favor the development of shunted areas of the microcirculation, which generates a heterogeneous distribution of blood flow between and within organ systems (**Fig. 1**) [10]. Weak microcirculatory units are well recognized in certain organs, such as the mucosal villi of the gut and the kidney cortex.

The functional consequence of microcirculatory shunting is that local microcirculatory PO_2 becomes lower than venous PO_2, a pathological condition that has been termed the "PO_2 gap" [8]. Using the Pd-porphyrin phosphorescence technique to measure microcirculatory PO_2, Ince et al. [21, 22] showed that the PO_2 gap was higher in septic shock than in hemorrhagic shock, reflecting the severity of oxygen shunting during sepsis. The systemic manifestation of this condition is a deficit in oxygen extraction by the tissues since the cells are still capable of extracting oxygen, but oxygen is not being delivered to where it is needed secondary to the presence of shunted hypoxic microcirculatory units. This explains the high mixed venous oxygen saturation that is typical of septic shock.

Many studies in clinical and experimental sepsis have demonstrated the presence of shunted microcirculatory units and the heterogeneous distribution of blood flow between and within organ systems. Ellis et al. [23], using *in vivo* spectrophotometric imaging, demonstrated in a rat model of sepsis that some local regions of tissue were clearly over-supplied with oxygen, whereas other areas, those supplied by capillaries exhibiting increased oxygen extraction, were under-supplied with oxygen. This study clearly illustrated the maldistribution of blood flow at the capillary level, the mismatching of local oxygen supply with local oxygen demand, and the possibil-

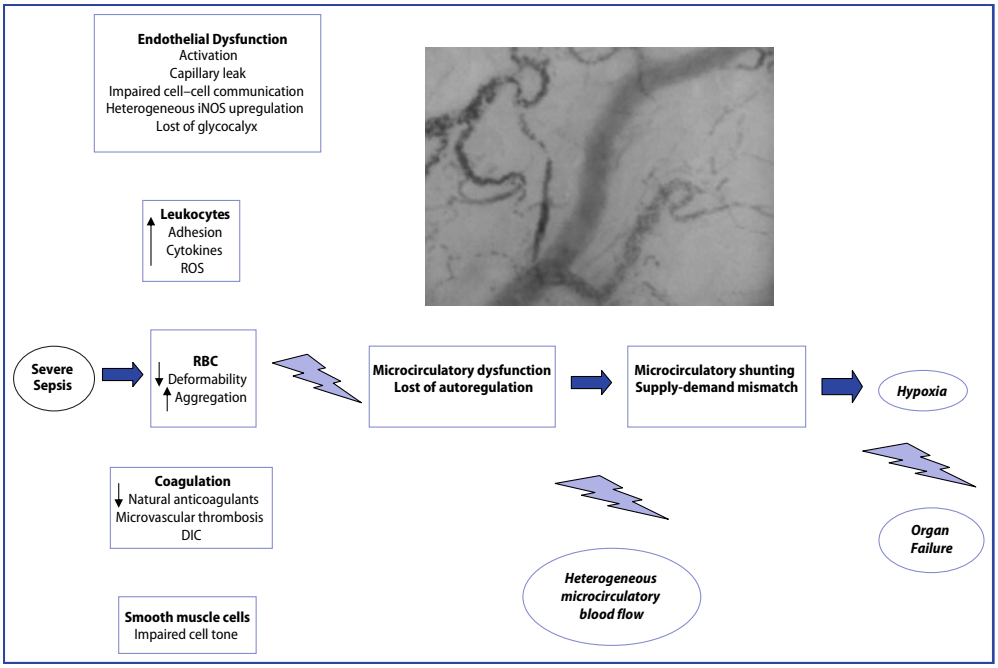

Fig. 1. During severe sepsis, all microcirculatory components are severely disturbed, resulting in the loss of autoregulation and the shutdown of weak microcirculatory units. This leads to a maldistribution of heterogeneous microvascular blood flow and a mismatch between oxygen delivery and oxygen demand in different tissues that seems to be the first step in the progression to organ failure. iNOS: inducible nitric oxide synthase; ROS: reactive oxygen species; RBC: red blood cells; DIC: disseminated intravascular coagulation

ity that hidden hypoxic microcirculatory units could be next to well perfused or even over-perfused normoxic units. These authors also found an increased proportion of fast flow vessels adjacent to stopped-flow capillaries, suggesting that blood might have been shunted through the capillary beds via these vessels.

There is ample evidence of the heterogeneity of the microcirculation within and between various vascular beds during sepsis from animal studies. These findings have been corroborated in various clinical studies using OPS and SDF. Boerma et al. [24] studied patients with abdominal sepsis and demonstrated that there was a complete dispersion between OPS-derived sublingual and intestinal microcirculatory parameters on day 1; however, on day 3, microcirculatory blood flow was almost normalized at both sites, with a significant correlation between the two vascular beds. This result underlies the time-dependency of microcirculatory alterations and heterogeneity in sepsis. The same authors studied the correlation between sublingual microcirculatory alterations and the central-to-toe temperature gradient as an easily accessible parameter of combined peripheral and central circulation [25]. Again, a significant correlation could not be demonstrated. Interestingly, in both of these studies, there were practically no correlations between microcirculatory variables and hemodynamic parameters. This lack of correlation between microcirculatory and hemodynamic variables has been reported in almost all of the clinical studies that have assessed the microcirculation in severe sepsis.

Using OPS and SDF imaging techniques in patients with septic shock, all classes of microcirculatory flow abnormalities have been found, especially at the capillary level, where the distributive defect occurs. The highly heterogeneous blood flow at this level, in contrast with the findings regarding the venular component of the microcirculation, shows a normal-to-hyperdynamic blood flow. Elbers and Ince [1] identified five classes of sublingual capillary flow abnormalities in distributive shock, arguing that each could be associated with a specific etiology.

To underscore the dissociation between the different types of shock and microcirculatory abnormalities, Nakajima et al. [26] used intravital microscopy to compare the effects of hemorrhage and endotoxin shock at the microvascular level (intestinal villi) in a rat model. These authors found that at the same level of hypotension, capillary density and RBC velocity were altered considerably more in endotoxin shock. Fang et al. [27], using OPS on the sublingual microcirculation, also compared hemorrhage and septic shock, demonstrating similar findings. These authors also found that improved global hemodynamics after resuscitation were not effective in improving capillary blood flow in septic shock; unlike in hemorrhagic shock, where improved global hemodynamics were found to be effective [27]. These data confirm that, in shock profiles other than distributive shock, microcirculatory alterations seem to be effectively corrected by resuscitating global hemodynamic variables because the microvasculature is still able to regulate microvascular perfusion. In septic shock, however, modalities aimed at recruiting systemic variables do not always seem to be effective in recruiting the microcirculation. These experimental studies have contributed to the view that sepsis is a disease of the microcirculation.

The NO system, which is severely disturbed during sepsis, is an important component in the pathophysiology of distributive septic shock. During sepsis, heterogeneous upregulation of iNOS occurs between and within different organs. There are areas with over-production of NO that have been associated with decreases in blood pressure, impaired vascular reactivity, abnormal RBC deformability, decreased functional capillary density, and reduced oxygen consumption [10]. On the other hand, there is the possibility of localized microvascular beds with relative NO deficiency, despite a state of total body NO 'excess'. This can be a major factor in the pathogenesis of sepsis, generating pathologic microcirculatory shunting and interfering with regional blood flow [28]. The complex role of NO in the pathophysiology of sepsis and its associated distributive shock could explain the contrasting results in animal and clinical studies with NO inhibitors and NO donors. Numerous clinical and animal studies of sepsis [29, 30] have demonstrated that NOS inhibition reverses hypotension, normalizes the cardiac index and systemic vascular resistance, and improves oxygen extraction. Despite these positive effects on global hemodynamic and oxygen-derived variables, the inhibition of NO over-production seems to be deleterious in the microcirculatory network [31, 32]. In addition, despite a favorable outcome on arterial pressure in septic shock patients, a phase III clinical trial with a non-specific NOS inhibitor was terminated because of increased mortality arising from increased cardiovascular failure [33]. Evidence from NO donor studies is also contradictory. Two studies have assessed the effect of administering nitroglycerin to fluid resuscitated septic patients. The first study, a small study with 8 patients, reported an improvement in microcirculatory flow [34]. The second study, a randomized study with 70 patients, did not note any improvement in the microcirculation with nitroglycerin [35].

Recruiting the Microcirculation Network During Distributive Shock

Microcirculatory abnormalities have in common a distributive defect caused by functional shunting of capillaries. This shunting of the microcirculatory network could explain why resuscitation strategies based on the correction of upstream hemodynamic variables may not correct tissue hypoxia, because they are unable to recruit shunted microcirculatory units [7]. In this sense, opening the microcirculation network and keeping it open by use of fluids and vasodilators would seem a logical therapeutic strategy. In theory, the systemic administration of vasodilatory agents in septic shock could recruit microcirculatory units, decrease microcirculatory shunting, and improve regional tissue oxygenation. This action on the part of vasodilators is caused by a shifting of the pressure gradient across the microcirculation downstream, thereby increasing the driving pressure at the entrance of the microcirculation network and/or decreasing the capillary afterload [36]. Vasodilatation also causes an increase in capillary hematocrit, which further contributes to improved oxygen delivery to tissues. It is important to consider that NO donors can recruit the microcirculation not just because of their vasodilatory effect, but also by improving hemorheology secondary to a reduction in platelet aggregation and leukocyte adhesion.

There is ample evidence from experimental animal studies regarding the beneficial effects of vasodilators in models of sepsis in terms of microcirculatory recruitment and improved tissue oxygenation [36]. On the other hand, few clinical studies have evaluated the effect of vasodilators on the microcirculation in severe sepsis patients. De Backer and colleagues [16, 37] demonstrated that topical application of acetylcholine fully normalized the sublingual microcirculation. As mentioned above, two studies have assessed the effects of administrating nitroglycerin to fluid resuscitated septic patients, with contradictory results. Using OPS, Spronk et al. [34] reported that microcirculatory blood flow improved significantly with nitroglycerin, while, using SDF, Boerma and colleagues [35] did not find any significant change in the microcirculation with nitroglycerin after resuscitation with fluids. Boerma's study, which is the first randomized controlled trial to assess changes in the microcirculation after a specific therapeutic intervention found no evidence to support the use of nitroglycerin under the conditions of resuscitation that they practiced. The effects of other vasodilators and other NO donors should be evaluated in clinical microcirculatory studies to assess whether any of these can improve the microcirculation.

Adequate resuscitation of severe sepsis should target oxygenation of the microcirculation as an essential endpoint. In this context, administration of vasopressors as a means of restoring blood pressure to improve systemic oxygen delivery may have adverse effects on microcirculatory oxygenation and may even cause greater distress because of the enhancement of shunting [8]. Nakajima et al. [38] studied the role of vasopressor agents in an experimental model, and demonstrated that norepinephrine administration (titrated to restore blood pressure) modestly but significantly improved microvascular density. Two independent recent clinical studies using SDF imaging in the sublingual region assessed the effects of increasing doses of norepinephrine targeted to achieve successively greater mean arterial pressure (MAP). In the first of these studies [39], norepinephrine was escalated to achieve incremental increases in MAP from 60 to 70, 80, and 90 mmHg; global oxygen delivery increased without significant changes in microcirculatory density or flow. In the second study, Dubin et al. [40] progressively increased norepinephrine doses to achieve MAP of

65, 75, and 85 mmHg, and obtained a significant increase in cardiac index without significant variations in microcirculatory density and flow. Despite the improvement in global oxygen delivery and cardiac index, the microcirculation did not improve, corroborating that this compartment is masked from the systemic circulation during severe sepsis. However, the microcirculation neither deteriorated nor improved with increasing doses of vasopressors, suggesting that increasing MAP above 60–65 mmHg is not an adequate approach to improve the microcirculation.

The effect of inotropic drugs on the microcirculation and their ability to recruit it has also been assessed. De Backer et al. [37] evaluated the effects of a dobutamine infusion on sublingual microcirculation using OPS in 22 septic shock patients and reported improved microcirculatory flow that was not related to changes in cardiac output and arterial pressure. The fact that dobutamine improved the microcirculation independent of its systemic effects is quite surprising, as capillaries are devoid of β-adrenergic receptors. However, the microvascular effects of dobutamine are supported by experimental data using intravital microscopy [41]. In experimental models, isoproterenol and dopexamine have been shown to prevent leukocyte and platelet adhesion to the endothelium. These results support the theory that β-agonists may increase microvascular blood flow by either limiting adhesion of white blood cells to the endothelium or by promoting endothelial integrity, independent of any contractile or local vasodilatory effects. More microcirculatory research must be performed to assess the role of inotropic drugs in the microcirculation during sepsis.

Finally, the combined effect of vasodilators and vasopressors has also been assessed. In an experimental model of endotoxemia, the effect of L-arginine, a precursor of NO, alone or in combination with norepinephrine or vasopressin was evaluated using intravital microscopy in the intestinal villi. Interestingly, L-arginine, norepinephrine and vasopressin alone all failed to improve the microcirculation, but the combination of L-arginine with norepinephrine or vasopressin significantly improved microcirculatory blood flow [38]. These results, though paradoxical from a mechanistic stance, show that combined administration of vasoconstrictive and vasodilatory agents may have an additive effect on improving microvascular perfusion during sepsis. Again, more microcirculatory research must be performed to clarify this issue.

Conclusion

The microcirculation is the system in which most of the key events of septic shock pathogenesis take place. Sepsis induces profound changes in the microcirculation, which involves all the microcirculatory components. This results in the shutdown of weak microcirculatory units, generating a heterogeneous distribution of blood flow between and within organ systems, and shunting of oxygen transport from the arterial to the venous compartment. This shunting of oxygen transport is the main pathogenic feature of distributive shock.

As the microcirculation is masked from the systemic circulation during septic shock, secondary to distributive alterations of normal or increased cardiac output, hemodynamic and oxygen-derived parameters fail to assess this compartment. However, in recent years, the development of imaging techniques that enable direct bedside visualization of the microcirculation has allowed monitoring of this compartment during the resuscitation and treatment of septic shock. Currently, there is ample clinical research on these techniques that evaluates the effects of different treatments in recruiting the microcirculation network.

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Targeted Treatment of Microvascular Dysfunction

J.H. Boyd

Introduction: Microvascular dysfunction is the Root Cause of Inflammatory Organ Dysfunction

Nearly all critically ill patients requiring advanced life support exhibit systemic inflammation. Septic shock, the most common disorder in the critically ill, results from the direct adverse consequences of infection combined with a maladaptive response resulting in fulminant systemic inflammation. This powerful interaction results in a mortality rate of up to 50 % for victims of this disease [1–4]. While septic shock is most often described as 'warm' hypotension (particularly lowering diastolic blood pressure) despite initial resuscitation, the patient often exhibits circulatory failure demonstrated by mottled extremities and low mixed or central venous oxygen saturation as a result of inadequate oxygen delivery. A key component of the shock due to severe sepsis, cardiac impairment, can be demonstrated in 50–100 % of patients diagnosed with septic shock [5–9]. While diagnosed at the macrovascular level, cardiac pump failure is itself due to microcirculatory dysfunction and impaired oxygen extraction in the heart [10]. A daily clinical challenge faced by those caring for the critically ill is that while the patient presents with circulatory failure, advanced studies such as echocardiography and measurement of central venous oxygen tension ($ScvO_2$) actually demonstrate normal or even supra-normal cardiac output. This picture is often accompanied by an increasing lactate level and progressive organ dysfunction. It is now believed that this failure to adequately perfuse vital organs despite an ostensibly normal macrocirculation is due to dysfunction of the microcirculation.

Traditional Therapies and Biomarkers have Centered on the Macrocirculation

Restoring normal physiology in patients suffering from septic shock has been the cornerstone of therapy. This target has also provided the rationale for the development of current biomarkers of disease progression. Intense vasodilation in conjunction with frequent cardiac dysfunction is treated with fluids, vasopressors and inotropes. The 2008 Surviving Sepsis Guidelines suggest that in hypotensive patients with a mean arterial pressure (MAP) less than 65 mmHg, first-line therapy includes intravenous fluids, followed by a vasopressor/mild inotrope such as dopamine or norepinephrine if required [3]. These agents are titrated to restore the patient's blood pressure, and the biomarkers of physiologic success with this treatment include achieving an $ScvO_2$ of $\geq$ 70 % along with decreasing systemic lactate levels.

Clinicians have targeted treatments to these biomarkers in the belief that they are good surrogates for an adequate cardiac output and oxygen delivery. However, tissue perfusion does not necessarily equate with cardiac output and oxygen delivery, particularly in the critically ill. An important study demonstrating this fact was performed by LeDoux et al. [11]. Patients suffering from septic shock were enrolled in this study and were resuscitated to MAPs of 65, 75, and 85 mmHg using fluids and norepinephrine. Cardiac outputs were measured and correlated with measures of organ function and global tissue oxygenation. Counter-intuitively, increases in cardiac output did not result in improved organ function. In patients whose cardiac output was driven by high doses of norepinephrine, urine output and capillary blood flow were actually less than in those with a normal cardiac output. Similarly, capillary PCO_2 and the gradient between arterial PCO_2 and gastric intramucosal PCO_2 trended upwards in those with augmented output, together suggesting worsened tissue perfusion. While fluid resuscitation alone offers some benefits to microvascular permeability [12, 13], it is clear that in addition to guiding resuscitation using MAP and cardiac output as targets, one must additionally consider the microcirculation.

New Methods of Assessing the Microcirculation

Microvascular dysfunction as a result of septic shock has been well documented in skeletal muscle [14, 15]. Capillaries, designed to dilate in response to increased oxygen requirements and elevated PCO_2, swing instead between stopped or sluggish blood flow and excessive vasodilation. In regions of high oxygen demand this results in tissue hypoxia [16]. These fundamental discoveries related to microvascular dysfunction have resulted in exciting new technology able to visualize the microcirculation (**Fig. 1**). This technique uses polarized light microscopy of sublingual microvessels. Using it, investigators found that septic shock results in a dramatic increase in the heterogeneity of microvascular blood [17]. Survivors, on the other hand, have much improved microvascular function during the course of treatment compared to non-survivors [18]. In a study that used the polarized lens to assess microcirculatory

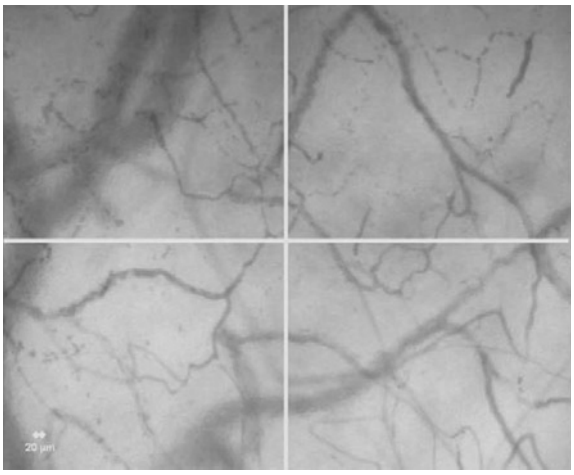

Fig. 1. De Backer et al. use direct visualization of the microcirculation to generate a semi-quantitative score (Mean Flow Index, MFI). They divide the image into four quadrants and grade the flow in vessels under 20 μm (absent = 0, intermittent = 1, sluggish = 2, and normal = 3). The MFI is an average of these scores over the four quadrants. This technique allows a reproducible score to be determined in real-time with minimal operator training. From [44]

flow while resuscitating patients according to the 2008 Surviving Sepsis Guidelines, organ function and survival correlated with improvements in the microcirculation [19]. Although this study addressed the feasibility of targeting the microcirculation, the efficacy of using this approach prospectively has yet to be established. It might be that the therapies of borderline benefit we discuss in the following sections may be more beneficial if properly titrated using a direct measure of microcirculatory flow rather than the current crude measures we employ.

Therapeutic Approaches

Suppression of Intracellular Inflammatory Signaling

Corticosteroids (Fig. 2-2)

Oral and intravenous corticosteroids are medications for which the ability to attenuate the inflammation associated with microcirculatory dysfunction depends completely on the underlying cause. Corticosteroids are an extremely efficacious class of medications for intense microcirculatory inflammation as a result of small vessel vasculitis, allergic inflammation, and other disorders due to classic immune

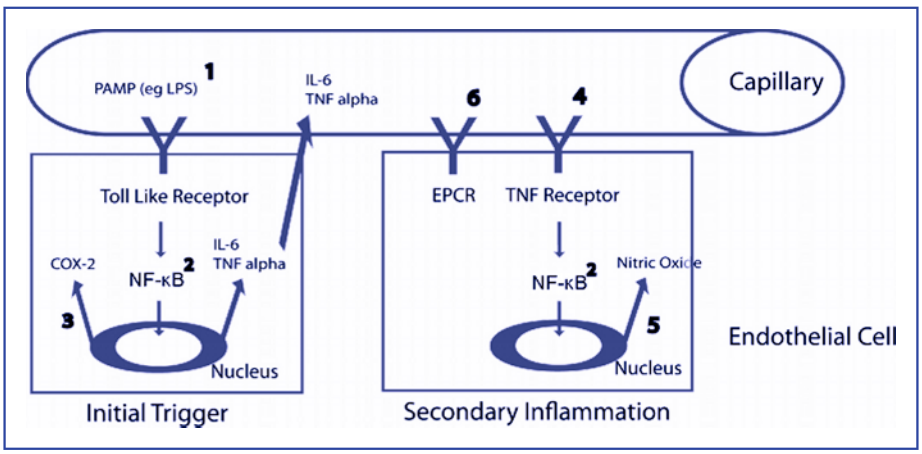

Fig. 2. Schematic diagram of proposed treatments for microvascular dysfunction. The initial Toll-like receptor (TLR)-mediated recognition of a pathogen-associated molecular pattern (PAMP) results in nuclear translocation of the key pro-inflammatory transcription factor, nuclear factor-kappa B (NF-κB). Blocking this TLR-PAMP interaction has been the aim of treatment with intravenous immunoglobulins (IVIG) and neutralizing antibodies, including HA-1A and the Enterbacteriaciae Common Antigen (**1**). NF-κB is mainly inhibited in the cytosol of the endothelial cell by corticosteroids which block its nuclear translocation (**2**). Nuclear translocation of NF-κB results in production of the enzyme, cyclooxygenase (COX)-2 and pro-inflammatory cytokines, including interleukin (IL)-6 and tumor necrosis factor (TNF)-α. Ibuprofen (**3**) inhibits the activity of COX-2, which catalyzes the formation of prostacyclin and thromboxane. The pro-inflammatory products (TNF-α most potently) then act locally and systemically via their cellular receptors (TNF receptor). Inhibition of this interaction has been trialed using antibodies to circulating TNF-α as well as the TNF receptor (**4**). TNF via NF-κB results in a profound upregulation of inducible nitric oxide (NO) synthase and thus to NO mediated vasodilation. The non-specific NO synthase inhibitor, L-NMMA, was used to inhibit this pathway (**5**). Systemic inflammation results in decreased circulating protein C, the active form of which interacts with the endothelial protein C receptor (EPCR) with a resultant net anti-inflammatory effect. Activated protein C has been used to restore this pathway (**6**).

mediated mechanisms. However, the use of steroids remains controversial in microvascular dysfunction induced by septic shock. More than two decades ago, three large randomized control trials (RCTs) treated patients with high-dose (30 mg/kg methylprednisolone or equivalent) steroids in patients with septic shock [20–22]. Despite improving blood pressure in the early phase of shock, patients treated with corticosteroids did not realize a mortality benefit, possible related to an increase in intensive care unit (ICU)-acquired infections. By using lower doses, it was believed that the anti-inflammatory benefits of steroids could be maximized while attenuating the immunosuppression during the delayed compensatory anti-inflammatory syndrome (CARS) phase of sepsis, so trials were recently performed using lower doses of steroids in patients with septic shock. A significant improvement in morbidity and mortality led to great enthusiasm and it was thought this might have clarified the way in which intensivists should use steroids in those with septic shock [23]. However, subsequent studies have not only failed to reproduce these findings, their results are in fact contradictory [4, 23]. When data from all the major steroid RCTs is examined, patients with profound shock and the most intense inflammation are most likely to benefit from therapy with corticosteroids. Unfortunately, due to the relative weakness of retrospective subgroup analysis, we are unable to draw definitive conclusions regarding the mortality benefit of steroids in sepsis.

Other inhibitors of cellular inflammation

As corticosteroids have myriad effects within the cell, only some of which lead to decreased inflammation, more specific therapies have been sought. Once innate immune receptors are stimulated by invasive pathogens, there is a rapid translocation of the transcription factor, nuclear factor-kappa B (NF-κB), to the nucleus and an explosive production of cytokines. This shifts the role of the endothelium to become inflammatory. This inflammation results in excessive production of nitric oxide (NO), a molecule which induces vasodilation despite ongoing physiologic signals indicating the need for augmented vascular tone. With the goal of blocking the detrimental vasodilatory effects of NO, a NO synthase (NOS) inhibitor, N-monomethyl-L-arginine (L-NMMA), was investigated in septic shock (**Fig. 2-5**). L-NMMA was found to be a potent drug to reverse the shock state and demonstrated impressive efficacy in animal models of septic shock. In a large RCT of L-NMMA in patients with septic shock, this effective reversal of shock was again demonstrated, however despite this the trial was stopped early due to an increased mortality rate in patients treated with L-NMMA [24]. A number of mechanisms has been proposed to explain the adverse effects of this drug. As a non-specific inhibitor of all NOS isoforms, L-NMMA not only inhibited the inducible NO found as a result of inflammation, but also the constitutive isoforms responsible for regulation of the microcirculation. There was no direct assessment of the microcirculation in this study so that this possibility must remain speculative. It has also been speculated that the increased mortality may have been a result of pulmonary hypertension [24]. Neither of these proposed mechanisms has been proven.

Ibuprofen is another anti-inflammatory drug with a different mechanism of action which has been studied in septic shock (**Fig. 2-3**). Ibuprofen inhibits inflammation via suppression of the prostacyclin and thromboxane signaling pathways, and, in a large RCT, downregulated the products of prostacyclin and thromboxane, while decreasing fever and systemic lactate production [25]. Despite this, and perhaps because these pathways are not central in innate immune signaling, there was no improvement in organ function or survival.

Suppression of Circulating Mediators of Inflammation

Pathogens, or more specifically pathogen-associated molecular patterns (PAMPS) such as endotoxin, trigger an inflammatory response which includes secondary production and secretion of cytokines, such as tumor necrosis factor (TNF)-α and interleukin (IL)-6. Interestingly, the PAMPs and cytokines result in a similar physiologic response, perhaps due to signaling pathways heavily shared between Toll-like receptors (TLRs) and cytokine receptors. This response includes vasodilation, hypotension and temperature alteration. Within hours of blood-borne sepsis there are, therefore, circulating PAMPs and cytokines, both responsible for organ dysfunction. Because of this there has been a great deal of attention devoted to removing or neutralizing these circulating molecules.

Large scale removal by hemofiltration

Using hemofiltration and hemodialysis as a tool to decrease the circulating levels of inflammatory mediators has been suggested as a means through which all mediators could be simultaneously removed. Two recent large RCTs, one published in 2008 [26] and one 2009 [27] studied whether a higher dose of dialysis may be more beneficial in critically ill patients. High dose was defined as 35 ml/kg/h hemofiltration and was compared to lower dose (20 ml/kg/h) in those with renal failure due to systemic inflammation. Neither study was able to demonstrate a benefit of higher dose treatment. This may in part be due to an underdosing of dialysis (for the purpose of inflammatory mediator removal) even in the high dose group. In the earlier study which sparked interest in this technique, the rate of plasma filtration was more than 9 l/hour, in contrast to 2 l/hour in the high dose dialysis group. In this series of 20 patients, the majority had large reductions in vasopressor dose and improvements in cardiac output and lactate levels [28]. However, due to practicalities surrounding nursing and other logistics, this very large volume hemofiltration is not amenable to everyday practice. Therefore, the possibility remains that with technical advances in hemofiltration devices, systemic removal of inflammatory mediators could have a place in the therapy of septic shock.

Intravenous immunoglobulin

Pooled intravenous immunoglobulin (IVIG) is thought to bind many PAMPs and block their interaction with their endothelial receptors (**Fig. 2-1**). A meta-analysis of numerous single center trials using IVIG treatment for the treatment of septic shock suggested that its use may improve mortality [29]. This spurred a large multicenter RCT to examine the utility of IVIG (isotype G) in septic shock, but this trial did not find a mortality benefit with treatment [30]. There does remain some hope for this therapy however, as subgroup analysis suggests that IVIG enriched in IgA and/or IgM perform better, perhaps due to enhanced PAMP clearance.

Neutralizing antibodies

If one could neutralize circulating PAMPs, the initial inflammatory trigger could be suppressed (**Fig. 2-1**). Endotoxin was the first PAMP for which a pharmaceutical grade antibody was successfully created. This antibody was named HA-1A. In a study published in 1982, HA-1A treatment generated impressive results, improving mortality in a single center study of patients with septic shock [31]. This led to a multicenter RCT, which was unable to reproduce the exciting findings of the smaller single center study, with HA-1A failing to reduce mortality [32]. Using a slightly dif-

ferent method of preparing the anti-endotoxin antibody (HA-1A was human derived while E5 was generated in mice), another large RCT published in 2000 again could not show any benefit to early administration of anti-endotoxin antibody in patients with septic shock [33]. The Enterbacteriaciae Common Antigen was also targeted by a neutralizing antibody and its use in septic shock studied in a multicenter RCT published in 2003 [34]. Again, treatment did not change mortality.

Secondary production of pro-inflammatory cytokines following PAMP recognition leads to the next wave of microvascular dysfunction. TNF-α is produced within hours of infection, its levels correlate with outcome and its administration experimentally mimics the multi-organ dysfunction seen in septic shock. Numerous trials using neutralizing antibodies to TNF-α and its receptor (**Fig. 2-4**) were performed over a ten year period [35–39]. Taken individually, none of these studies resulted in a treatment-induced survival benefit; however subgroup analysis does suggest that patients with the most intense inflammatory reaction to infection (as defined by IL-6 levels > 1000 pg/ml) may benefit from anti-TNF-α agents. Given the retrospective nature of these data, no firm recommendation can be given at this time, but perhaps with appropriate stratification according to microvascular dysfunction and systemic inflammation, patients who will benefit could be identified.

Levels of another pro-inflammatory cytokine, macrophage migration inhibition factor (MIF), have been shown to correlate with outcome and MIF reversed shock in animal models [40]. MIF is interesting in that it exerts its effect partly through re-sensitization of tissues to corticosteroids. A clinical trial with anti-MIF antibodies in patients with septic shock is underway.

Coagulation

Severe sepsis results in markedly decreased concentrations of circulating protein C and antithrombin with increased activity of tissue factor. In addition to the small vessel thrombosis as a result of these abnormalities, there exists an interplay between coagulation and inflammatory microvascular dysfunction. On the endothelial cell surface, a thrombin-thrombomodulin complex cleaves protein C to produce activated protein C (APC). This activated protein then binds the endothelial protein C receptor (EPCR) which goes on to suppress inflammatory cytokines and apoptotic pathways. Investigators have performed RCTs in septic shock with antithrombin and APC, attractive targets given their dual roles in coagulation and inflammation. Treatment with antithrombin in a large RCT in septic shock did not improve mortality or any measure of organ function measured out to 90 days [41]. Recombinant tissue factor inhibitor similarly failed to confer any survival advantage in another large RCT [42]. Although the molecular mechanism underlying its efficacy is unclear (i.e., whether it can be attributed to anti-inflammatory or coagulation effects), a large RCT of APC in septic shock demonstrated that this agent was associated with decreased organ dysfunction and improved survival (**Fig. 2-6**) [43]. Of great interest to the clinician is that this benefit was most pronounced in the most severely ill patients.

Conclusion

As is evident from the preceding sections, the initial promise of many therapies has faded when studied in large clinical trials. Interestingly, the molecular targets of therapy have generally been successfully modified with treatment (such as ibupro-

fen's effects on reducing prostacyclin and thromboxane activity), despite failure to modify the mortality rate. Might the dose and timing of therapy be as important as the efficacy? To date clinicians have struggled with the diagnosis of inflammatory microvascular dysfunction as well as with subsequent titration of therapy. Physicians have had to rely on indirect measures, such as systemic oxygen delivery and lactate production, rather than having a specific diagnostic tool. Perhaps by incorporating direct visualization of the microcirculation into a treatment algorithm, clinicians will soon be closer to attaining the goal of quenching the inflammatory fire without fueling the subsequent CARS syndrome and contributing to lethal secondary infections.

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II Hemodynamic Monitoring

Diagnosing Hypovolemia in Critically Ill Patients

A. Perner and U.G. Pedersen

II

Introduction

Hypovolemia is frequent in critically ill patients. There is little doubt that when left unrecognized and thus untreated hypovolemia will worsen patient outcome [1]. Therefore, it is more than likely that adequate fluid resuscitation could improve the outcome of a huge number of critically ill patients worldwide. The administration of fluid is a simple and inexpensive procedure, so one of the barriers for optimal fluid therapy is likely to lie in the diagnosis of hypovolemia.

Defining Hypovolemia

Hypovolemia can be defined as a state of reduced blood volume. In clinical medicine, however, this definition is less useful, because there are no clinical methods to quantify blood volume. There is no consensus on the clinical definition of hypovolemia, but in broad terms it is a state in which a patient has hypoperfusion, which will improve with fluid therapy. In clinical studies, hypovolemia is most often defined pragmatically as the patient with shock in whom stroke volume or cardiac output increases after a fluid bolus. This is also termed preload, volume or fluid responsiveness.

Diagnosing Hypovolemia

When we assess a patient prior to fluid treatment we are performing a diagnostic test to answer the question 'does this patient have hypovolemia?' To give a reasonable answer to this question, we have to know the limitations of the different test options and apply the appropriate test to the specific patient. We also need to know the best cut-off point of the diagnostic test and its accuracy for hypovolemia, e.g., the positive and negative predictive values. Ideally, the test should be simple and quick to perform, operator-independent, non-invasive, inexpensive and applicable to the majority of patients in shock. Both high positive and negative predictive values are important, because fluid in excess is likely to have negative consequences for the patient [2]. The need for accurate diagnostic tests for hypovolemia is highlighted by the observation that only half of the patients included in trials of fluid responsiveness responded to the fluid challenge studied [3]. Translated to daily practice, only half of the patients we treat with resuscitation fluid will improve their cardiovascular function; the other half may show the side effects of overloading.

II

Static Diagnostic Tests

For 30 years, we used central venous pressure (CVP) and pulmonary artery occlusion pressure (PAOP) to diagnose hypovolemia. These markers of preload have been an integral part of patient monitoring, which is perhaps why we were late to assess them as diagnostic tests in clinical trials. When trialed, filling pressures were shown to have no predictive power for hypovolemia in the majority of patients [4]. Advances in technology allowed clinicians to measure heart volumes and areas, including those of the right and left ventricles at end-diastole. These static indices of preload were also shown to have low predictive power for hypovolemia [4]. It is likely that extreme values of filling pressures or heart volumes/areas have predictive power for hypovolemia, but the cut-off points for what is a low or what is a high value have not yet been established.

Within the last ten years, clinical researchers have challenged the static markers of preload in studies of dynamic tests for the diagnosis of hypovolemia.

Dynamic Diagnostic Tests

These tests involve changes in preload followed by the assessment of potential changes in markers of stroke volume or cardiac output.

Fluid challenge

The simplest diagnostic test is to administer a fluid bolus of 250 – 500 ml and observe changes in blood pressure. This technique is often used during the initial phase of resuscitation, but once severe hypovolemia has been corrected, better markers of stroke volume or cardiac output are needed. A fluid challenge with the assessment of cardiac output by thermodilution is still the gold standard diagnostic test for hypovolemia and the reference method when new tests are being studied. This method has the obvious drawback that the clinician has to give fluid to assess whether the patient needs it. As mentioned above, a fluid bolus may be futile in half of the patients. The tests described below are being developed to avoid this in-built risk of fluid overloading when diagnosing hypovolemia.

Arterial waveform-derived variables

These tests rely on heart-lung interactions. In the presence of hypovolemia, stroke volume will change during the changes in preload induced by the cyclic changes in pleural pressure under positive pressure ventilation [5]. Quantification of the variations in stroke volume can be made by the continuous assessment of arterial waveform-derived variables including systolic pressure (**Fig. 1**), pulse pressure or pulse contour or power analyses [6 – 11].

In a recent meta-analysis, Marik and colleagues aggregated the results of a systematic review of the use of dynamic changes in arterial waveform-derived variables during mechanical ventilation to diagnose hypovolemia in critically ill patients [3]. The results of the meta-analysis of the 29 included studies were straightforward. Systolic pressure variation, pulse pressure variation, and stroke volume variation accurately predicted fluid responsiveness in critically ill patients in sinus rhythm who were sedated and on controlled ventilation with a tidal volume greater than 7 ml/kg. The best cut-off point was around 12 % for hypovolemia, with positive and negative likelihood ratios around 6 and 0.15, respectively. The review confirmed that static indices of preload, including CVP and end-diastolic volumes/areas, had no predic-

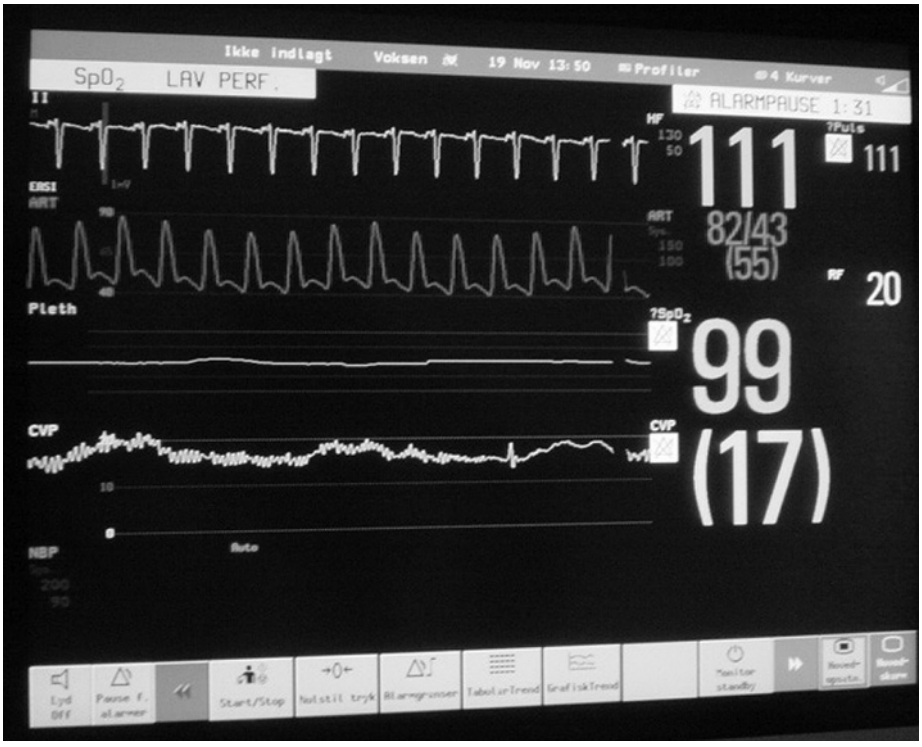

Fig. 1. Marked changes in the arterial waveform caused by controlled, positive pressure ventilation in a patient with shock.

tive power for hypovolemia. As mentioned above, only half of the 685 patients in the analysis responded to the fluid challenge, which again underlines the need for accurate diagnostic tests for hypovolemia in critically ill patients.

The limitation of the meta-analysis lies in the limitations of the included studies. In general these were small, single center studies; most were performed in patients in the perioperative period and most were done in cardiac surgical patients. Some studies were statistically flawed by the inclusion of more datasets from each patient into the analyses. If data are not independent, observations from the patients with more assessments may alter the estimate of the diagnostic accuracy depending on the relationship between the variables in that specific patient. In some studies, data were only analyzed by correlation analyses, which may be used for associations, but not for the assessment of diagnostic tests. The study results have to be presented so that the predictive values of the test for hypovolemia can be calculated. For clinicians, the positive and negative predictive values or likelihood-ratios of a specific cut-off point are of value, because these describe the accuracy when only the test result is known. It is less relevant to know the sensitivity and specificity of the test, because these describe the accuracy when the diagnosis is known. Surprisingly few papers report positive and negative predictive values or likelihood-ratios.

Taken together, the arterial waveform-derived variables have been shown to accurately predict fluid responsiveness in mainly critically ill surgical patients in sinus rhythm, who are sedated and on controlled ventilation with a tidal volume greater

than 7 ml/kg. In addition to these prerequisites, right ventricular failure [12] or a low heart rate to respiratory frequency ratio [13] may result in false positive or negative results, respectively. The main problem may be that the number of patients who fulfill the prerequisites for these tests may be limited, at least in emergency departments and general intensive care units (ICUs). For those patients who do fulfill the prerequisites, we need larger multicenter studies in mixed groups of critically ill patients to confirm the generalizability of these tests as diagnostic tests for hypovolemia.

Passive leg raising

The lower limbs hold blood which may be shifted to the central blood volume. A reversible autotransfusion maneuver by passive leg raising combined with the assessment of changes in stroke volume has the potential to diagnose hypovolemia without the risk of volume overloading the patients. This test has been less studied than those above, but may turn out to be applicable to more patients, at least in emergency departments and general ICUs. Boulain and co-workers were the first to describe the correlation between changes in radial artery pulse pressure during passive leg raising and the change in stroke volume after a subsequent fluid bolus in mechanically ventilated patients [14].

This initial study was followed up by Monnet and colleagues [15], who assessed fluid responsiveness in 71 ICU patients, some of whom had spontaneous breathing activity and irregular cardiac rhythm. The effect of passive leg raising on stroke volume was assessed as the change in aortic blood flow using esophageal Doppler. As shown in **Figure 2**, passive leg raising was performed from the semi-recumbent position and the authors found high values of sensitivity and specificity of the test. The predictive values were not reported, but positive and negative likelihood ratios can be calculated as 16 and 0.03, respectively. A smaller study partly confirmed these findings [16], but differences in ventilator settings and method of passive leg raising, hamper direct comparison with the findings of Monnet and co-workers.

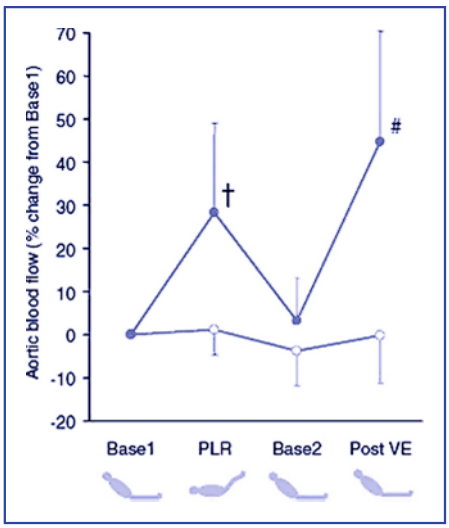

Fig. 2. Aortic blood flow in fluid non-responders and responders during the study procedures performed by Monnet and colleagues [15]. Open circles: Fluid non-responders – neither passive leg raising (PLR) nor the subsequent volume expansion (VE) changed aortic blood flow. Filled circles: Fluid responders – both PLR and the subsequent VE increased aortic blood flow. † $p < 0.05$ vs base 1, # $p < 0.05$ vs base 2. From [15] with permission.

A crucial aspect in interpreting the hemodynamic response to a passive leg raise is to have a continuous measure of cardiac output or a surrogate marker. Both transthoracic Doppler ultrasound and echocardiographic measurement of flow or stroke volume can predict volume responsiveness in mixed medical ICU patients, including those with spontaneous breathing and arrhythmias [17, 18, 19]. An important point is that the passive leg raising test using echocardiography is feasible in awake patients with minimal patient-discomfort in contrast to the use of esophageal Doppler [18, 19, 20].

Generally an increase in aortic blood flow of between 8 and 15 % has been reported to be diagnostic for hypovolemia. Fifteen percent may, however, be close to the combined error in the repeated measurements of aortic flow. Consequently, clinicians should be cautious when interpreting an increase between 8 and 15 % in aortic blood flow after passive leg raising [21].

Moreover, the optimal technique for performing passive leg raising is debated. Some investigators have used a passive leg raising maneuver starting with the patient in the supine position while others have started with the patient semi-recumbent. The former maneuver has been shown to false-negatively classify almost half the patients as non-responders, because the volume shift from the lower extremities is likely to be insufficient to result in an increase in preload [22]. When performing passive leg raising from the semi-recumbent position, the venous blood from the splanchnic bed as well as that from the lower limbs is shifted upwards by the gravitational force. To this end, it has been suggested that the ability of the passive leg raise to recruit a sufficient shift of blood should be controlled using a marker of cardiac preload, e.g., filling pressure or end-diastolic volume/area [23].

Taken together, passive leg raising with the assessment of cardiac output or a continuous surrogate marker, is likely to be an accurate and safe diagnostic test for hypovolemia in mixed ICU patients without the prerequisites of sedation, controlled ventilation, and sinus rhythm. The method, therefore, has the potential to be more useful in clinical practice than arterial waveform-derived variables. However, controversies still exist as to whether the passive leg raising maneuver should be performed from the supine or semi-recumbent position and whether a marker of preload should be used to ensure that a sufficient shift of blood volume has occurred. Once these issues have been solved, the best cut-off values for hypovolemia should be determined in multicenter studies of patients in shock.

Perspective

Improvements in cardiovascular diagnostics have the potential to improve outcomes for a large number of patients with shock. The tests described above hold some promise, but more studies should be performed in emergency departments and general ICUs in patients who are likely to have the largest potential benefit. An accurate diagnosis of hypovolemia is more likely to benefit a patient with septic shock and impaired cardiac function than a patient after cardiac surgery. Moreover, authors should adhere to the Standards for Reporting of Diagnostic accuracy (STARD) initiative [24], so that results can be easily interpreted and aggregated in systematic reviews.

It may however be difficult to alter the outcome of critically ill patients by diagnosing circulatory abnormalities, a problem observed with the use of the pulmonary artery catheter in ICU patients [25]. Eventually, protocol-based treatment algorithms

incorporating dynamic diagnostic tests for hypovolemia should be assessed in large randomized trials of shock patients using patient-centered outcome measures.

Conclusion

As we are still unclear as to which approach represents the ideal diagnostic test for hypovolemia, strong recommendations cannot be made. For static markers of preload either very low or very high values are likely to have some positive or negative predictive value, respectively, for hypovolemia. Arterial waveform-derived variables may guide clinicians in selected groups of patients, who fulfill the prerequisites for these tests. However, we need larger multicenter studies in mixed groups of critically ill patients to confirm the generalizability of these as diagnostic tests for hypovolemia; this also applies to the passive leg raising test, even though more patients may qualify for this test. Until results from such studies are available, dynamic tests for hypovolemia should be used with caution, particularly in settings where they have been less studied, i.e., the emergency department and the general ICU.

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Measuring Stroke Volume Using Electrical Impedance Tomography

II

H. Luepschen, S. Leonhardt, and C. Putensen

Introduction

Electrical impedance tomography (EIT) of the lungs is a bedside-available, non-invasive, and radiation-free medical imaging modality which allows real-time imaging of electrical impedance (i.e., resistance to alternating currents) changes in the thorax [1]. During breathing, lung tissue, with its relatively high impedance oscillations, is the main contributor to these changes which has led to a multitude of applications in monitoring regional lung ventilation [2–5, for review see 6, 7].

In addition to changes caused by ventilation, the detection of cardiac-related impedance changes in the heart and lung regions has been examined for more than 20 years [8]. Despite these efforts, the non-invasive measurement of stroke volume by means of impedance measurements is still far from being sufficiently accurate. However, the prospect of obtaining non-invasive cardiac output measurements right at the bedside is tantalizing enough to spur an ongoing interest into developing more sophisticated methods which are accurate and robust enough for clinical application.

In this article, we will discuss the fundamentals and pitfalls of cardiovascular EIT measurements by reviewing the recent literature and by illuminating the underlying physical and physiological processes.

Why do we need Non-invasive Cardiovascular Measurements?

In numerous clinical conditions, including cardiovascular disease, congestive heart failure, and hypertension, the cardiac stroke volume has a major diagnostic value. Non-invasive measurement of stroke volume would be a large step forward towards increased patient safety in standard care. A non-invasive bedside-available monitoring system would be of invaluable help especially for the assessment of the hemodynamic consequences of lung recruitment and positive end-expiratory pressure (PEEP) titration maneuvers. When combined with regional information on ventilation and with global respiratory parameters [9–12], treatment could be individually tailored to the specific patient's need. In addition to minimizing the static and dynamic stress and strain of the lung tissue [13], it would also become possible to closely monitor the burden on the cardiovascular system which would be particularly beneficial for patients suffering from cardiac insufficiency.

Electrical Impedance Tomography

EIT systems produce cross-sectional images of the electrical impedance distribution within electrically conducting objects. In the case of thoracic EIT, small harmless alternating currents (e.g., 5 mA at 50 kHz) are injected through 16 or 32 electrodes into the thorax. The currents' pathways through the body mainly depend on the impedance distribution in a 3D-volume ranging from 3–4 cm above to 3–4 cm below the cross-sectional area spanned by the electrodes (**Fig. 1**). The resulting electric potentials, V_i, on the surface are then measured and used to reconstruct the impedance distribution inside the thorax by solving an ill-posed non-linear problem, related to the reconstruction of computed tomography (CT) images [7, 14]. **Figure 2** shows a typical electrode configuration for a thoracic EIT measurement.

Many algorithms rely on Newton's iterative method to approximate the best solution to the inverse problem making additional use of a-priori assumptions, also called regularization [15, 16]. As thoracic shape and exact electrode placement play a major role in the distribution of surface potentials when trying to create absolute impedance images, all clinically available EIT devices use another approach called dynamic or difference imaging where only relative changes in impedance in relation to a previous reference measurement are calculated [7]. This approach results in a much better image quality when compared to absolute measurements. A drawback, however, is that only regions of the thorax that change their respective impedances over time are represented in the difference images.

The spatial resolution of EIT systems is comparably low and depends on many factors such as number of electrodes, contact impedances, and measurement noise. In a typical adult patient, the resolution is about 2–3 cm in the cross-sectional plane. Theoretically, the resolution can be increased if more electrodes are used. However, there exists a tradeoff between signal-to-noise-ratio and electrode size and distance. In contrast, the temporal resolution is very high and reaches up to

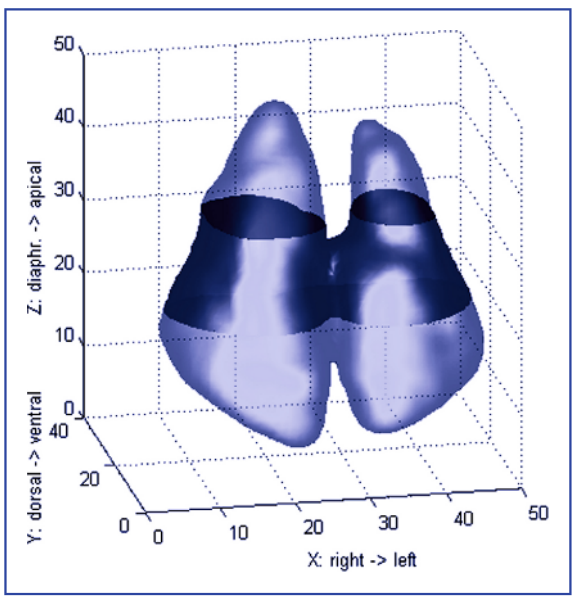

Fig. 1. Estimated slice thickness (approx. 7 cm) for cross-sectional thoracic electrical impedance tomography measurements. The sensitivity at the upper and lower border will be much smaller than in the center. Nevertheless, there will be an interference of respiratory impedance changes (i.e., noise) in the heart region which has to be carefully filtered before stroke volume calculation.

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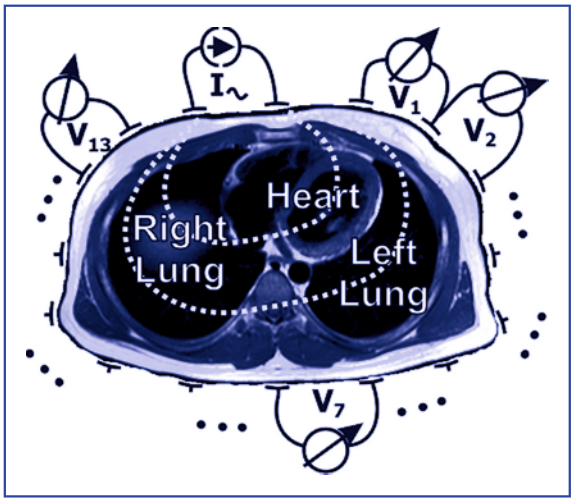

Fig. 2. Magnetic resonance tomography cross-section of the human thorax with schematically drawn electrodes at one specific current injection position (alternating current $I_{\sim}$). For the reconstruction of a complete EIT image, the injecting current pair is circled around the thorax while subsequently measuring the voltages at the remaining electrode pairs V_k. The current pathways depend on the impedance distribution inside the thorax.

50 frames per second, so that even the high-frequency cardiac activity can be closely monitored. Moreover, the high frame rate can be exploited to further improve the spatial resolution by combining the information of subsequent frames [17].

EIT-based Methods to Measure Stroke Volume

Several methods have been explored to extract cardiac-related electrical impedance changes from the ventilation-induced changes. The most promising will be briefly summarized in the following section.

Holding the Breath

The most straight forward method to get rid of the ventilation component of impedance changes is to stop breathing activity for a predefined period of time. In this way, cardiac-related changes become predominant and easy to detect in the remaining EIT signal. Even during the first attempts to localize cardiac-related changes with rudimentary EIT hardware, Eyüboglu et al. [8] were able to see changes well above the noise level (using an electrocardiogram [EKG]-gated averaging filter, see next subsection) at a rate of 10 frames per second. Nowadays, the signal-to-noise ratio and temporal resolution of modern EIT devices has significantly increased, so that real-time imaging of cardiac-related changes during apnea can even be achieved without, or at least with much less, filtering. This method has the obvious disadvantage of forcing the patient to stop breathing during a stroke volume measurement.

EKG Gating

Even though modern EIT devices have high signal-to-noise ratios, averaging over many heart cycles is still an important and widely used method for the extraction of cardiac-related impedance changes, especially if the patient continues breathing during the measurements. Technically, this process is known as “synchronous averag-

ing" [18] and aims at reducing the noise level by averaging datasets synchronized with a reference signal (e.g., the R-wave of an EKG). Experience has shown that averaging over $N = 100$ cardiac cycles will be necessary to sufficiently attenuate the respiratory component [19]. In terms of noise, this will reduce random noise by a factor of 10 as the signal-to-noise ratio (SNR) gain for synchronous averaging can be calculated as (assuming uncorrelated noise with zero mean [20]):

$$SNR_{\text{gain}} = \frac{SNR_{\text{averaged}}}{SNR_{\text{non-averaged}}} = \sqrt{N} = 10\log_{10} N\text{dB}$$

There are two main disadvantages of EKG-gated averaging: A) if the heart rate is an exact multiple of the respiratory rate, the extraction may fail; and B) the averaging process acts as a temporal filter and, therefore, adds a time delay and reduces the temporal resolution. **Figure 3** depicts a typical example of the Fourier spectrum of EIT signals in the thorax. A low-frequency ventilation signal with distinct higher harmonics partly overlaps a smaller cardiac signal. During mechanical ventilation, the higher harmonics are particularly pronounced which leads to an even more difficult separation.

Optimized Separation in the Temporal and Spatial Domains

Assuming that the cardiac and respiratory signals are well separated in frequency and, for the heart region, additionally in space, or there is some a-priori knowledge, it is possible to use optimized filtering approaches (if compared, e.g., to the standard EKG gating) to separate both fractions. Optimally, separation only adds a small time delay, but avoids reduction of the temporal resolution. Leathard et al. [21] were the first to propose use of a repeated temporal moving average filter having a rectangular window with a window width equal to the reciprocal of the heart rate. This helped to reduce the number of frames used in the subsequent synchronous averaging and, thus, the time delay. However, only after introduction of more sophisticated signal processing methods, such as principal component analysis and template matching [22, 23], did it become possible to maintain the full temporal resolution in order to observe highly dynamic cardiac changes. Deibele et al. [23] presented a cascaded multi-step approach that initially creates a set of orthogonal template functions representing the ventilation signal using temporal and spatial information which are afterwards fitted into the combined signal of ventilation and heart

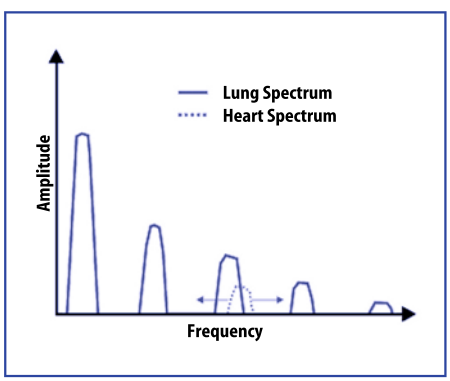

Fig. 3. Example of Fourier spectrum of respiratory and cardiac activity. Depending on the exact heart rate, the strong higher harmonics of the lung spectrum may overlap the cardiac component making a frequency-based separation difficult. During mechanical ventilation the higher harmonics can be particularly pronounced.

II

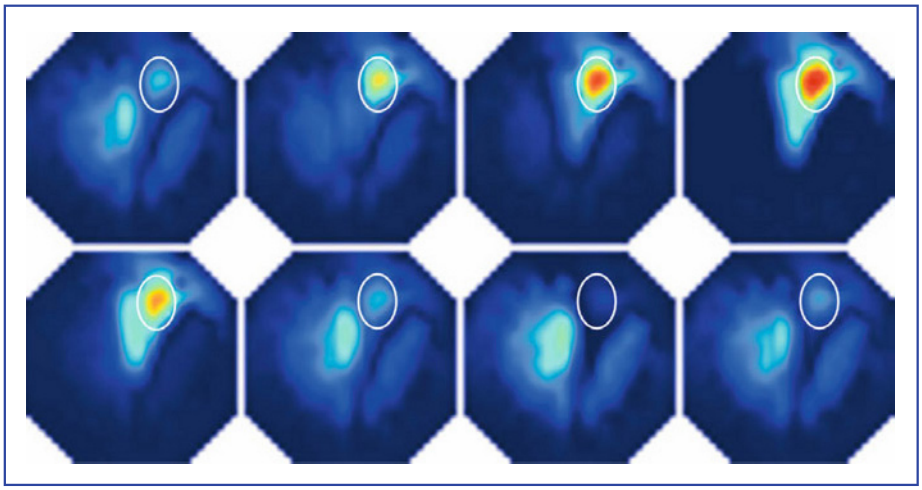

Fig. 4. Sequence of cardiac related impedance changes in the human thorax starting at end of diastole (upper left), extracted using a principal component analysis-based approach as described in [23]. The estimated region of the ventricles is marked, but has to be individually detected. High impedance values are shown in red.

activity. After subtraction of the ventilation signal and a second filtering step an estimate of the cardiac component can be extracted. In **Figure 4**, a sequence of cardiac impedance images of a spontaneously breathing human volunteer is shown. The extraction is based on the principal component analysis-template approach described in [23]. One of the remaining challenges lies in the exact determination of the heart area and subsequent calculation of the stroke volume.

Contrast Agents

As the cardiac-related impedance change usually amounts to only 3 – 10 % of the ventilation-induced change [24], contrast agents may be used to better distinguish both components. For this, it is necessary to alter the electrical conductivity of the blood by, e.g., intravenously injecting a bolus of hypertonic saline (1 % – 10 % solution) [8]. 0.9 % saline has a conductivity of 1.66 Sm^{-1} whereas blood is less conductive, with an average of 0.62 Sm^{-1}. When mixing a volume, V_1, of conductivity, σ_1, with a volume, V_2, of conductivity, σ_2, we can calculate the percentage change in conductivity from the following formula [25]:

$$\sigma^{\%} = \frac{300 \cdot V_2/(V_1 + V_2) \cdot (\sigma_2 - \sigma_1)}{2\sigma_1 + \sigma_2 + V_2/(V_1 + V_2) \cdot (\sigma_1 - \sigma_2)}$$

This approach not only has the advantage of increasing the stroke-by-stroke amplitude of cardiac-related impedance change, but additionally creates large superimposed thermodilution-like impedance curves in the surrounding tissue. By fitting gamma curves (modeling the indicator wash-in) to the impedance-time trace, it may become possible to even derive perfusion maps of the lung [7]. **Figure 5** depicts a typical impedance-time curve after intravenous injection of a saline bolus (the impedance decreases after injection). After recirculation and artifact

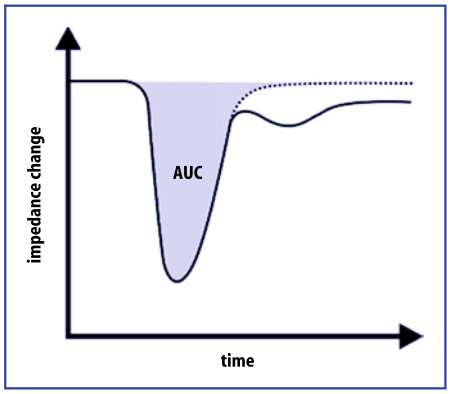

Fig. 5. Impedance-time curve after intravenous injection of a saline bolus. The area under the curve (AUC) is proportional to the volume flow, i.e., the cardiac output.

correction, cardiac output (cardiac output) is proportional to the area under the curve (AUC):

$$\text{cardiac output} = C_{EIT}\frac{Q_{saline}}{AUC}$$

where Q_{saline} is the amount of iodine in the bolus and C_{EIT} is a calibration factor mainly depending on the state of the lung [26]. Values remain more or less constant over time as long as no severe ventilatory or hemodynamic changes occur. When compared to standard thermodilution, the cardiac output calculation is more complicated, mainly due to the low spatial resolution of the EIT imaging modality and, thus, the superposition of cardiac-related impedance changes in lung and heart. Apart from that limitation, the use of contrasts agents looks promising regarding stroke volume quantification, but unfortunately increases the invasiveness of the intrinsically non-invasive EIT method.

Deriving Stroke Volume from Cardiac Impedance Images

After extraction of the cardiac-related impedance signal, cardiac stroke volume has to be deduced. Therefore, the exact heart region in the EIT image needs to be determined. Several methods have been used:

- Hahn et al. [27] applied the so-called filling capacity method, which is based on estimating the slope of a linear fit of regional versus global impedance change.
- Deibele et al. [23] used the first principal component analysis component of the cardiac signal.
- Vonk-Noordegraaf et al. [28] combined a filtering and thresholding approach, similar to that used in [8].

One major problem is the regional overlapping of left and right ventricles, left and right atria and aorta in the 2D EIT image [19] (**Fig. 6**). Furthermore, even after spatial filtering, respiratory impedance changes will be found in the heart region, because A) the slice thickness of EIT measurements is often larger than the heart size (**Fig. 1**), and B) the heart will be compressed by the surrounding lung tissue at the respiratory frequency, particularly during high PEEP ventilation.

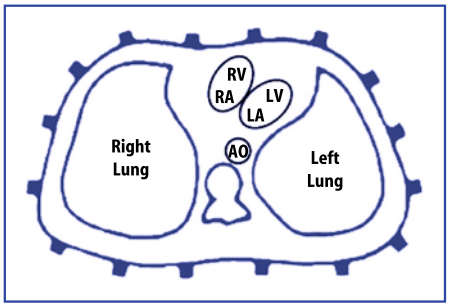

Fig. 6. Regional overlapping of the right and left ventricles (RV, LV), the right and left atria (RA, LA) and the aorta (AO). Due to the examined slice thickness of EIT measurements (cf. **Fig. 1**) and the low spatial resolution there will be a noticeable influence of respiratory and aortic impedance changes in the heart region, even after spatial filtering.

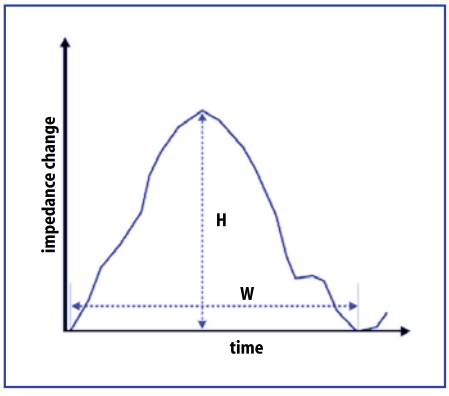

Fig. 7. Impedance-time curve of an averaged cardiac cycle in the heart region of interest (ROI). The width, W, and height, H, of the curve are used to calculate the stroke volume [28].

For the stroke volume derivation, it is possible to simply look at the change in amplitude during the cardiac cycle, but more sophisticated methods have also been developed.

Impedance-time Curves

Vonk-Noordegraaf et al. [28] averaged 200 heart cycles and determined the width W and height H of the averaged impedance-time curve (**Fig. 7**). Afterwards, they calculated stroke volume as

$$\text{Stroke volume} = C_1 \cdot W \cdot \sqrt{H \cdot A_{ROI}} + C_2$$

where A_{ROI} is the pixel area of the heart region of interest, and C_1 and C_2 are stroke volume calibration constants. Furthermore, these authors improved the measurement design by applying an oblique instead of a horizontal plane [29]. Overall, they found a high correlation between EIT-based and thermodilution stroke volume measurements in 26 patients scheduled for a diagnostic right side heart catheterization (due to previous infarction or valvular disease). The correlation coefficient was r = 0.86 [28]. Additionally, this group depicted a Bland-Altman plot for a group of 11 healthy patients comparing the EIT measurements with a magnetic resonance imaging (MRI) reference method, finding a mean difference of 0.7 ml and a standard deviation of 5.4 ml (approx. 10 % of the mean value).

Parametric EIT

Zlochiver et al. [30], instead, constructed an impedance model of the thorax from segmented MRI images, simulated the heart region as a 2D ellipsoid, and optimized the reconstruction based on their model. The ellipsoid's axes' length is then used to estimate the left ventricular volume, V_{LV}, by applying the following equation, known as the ellipsoid single-plane area-length model:

$$\text{Stroke volume} = \frac{8}{3\pi}\frac{(\pi \cdot r_{minor} \cdot r_{major})^2}{r_{major}},$$

where r_{minor} is the shorter and r_{major} is the longer axis. These authors also reported a high correlation of r = 0.86 between EIT and impedance cardiography measurements in 28 healthy patients.

Conclusion

EIT is gradually gaining acceptance as a cheap, non-invasive and bedside-available monitoring tool for critical care patients, particularly for the surveillance of regional lung mechanics. Furthermore, as dynamic changes in blood volume cause impedance oscillations in the cardiac frequency range which can be detected by EIT [8, 31], this technique additionally allows for continuous non-invasive monitoring of stroke volume [28, 30]. It, therefore, becomes necessary to separate higher cardiac from lower respiratory frequencies, and to combine this with spatial information about the heart region. Finally, the multivariate temporal and spatial information has to be mapped into an estimation of the cardiac stroke volume.

The main challenges are:

1. Low signal amplitude of relatively high-frequency cardiac-related impedance changes close to noise level [21],
2. Frequency overlapping of respiration-induced impedance oscillations, most notably if the heart rate is a multiple of the respiratory rate (at high PEEP ventilation, this is further aggravated due to tidal compression of the heart) [23],
3. Spatial overlapping because of the low spatial resolution of EIT images (especially in the caudal-cranial direction [19], see **Figure 1**), and
4. Drift of stroke volume calibration constants over time depending on the amount of atelectasis, lung edema, and the position as well as the geometry of the heart [32].

Most challenges have already been satisfactorily met by: A) developing new EIT hardware with improved signal-to-noise ratios and higher frame rates; B) improving signal processing algorithms allowing a separation of respiratory and cardiac components at full temporal resolution [22, 23]; and C) using different electrode planes focusing on the position and pitch of the heart [29]. However, the problem of calibration has not been fully addressed yet. Experimental results are encouraging, with correlation coefficients up to r = 0.86 [28, 30], but the number of examined cases is still too low and has not been extended to different diseases, such as congestive heart failure or acute respiratory distress syndrome (ARDS). It is very likely that changing fluid balances in the thorax will lead to severe drifts in stroke volume calibration constants, similar to those found in pulse contour analysis [33]. The use of contrast agents may help to increase the accuracy of EIT-based stroke volume mea-

surements, but likewise invasiveness and will, therefore, not be applicable in all patients. EIT imaging with hypertonic saline will probably even lead to bedside monitoring of regional lung perfusion [7], although the precise physiological origins of cardiac-related impedance changes are still unclear and need further investigation [34].

Future research should focus on comparing EIT-based stroke volume measurements with established reference methods in critically ill patients and on finding ways to easily calibrate the device when vascular tone, general hemodynamics, or fluid balance change distinctly. Minimal invasiveness will be of utmost importance as accurate invasive methods are well established. Using transthoracic echocardiography may help to achieve this goal.

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II

Direct Arterial Pressure Monitoring: Pattern Recognition in the Management of Circulatory Failure

M. Nirmalan and M.R. Pinsky

Introduction

Direct arterial blood pressure monitoring is frequently undertaken in operating rooms, critical care units, emergency departments and coronary care units where rapid alterations in hemodynamic status may occur in response to the underlying disease and/or treatment. In addition to providing a beat-to beat measurement of blood pressure, a careful study of the individual components of the arterial pressure waveform will also enable a more comprehensive assessment of several other hemodynamic parameters that may influence treatment [1–4]. Changes in circulating volume (or ventricular preload), stroke volume (an important determinant of cardiac output), volume responsiveness and peripheral vascular resistance (or afterload) are some of the more important variables that may be inferred from the arterial pressure trace. Understanding the significance of all the components of an arterial pressure waveform is, therefore, an essential skill for hospital doctors involved in the care of acutely ill patients. In this case-based discussion we will present a series of arterial pressure recordings that illustrate some of the clinically important concepts.

Case Study 1: Components of an Arterial Pressure Waveform

Figure 1a shows a model arterial trace recorded from a patient with severe atherosclerosis presenting for major vascular surgery. The resting pressure within the artery at the beginning of the cardiac cycle is referred to as the diastolic pressure and the peak pressure achieved during ventricular contraction is referred to as the systolic blood pressure. The difference between the systolic and diastolic pressures gives an estimate of the pressure swings within the arterial system during each cardiac contraction (or pulse) and hence is referred to as the pulse pressure. The mean pressure during the entire cycle is known as the mean arterial pressure and in practice this is approximately equal to the diastolic pressure + 1/3 × pulse pressure. The peak systolic pressure wave is often followed by a smaller pulse of reflected pressure wave. Such reflected waves are particularly prominent in patients with a stiff aorta due to atherosclerosis or chronic hypertension. The peak systolic pressure waves and reflected waves usually occur during the ventricular ejection phase prior to the closure of the aortic valve [5]. The presence of significant small vessel disease or intense vasoconstriction may, however, result in multiple pressure wave reflections as shown in **Figure 1b**. In such situations, reflected pressure waves may also be seen during diastole after the closure of the aortic valve.

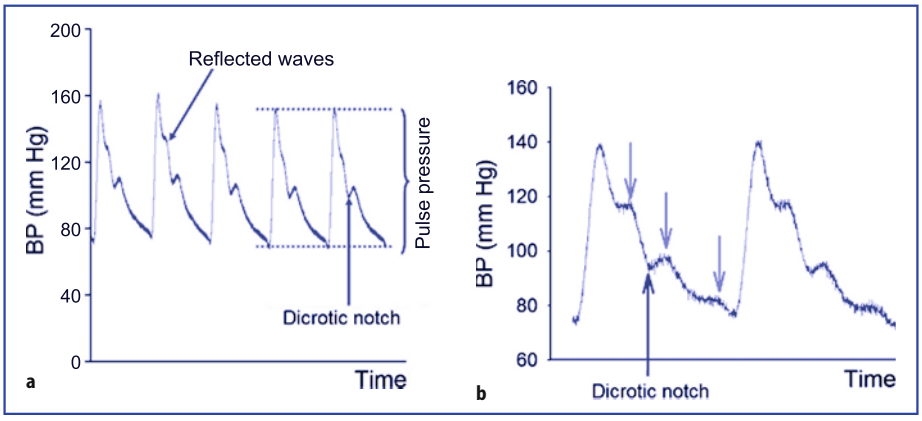

Fig. 1. a Radial arterial pressure recorded in an anesthetized/ventilated patient with severe atherosclerosis. Note the following: 1. Increased systolic pressure; 2. lower diastolic pressure; 3. wide pulse pressure; 4. sharp decline in pressure towards the dicrotic notch and 5: additional reflected pressure wave following the systolic peak. All of the above are typical features caused by a low compliant aorta due to atherosclerosis. **b** Radial arterial pressure recording in a patient with significant small vessel disease due to systemic lupus erythematosus (SLE). Note multiple pressure wave reflections (arrows) during the systolic and diastolic periods

The dicrotic notch is a notch or nadir pressure reflecting the fall in aortic pressure during ventricular relaxation until the closure of the aortic valve. The less compliant the aorta is, as in patients with severe atherosclerosis, the greater the pressure drop at the dicrotic notch and *vice versa*. The timing of the nadir pressure in relation to the peak aortic pressure is a function of the stroke volume, central aortic compliance and peripheral vascular resistance [5]. The secondary pressure peak that follows the dicrotic notch represents the 'ringing' of the system following no flow closure of the aortic valve and, as such, the timing of the dicrotic notch and the secondary pressure wave are dependent on the time taken for the aortic pressure to exceed that of the falling ventricular pressure during relaxation [5].

Case Study 2: Hypovolemia

Figure 2 illustrates the typical arterial pressure waveform in an anesthetized/mechanically ventilated experimental animal with severe hypovolemia and shows

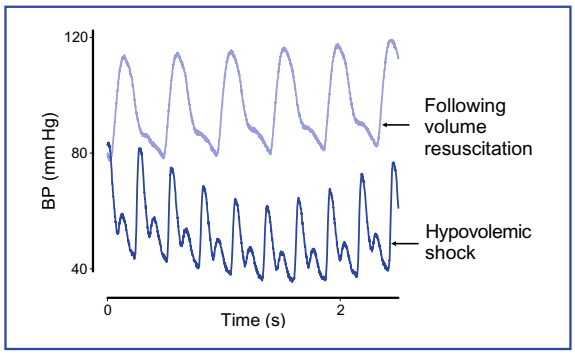

Fig. 2. The effect of severe hypovolemia and volume resuscitation in an anesthetized, mecahnically ventilated pig. Note the marked oscillation in the baseline which follows the ventilator cycles. In addition there is considerable beat-to-beat variation in pulse pressure and the area under the pressure curve, reflecting beat-to-beat variations in stroke volume.

the effect of fluid resuscitation. The changes in the arterial pressure waveform can be attributed to an exaggerated 'Valsalva' effect associated with positive pressure ventilation in the presence of hypovolemia. The oscillation in the baseline pressure and beat-to-beat changes in pulse pressure and 'area under the curve' are some of the first changes that one observes in subjects with even milder degrees of hypovolemia.

Case Study 3: Pulse Pressure as a Measure of Stroke Volume

The pressure rise during ventricular ejection is predominantly a function of:

1. The amount of blood ejected with each beat (stroke volume)
2. Central aortic stiffness or 'compliance'
3. Peripheral run-off of the ejected blood or peripheral vascular resistance.

During relatively short time periods, vascular compliance and peripheral vascular resistance can be assumed to be constant and under these conditions stroke volume is the main determinant of pulse pressure [2]. **Figure 3a** shows the arterial pressure traces recorded from a patient during volume resuscitation using a rapid infusion of a plasma substitute (Voluven). The increase in stroke volume associated with plasma volume expansion is reflected as a corresponding increase in pulse pressure. The progressive changes in pulse pressure during such a fluid challenge can even be plotted against time as shown in **Figure 3b** to produce a bed-side adaptation of the familiar Frank-Starling curve – which can be extremely informative in assessing volume responsiveness in high risk patients. Most currently available bedside monitors may be easily adopted for this purpose. Due to the direct relationship between stroke volume and pulse pressure [2], hypovolemia is characterized by a reduction in pulse pressure which is usually associated with a reduced systolic pressure (reduction in stroke volume) and raised diastolic pressure (vasoconstriction).

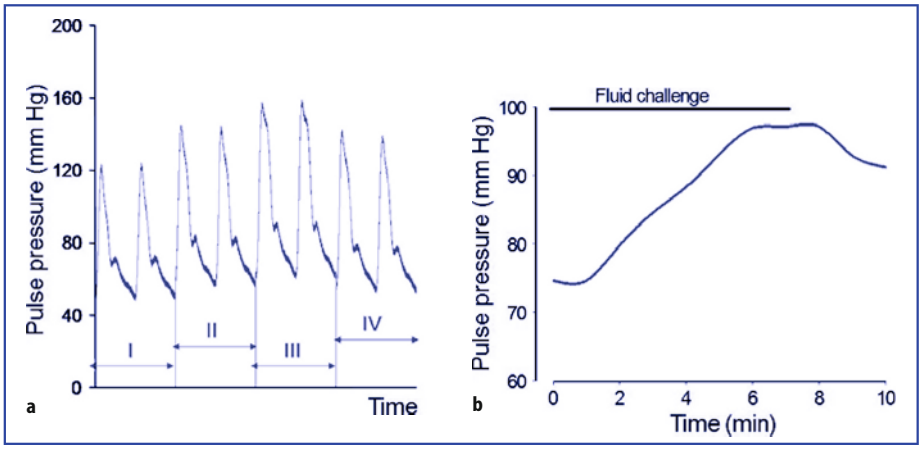

Fig. 3. a Radial arterial pressure waves in patient during a 250 ml fluid challenge over a 10 minute period. Two representational pressure transients during four stages of the fluid challenge are shown. **b** The pulse pressure-time relationship plotted off-line to derive a bedside surrogate of a Frank-Starling curve.

Case Study 4: Effect of Aortic Capacitance on Pulse Pressure

An acute change in central aortic compliance can, however, distort the direct relationship between stroke volume and pulse pressure alluded to in the previous section. This is best illustrated by studying the immediate changes in the shape of the arterial pressure trace brought about during cross clamping of the abdominal aorta (**Fig. 4**) – a necessary step during surgical repair of an abdominal aortic aneurysm. In this patient, following aortic cross clamping, blood is ejected into a less compliant compartment. This typically results in a greater increase in systolic pressure. The additional static energy transferred to the proximal aortic wall during ventricular ejection enables a greater forward flow of blood during ventricular relaxation and, therefore, a lower diastolic pressure and wider pulse pressure even in the presence of a reduced stroke volume. Blood pressure profiles seen in elderly patients with 'systolic hypertension' – a well-recognized phenomenon – can be understood through the above mechanisms. Such patients, with a stiff arterial tree, usually demonstrate a higher systolic, lower diastolic and a wide pulse pressure (**Fig. 1**). Even in these subjects, however, although absolute values may be misleading, short term changes in pulse pressure can be safely extrapolated to track changes in stroke volume.

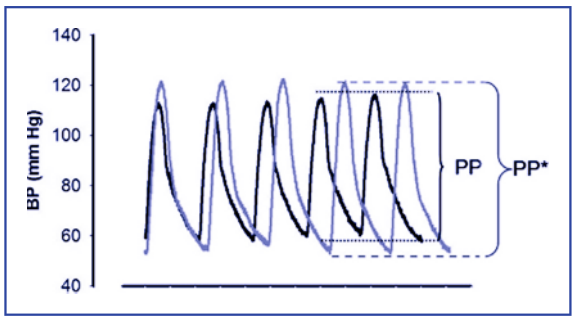

Fig. 4. Radial arterial pressure recordings in an anesthetized patient undergoing surgical repair of the abdominal aortic aneurysm. Five pressure transients showing the pulse pressure before (PP- black) and after (PP*- blue) aortic cross clamping are shown. The increase in pulse pressure in this example is due to an acute reduction in aortic capacitance rather than to an increase in stroke volume.

Case Study 5: Effect of Vasoconstrictor Drugs on Pulse Pressure

The previous case study showed the typical pressure changes when aortic compliance is reduced in the presence of normal peripheral vascular resistance. In clinical practice, however, reduced vascular compliance is frequently associated with increased peripheral vascular resistance due to systemic vasoconstriction down to the level of resistance vessels. These changes are typically seen in patients with generalized vasoconstriction due to pain, anxiety and other flight/fight/fright conditions associated with excess catecholamine production. Profound vasoconstriction is usually associated with increased systolic pressure (due to reduced compliance and reduced peripheral run-off) and raised diastolic (due to vasoconstriction) pressures as shown in **Figure 5**. In this example, blood pressure changes associated with a bolus intravenous injection of 0.5 mg metaraminol (a pure α-agonist agent with profound vasoconstrictor properties) is shown.

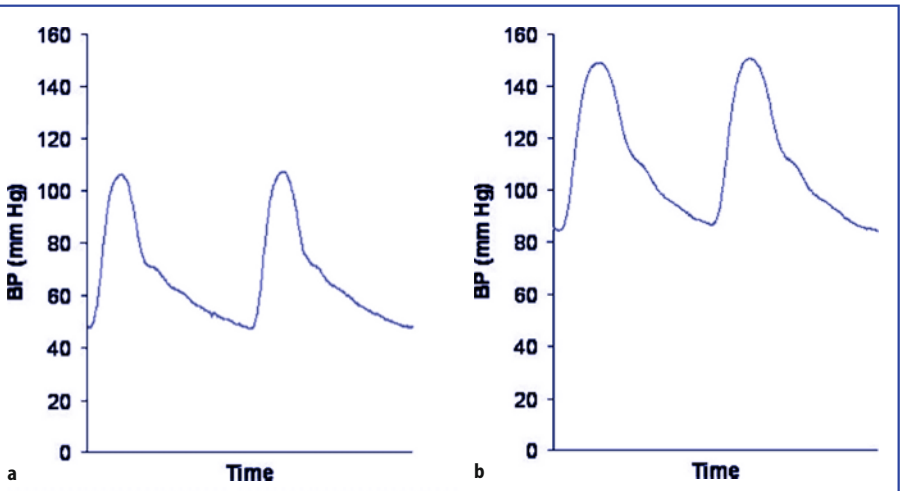

Fig. 5. a Baseline blood pressure in an anesthetized patient undergoing carotid endarterectomy; **b** Changes in blood pressure waveform morphology following generalized vasoconstriction due to an intravenous injection of 0.5 mg metaraminol – which is a potent α-agonist agent frequently used to increase mean arterial pressure through vasoconstriction. Note the increase in systolic and diastolic pressures (unlike in **Figure 4**). **c** Decrease in systolic and diastolic pressure and widening of pulse pressure as the effect of metaraminol wears off.

Case Study 6: Effect of Vasoconstriction on the Dicrotic Notch and Secondary Pressure Waves

The position of the dicrotic notch and the height of the secondary pressure wave are valuable bedside tools in the assessment of peripheral vascular tone. In the presence of peripheral vasodilatation, the time required for aortic pressure to exceed ventricular pressure is lengthened, causing delayed closure of the aortic valve and therefore a delayed dicrotic notch. This phenomenon is frequently seen in patients with severe sepsis. The extensive vasodilatation induced by severe sepsis typically manifests as low systolic, low diastolic, normal (or wide) PP, a delayed dicrotic notch and a flat secondary pressure peak as shown in **Figure 6a**. Sudden vasoconstriction due to high dose norepinephrine in this patient restored the position of the dicrotic notch and the height of the secondary pressure wave (**Fig. 6b**), but as the vasoconstriction wears off, the dicrotic notch returns to its delayed position (**Fig. 6c**). In spite

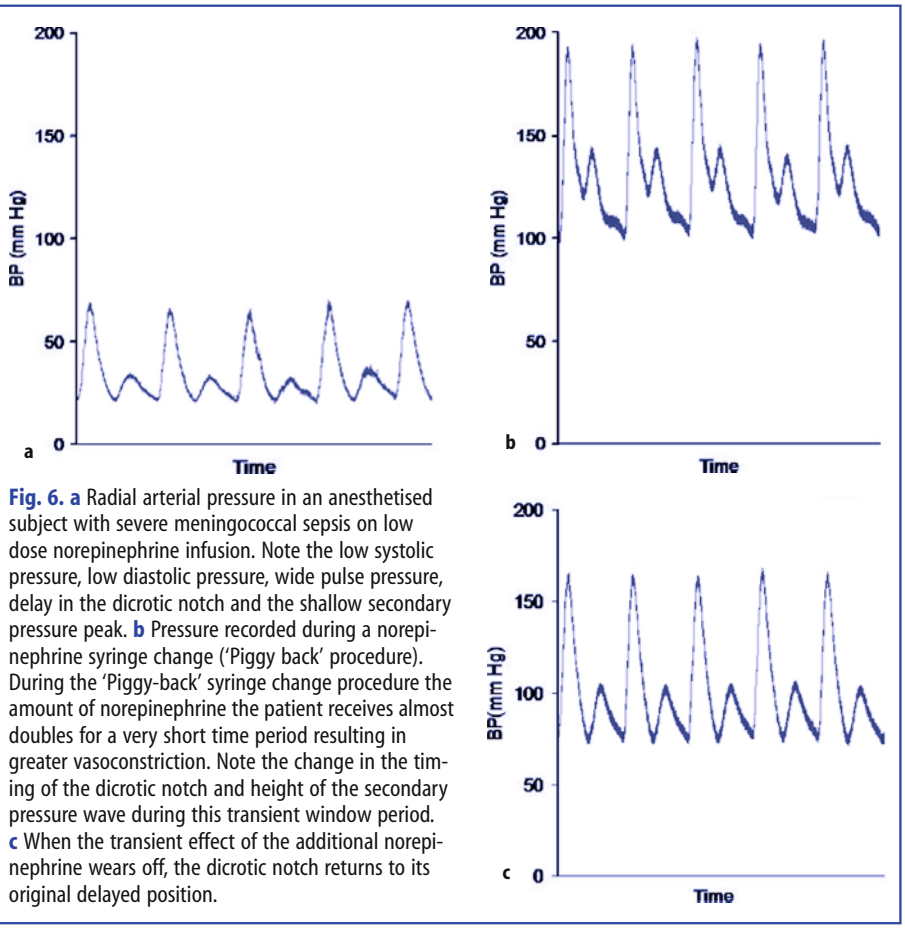

Fig. 6. a Radial arterial pressure in an anesthetised subject with severe meningococcal sepsis on low dose norepinephrine infusion. Note the low systolic pressure, low diastolic pressure, wide pulse pressure, delay in the dicrotic notch and the shallow secondary pressure peak. **b** Pressure recorded during a norepinephrine syringe change ('Piggy back' procedure). During the 'Piggy-back' syringe change procedure the amount of norepinephrine the patient receives almost doubles for a very short time period resulting in greater vasoconstriction. Note the change in the timing of the dicrotic notch and height of the secondary pressure wave during this transient window period. **c** When the transient effect of the additional norepinephrine wears off, the dicrotic notch returns to its original delayed position.

of the complex determinants of the timing of the dicrotic notch and the size of the secondary pressure wave, in clinical practice, a delayed dicrotic notch associated with a relatively flat secondary pressure peak is most often confirmatory of reduced central arterial tone down to the level of the small resistance arterioles and is an extremely useful discriminator of septic shock.

Case Study 7: Sympathetic Stimulation and Reflected Pressure Waves

As mentioned in the previous case study, the position of the dicrotic notch and the timing of the secondary reflected pressure wave in relation to the systolic peak are determined by peripheral vascular resistance. Increased peripheral vasoconstriction associated with increased sympathetic activity will cause these events to occur early due to wave reflections from the constricted proximal vascular beds. This well-recognized phenomenon has previously been demonstrated in a laboratory model of hypovolemic shock [1]. Similar observations can also be seen in critically ill patients as illustrated in **Figure 7**, which shows the arterial waveform changes in a subject with

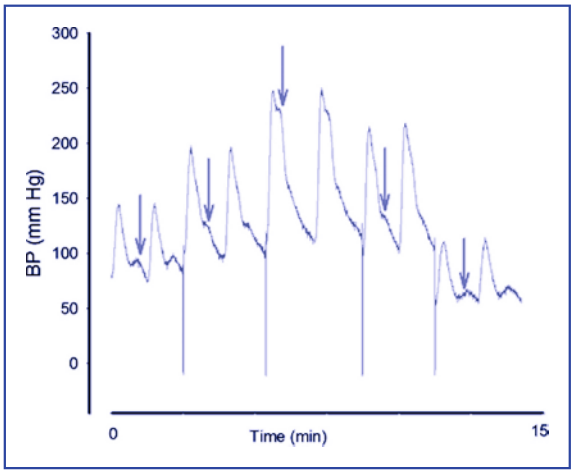

Fig. 7. Changes in arterial pressure trace during an episode of sympathetic stimulation associated with the acute opiate withdrawal syndrome. Two sample pressure transients from five stages over a 15 minute period are shown. Note the gradual increase in systolic and diastolic pressure to a maximum which was associated with wakening of the patient followed by gradual decline in pressure with the patient falling asleep spontaneously. No other intervention was performed during this period. Note the widening of pulse pressure and the change in position of the secondary reflected pressure wave (arrow) during each of the stages.

marked sympathetic stimulation associated with acute opiate withdrawal in the intensive care unit (ICU). The patient concerned was sedated in the ICU with large doses of opiates and benzodiazepines over a prolonged period. On withdrawal of sedation the patient developed recurrent episodes of acute opiate withdrawal syndrome ('cold turkey' syndrome) associated with waking episodes. Each episode lasted for approximately 15 – 20 minutes and settled spontaneously as the patient settled back into sleep. These episodes were characterized by severe hypertension, tachycardia, tachypnea, sweating and papillary dilatation-features of sympathetic overactivity. The arterial pressure waveforms recorded during one of these episodes clearly illustrate the effects of progressive increase in sympathetic activity (and the resultant generalized vasoconstriction) on the timing and position of the secondary reflected pressure wave.

Conclusion

The ability to distinguish between the different causes of hemodynamic failure is important in the management of shock. Arterial pressure waveform analysis is a simple, minimally invasive tool which is invaluable in these situations. In spite of the relatively complex mechanisms involved in regulating the shape, timing and the relative sizes of the individual components, most hemodynamic abnormalities can be distinguished through simple pattern recognition as illustrated in the above examples. A detailed study of the arterial pressure waveforms and the underlying physiological principles is highly desirable for all hospital doctors involved in the care of acutely ill patients.

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Choosing Patient-tailored Hemodynamic Monitoring

II

C. Slagt, R.-M.B.G.E. Breukers, and A.B.J. Groeneveld

Introduction

Currently, the number and (worldwide) availability of techniques for hemodynamic monitoring in the critically ill patient is overwhelming, as nicely summarized elsewhere [1–11]. Techniques vary from completely invasive to non-invasive, from intermittent to continuous, and differ in basic principles, methods, parameters, and costs, among others. The older a device, the more literature is available, but the latter may not always help in choosing hemodynamic monitoring tools for departments or for individual patients, i.e. patient-tailored monitoring.

This chapter is not intended to compare one technique to another, which has been done abundantly in the literature, but to provide a conceptual framework to guide therapy of individual patients in various hospital settings by defining the elements that may help to choose among the available techniques, in the absence of a clear evidence-based survival benefit of any hemodynamic monitoring tool [12–16]. First, a brief discussion of what is available and of underlying basic principles seems warranted, since knowledge of possibilities, limitations and pitfalls is required before responsible choices can be made. We will not address tools to monitor the microcirculation.

What Do We Have and What Can they Do?

A physical examination remains the cornerstone of assessing patients with hemodynamic compromise, even though signs and symptoms often poorly predict measured hemodynamic variables [13, 17]. Nevertheless, clinical signs and symptoms help to clearly define the clinical problem and its differential diagnosis. As an adjunct, some type of hemodynamic monitoring is often decided upon, depending on the clinical severity of disease and the (department of) presentation of the patient, among other factors. **Table 1** briefly summarizes the currently available equipment for advanced hemodynamic monitoring, beyond that of mean arterial pressure (MAP) and heart rate/rhythm. As indicated, a wide variety of hemodynamic parameters can be monitored by the different techniques, in addition to cardiac output. The parameters pertain to cardiac filling and function and its adequacy related to tissue needs. In addition, pulmonary variables pertaining to edema and gas exchange can be assessed with some devices.

There is a large amount of literature concerning the comparability of techniques and derived parameters, such as (absolute values and changes in) cardiac output and preload indicators [4–7, 18, 19]. However, the manner in which the comparability

Table 1. What do we have and what can they do?

Equipment
Central venous catheter (many companies)
Pulmonary artery catheter and modifications (some companies)
PiCCO^{II} (Pulsion)
LiDCO^{plus} (LiDCO)
NICO (Novametrix)
Modelflow pulse contour analysis (BMI-TNO)
Nexfin (Bmeye)
Flotrac/Vigileo (Edwards Life Sciences)
Pulse-dye densitometry PDD (Nihon Kohden)
Bioimpedance cardiography (Aesculon, Osypka Medical)
Hemosonic (Arrow)
CardioQ (Deltex Medical)
Ultrasonic cardiac output monitors (Uscom)
Echocardiographs (some companies)
Parameters
Cardiac pressures and volumes
Cardiac output, flow, velocity/time
Dynamic indices
Cardiac anatomy and regional function
Oxygen-related variables
Carbon dioxide-related variables
Vascular diameters

Manufacturers in parentheses.

(or clinically important absence thereof) is judged varies greatly among studies. Uniformly accepted criteria to assess the clinical relevance of comparability of monitoring techniques and parameters are lacking. For instance, comparability of techniques for tracking changes and trends in cardiac output may be more relevant in clinical practice than the degree of agreement of absolute values, provided that 'low' and 'high' values can be separated [19]. Moreover, literature on the practical utility of many of these devices and parameters is scarce, so that negativism regarding their practical value may predominate [16, 20]. There is, however, some literature to suggest that insertion of a pulmonary artery catheter (PAC) and measuring hemodynamic variables may influence the clinical appraisal of hemodynamics at the bedside and may help or prompt the treating physician to change treatment.

Since its introduction in the 1970s, the PAC has indeed become the reference standard for hemodynamic monitoring and measurement of cardiac output [13–15]. A substantial knowledge database has been built up since then, in a variety of institutions, patient populations, and circumstances [16]. However, in the absence of any rigidly proven survival benefit, the catheter has become discredited in critical care medicine [12–16]. The lack of apparent benefit may relate, in part, to adverse effects of insertion, improper use, poor interpretation of hemodynamic data, and inadequate treatment decisions based on the collected variables, or combinations of these factors [20]. Conversely, the value of pulmonary artery pressures, pulmonary artery occlusion pressure (PAOP), mixed venous oxygen saturation (SvO_2), and right heart volumes, some of the variables that can be uniquely assessed at the bedside of the critically ill patient with help of the PAC and right-sided thermodilution, remains hotly debated [13–15, 20]. The patient population or circumstance that is

most likely to benefit from pulmonary artery catheterization is, therefore, still being actively looked for [13–15, 21, 22].

A second generation hemodynamic monitoring principle includes the less invasive transpulmonary (dye-)thermodilution technique, e.g. PiCCO. This technique offers the unique possibility of estimating cardiac preload volumes, measurements of which are not confounded by mechanical ventilation in contrast to pressure and dynamic indices of preload and fluid responsiveness, and of extravascular lung water as a direct measure of pulmonary edema and permeability. Dilutional methods to measure cardiac output include the transpulmonary lithium and indocyanine green (pulse dye) techniques, allowing peripheral injections and peripheral and, for pulse dye, non-invasive detection.

Pulse-contour or pulse-power methods, needing relatively frequent recalibration for optimal performance in tracking changes in cardiac output, are often incorporated in dilutional cardiac output measurement devices needing arterial access [5, 18]. Some of these methods are truly non-invasive, however. The algorithms used differ from one method to the other, some perform better than others, and the need for recalibration upon changes in time or in vascular tone upon treatment continue to limit their independent applicability [5, 18]. Calibration can also be performed by ultrasonically obtained aortic diameter for the otherwise well performing Modelflow method [23]. The algorithm used in the latter method computes the aortic flow waveform from pulsating arterial blood pressure by simulating a non-linear, self-adaptive (three-element Windkessel) model of the aortic input impedance. Characteristic impedance and compliance of the aorta non-linearly depend on arterial pressure, and peripheral resistance adapts to changes in blood flow. The degree of non-linearity depends on the subject's sex, age, height, and weight.

An arterial waveform analysis without external calibration, the FloTrac/Vigileo system, is supposed to be relatively independent of vascular tone [9]. Each arterial waveform detected via an arterial catheter is analyzed with a frequency of 100 Hz. The arterial waveform is analyzed for 8 different characteristics, including the upstroke and downslope of the curve. Each curve is analyzed separately and additional curves are analyzed and compared with former and subsequent curves. From this analysis, which takes 20 seconds, the average curve is given, by means of the standard deviation of the given characteristics of the curves. From the given stroke volume and heart rate, the cardiac output is determined, which is updated every 20 seconds. A filter is embedded in the computer to adjust for excesses in systolic blood pressures and heart rates. The accuracy of this method has increased with consecutive software versions.

Doppler ultrasound methods estimate cardiac output by measuring aortic blood flow velocity [10, 11, 24, 25] and multiplying it by the cross-sectional area of the aorta at the insonation point. The probe is introduced orally or nasally and placed at the level of the descending aorta. Some systems measure the descending aortic diameter; others use a monogram to estimate it. Limitations of the technique include operator-dependency in finding the optimal angle of insonation, turbulent flow, and changes in relative perfusion of upper and lower body parts via the aorta. Obviously, echocardiography yields clinically useful information on cardiac anatomy and (regional) function that is hard to obtain otherwise, in addition to non-unique parameters, such as cardiac filling and output [26, 27]. The technique is highly dependent on available expertise and commitment.

Factors Affecting Choices

Tables 2–4 describe the issues that may be relevant for decision making, including theoretical considerations, the hardware involved, and patient-bound factors. Indeed, demands put on technologies may vary according to need in different hospital environments and patient populations. We will highlight just some of the considerations mentioned in the Tables. **Table 2** essentially notes theoretical considerations, suggesting that the ideal hemodynamic monitoring tool should be simple, safe, relatively versatile, uniformly applicable and beneficial for survival in each patient subjected to that tool, at low or at least affordable costs. Obviously, no method yet fits this 'ideal' list, and perhaps never will, so some compromise on these issues remains necessary.

Some hemodynamic optimization strategies, such as fluid management guided by prediction of fluid responses, early goal-directed therapy, and perioperative hemodynamic optimization or fluid restriction, may help to improve patient outcomes, in terms of reducing complications, lengths of stay, and prevention of overhydration, for example, even irrespective of vital status [1, 16, 25, 28–33]. Devices and parameters to assess fluid responsiveness include transpulmonary dilution-derived cardiac volumes, esophageal Doppler flow and echocardiographic indices, and dynamic indices provided by pulse-contour methods [10, 11, 24, 25, 33, 34). In contrast, central venous pressure (CVP) monitoring may suffice in successful fluid restriction policies [32]. The well-known outcome (survival) benefit of early goal-directed therapy in septic shock, with treatment guided by CVP, central venous oxygen saturation ($ScvO_2$) and MAP, has been confirmed by others, since the landmark paper by Rivers et al. [35] and this approach is included in current guidelines on the management of septic shock [1, 31], even though CVP may poorly predict fluid responses [36]. Hence, monitoring tools could be judged on their ability to provide parameters that help physicians to implement the strategies mentioned, even if these are slightly different from those originally used in demonstrating benefit but apply similar physiologic and clinical concepts [1, 15, 30, 37–39]. For example, the benefit of perioperative hemodynamic optimization with help of the PAC [28], transpulmonary/lithium dilution [29, 30], esophageal Doppler [10, 11, 24, 25], or dynamic indices [38] could translate into a benefit of optimization of central/mixed venous oxygen saturation since all are intended to optimize tissue oxygenation [37]. Nevertheless, not all devices and parameters have been successfully evaluated yet in hemodynamic optimization strategies and these issues continue to be subject to ongoing research and debate [1, 15, 37, 39, 40]. Thus, we may need to formulate and test hemodynamic monitoring strategies, rather than to evaluate performance and efficacy of single devices and parameters. The rationale of these strategies may be enforced if led by physiological and clinical considerations as well as by epidemiological and economic

Table 2. Theoretical considerations for choosing among hemodynamic monitoring tools

- Safety and side effects
- Versatility, number, relevance and utility of parameters
- Can be utilized by nurses and physicians: Ease of use, user-friendliness, education, learning curve
- Possibilities for assessing fluid responsiveness, goal-directed therapy and other resuscitation strategies of proven outcome benefit even if not decreasing mortality
- Demonstrated treatment alterations
- Acceptable cost-effectiveness

Table 3. Hardware considerations for choosing among hemodynamic monitoring tools

- Availability
- Expertise: Personal, colleagues, and in the literature
- Ease of use and interpretation; operator-dependency
- Level of integration in monitors
- Uniformity of applicability
- Continuous vs intermittent
- Invasive vs non-invasive
- Accuracy/reproducibility of parameters
- Response time to interventions and accurate trending

Table 4. Patient-bound considerations for tailoring hemodynamic monitoring

- Cardiac rhythm, function, and valvular disease
- Mechanical ventilation: Tidal volume, frequency, positive end-expiratory pressure
- Type, severity and stage of (anticipated) disease warranting hemodynamic monitoring, such as shock and acute lung injury
- Type of circulatory support and change contemplated therein: Fluids, drugs, devices for circulatory support
- Vascular access and other anatomic factors (contraindications)
- Tolerance

issues. Finally, effectiveness could be defined in terms of the clinical utility of devices and parameters that may go beyond their formally reported efficacy.

Hardware considerations (**Table 3**) include the environment where the hemodynamic monitoring is used. Different departments may have different facilities, patient populations and staffing, and pressures on time by emergencies may drive choices for less invasive techniques that can be applied immediately by most of the available staff. Non-invasive hemodynamic monitoring devices may also be of help in departments without facilities for invasive techniques, such as step-down units, long-term facilities, and stroke units. By virtue of definition, any device that is able to accurately detect rapid changes in cardiac output upon fluid challenge would suffice in evaluating fluid responsiveness and some methods may be too slow to fulfill this criterion.

General considerations regarding patient-bound factors (**Table 4**) include the notion that the sicker the patient the greater the need for accurate hemodynamic parameters to be collected to supplement clinical judgment and the greater likelihood that invasive, rather than less invasive, techniques will meet these needs. In the patient with severe septic shock admitted to the intensive care unit (ICU) for instance, non-invasive arterial waveform analysis-derived cardiac output measurements are less useful as they are affected by vascular tone and require repeated recalibration, at least in the initial resuscitation phase. In patients with or at great risk of pulmonary edema, hemodynamic monitoring by transpulmonary dilution and measurements of extravascular lung water could be chosen to help to prevent harmful overhydration and prolonged mechanical ventilation, unless the patient will anyway need to be intubated and mechanically ventilated. Catheters in the femoral artery are relatively contraindicated during/after aortic-bifemoral reconstruction, and transesophagal echocardiography is not feasible during/after esophageal resection. Esophageal disease may be a contraindication for the use of esophageal Doppler probes, which are also poorly tolerated in awake, non-intubated patients [10, 20,

25]. The presence of cardiac disease and mechanical ventilation may also affect choices. It is likely that a PAC and measurement of PAOP is more helpful in guiding (fluid) management in the presence of systolic/diastolic cardiac dysfunction than during hypovolemic shock, for example [21, 34]. In severe left-sided valvular disease, right-sided measurements of cardiac output are probably preferable to transpulmonary ones, even though the debate on the confounding effect of even minimal tricuspid regurgitation on these measurements has not yet ended. In the presence of endocarditis, intracardiac catheters may be relatively contraindicated. In contrast, a suspected ventricular septal defect may require monitoring with help of a PAC, echocardiography, or both. In mechanically ventilated patients, filling pressures that are confounded by airway pressures may be less useful in predicting and guiding fluid responses than volumetric preload measurements [34, 36], whereas the currently proposed superiority of dynamic indices [33] can be questioned, as they are affected by ventilatory frequency and tidal volume. Finally, pulse-contour methods are sensitive to arrhythmias, aortic valve regurgitation, intra-aortic balloon pumping and peripheral vascular disease.

Conclusions and Perspective

This chapter attempts to provide a conceptual framework for choosing patient-tailored hemodynamic monitoring from available techniques, in an era dominated by lack of proven survival benefits for any hemodynamic monitoring device. Decisions for implementing different hemodynamic monitoring devices may improve when systematically considering the relevant issues, according to a predefined checklist, for example. This approach may help to end debates on the use of hemodynamic monitoring equipment from single perspectives only, but obviously choices may differ from one hospital, unit, patient and physician to another, given the variability in facilities, clinical presentations, and expertise. One tool may supplement another, so that it is advisable to gain expertise in more than one method, particularly in training environments. Health technology assessment institutions and agencies can be of help in advising on these complex issues and emergency and intensive care medicine organizations could benefit from their expertise [1, 12, 13, 25, 41]. The underlying idea, of course, is that helping physicians to direct therapy using numbers rather than signs and symptoms, and helping the medical community by providing clear clinical guidelines on hemodynamic monitoring strategies will effectively result in health care improvements. Perhaps, we also need a new research agenda on these issues.

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III Resuscitation Issues

Airway and Ventilation during CPR

J.P. Nolan and J. Soar

III

Introduction

The primary components of standard cardiopulmonary resuscitation (CPR) are chest compressions to circulate blood, defibrillation to convert a 'shockable' rhythm into one that will produce a spontaneous circulation, and ventilation of the lungs to enable oxygenation of the blood and removal of carbon dioxide (CO_2). Effective ventilation of the lungs requires a patent airway, while protection of the lungs from aspiration of gastric contents requires reliable separation of the gastrointestinal tract from the airway. Traditionally, the single airway device deemed capable of maintaining airway patency and protecting from aspiration is the tracheal tube. However, the unique status of tracheal intubation is now being challenged. Tracheal intubation is associated with several complications and it is possible that it would be better for healthcare professionals who are not highly skilled in this intervention to use alternative airway devices. After primary cardiac arrest, based mainly on animal data, but also on some low-level human data, ventilation may not be necessary for several minutes. Recent observational clinical studies suggest that chest compression-only CPR by bystanders results in the same or better outcomes than bystander CPR that includes both mouth-to-mouth breathing and chest compressions. There are data indicating that excessive ventilation is harmful during CPR and, possibly, after return of spontaneous circulation. This chapter will focus on the evidence supporting new strategies for management of the airway and ventilation during CPR.

Regurgitation and Aspiration after Cardiac Arrest

At the onset of cardiac arrest, the esophageal sphincter pressure decreases rapidly from the normal value of approximately 20 cmH_2O to less than 5 cmH_2O [1], increasing significantly the risk of regurgitation of gastric contents and subsequent aspiration. Regurgitation occurs in about one third of out-of-hospital cardiac arrests, but in at least two thirds of these cases it occurs before arrival of emergency medical services (EMS) personnel [2, 3]. In a study of 182 patients resuscitated after out-of-hospital cardiac arrest, the incidence of regurgitation was 20 % [4]. Just under half of these patients had radiological evidence of aspiration; however, 19 % of the patients without signs of regurgitation at the scene also had radiological evidence of aspiration. The precise impact of regurgitation and aspiration on long-term survival is uncertain, but in a multivariate logistic analysis regurgitation was associated with a reduced odds ratio (OR) of survival (OR = 0.5 [0.28 – 0.89]) [3].

The Pros and Cons of Tracheal Intubation

It is widely assumed that tracheal intubation improves outcome from cardiac arrest, but this is unproven. There are several reasons why attempted prehospital intubation can be harmful, particularly when undertaken by inexperienced individuals [5]. A recent systematic review of randomized controlled trials (RCTs) comparing tracheal intubation versus alternative airway management in acutely ill and injured patients identified just three trials [6]: Two were RCTs of the Combitube versus tracheal intubation for out-of-hospital cardiac arrest [7, 8], which showed no difference in survival. The third study was a RCT of prehospital tracheal intubation versus management of the airway with a bag-mask in children requiring airway management for cardiac arrest, primary respiratory disorders, and severe injuries [9]. There was no overall benefit of tracheal intubation; on the contrary, of the children requiring airway management for a respiratory problem, those randomized to intubation had a lower survival rate that those in the bag-mask group. The Ontario Prehospital Advanced Life Support (OPALS) study documented no increase in survival to hospital discharge when the skills of tracheal intubation and injection of cardiac drugs were added to an optimized basic life support-automated external defibrillator (BLS-AED) system [10].

Advantages of Tracheal Intubation

The potential benefits of placing a cuffed tube in the trachea during CPR include: Enabling ventilation without interrupting chest compressions [11]; enabling effective ventilation, particularly when lung and/or chest compliance is poor; minimizing gastric inflation and, therefore, the risk of regurgitation; and protection against pulmonary aspiration of gastric contents.

Disadvantages of Tracheal Intubation

A study of first year anesthesiology residents indicated that the learning curve for tracheal intubation in anesthetized patients required about 60 attempts to achieve a 90 % success rate [12]. Once competence is achieved, maintaining the skill requires ongoing practice. Seventy-five percent of paramedics in the UK undertake just one or no intubations each year [13]. Several studies indicate that in inexperienced hands the success rate is as low as 50 % and complication rates are unacceptably high [5]. The risks of attempting tracheal intubation include: Unrecognized esophageal intubation – 2.9 – 16.7 % in several cardiac arrest studies [5]; unrecognized main stem bronchial intubation; unrecognized dislodgement; and interruption of chest compressions during the procedure. The interruptions in CPR in order to achieve tracheal intubation may negate any theoretical benefits of securing the airway. The interruptions in CPR have been quantified recently in a study of prehospital intubation by paramedics [14]. Using defibrillators that recorded chest compressions, ventilations and end-tidal CO_2, as well as the electrocardiogram (EKG), data on 100 out-of-hospital resuscitation attempts were analyzed to determine the interruptions associated with tracheal intubation attempts. The total duration of the interruptions in CPR associated with tracheal intubation attempts was 110 s (IQR 54 – 198 s; range 13 – 446 s) and in 25 % the interruptions lasted more than 3 min. Tracheal intubation attempts accounted for almost 25 % of all CPR interruptions.

The high complication rates associated with prehospital intubation are not confined to paramedics: In a German study of 149 consecutive out-of-hospital tracheal intubations attempted by emergency physicians, intubation of the right main bronchus occurred in 16 cases (10.7 %) and unrecognized esophageal intubation in 10 (6.7 %) [15].

Reducing the Risk of Unrecognized Esophageal Intubation

Unrecognized esophageal intubation could be eliminated either by using a method of confirming tube position that is completely reliable during cardiac arrest, or by using alternative airway techniques such as one of the supraglottic airway devices [16].

The use of exhaled CO_2 detectors reduces the incidence of unrecognized esophageal intubation [17]; however, these are unreliable in low flow states such as cardiac arrest [18]. Although the esophageal detector device is highly sensitive for the detection of misplaced tracheal tubes in the esophagus, it has poor sensitivity for confirming tracheal placement of a tracheal tube, resulting in the removal of up to 30 % of correctly placed tubes. Other pitfalls include the detection of CO_2 from an esophageal tube in cardiac arrest victims who have received mouth-to-mouth ventilation [19].

Supraglottic Airway Devices

Several supraglottic airway devices have been evaluated for use during CPR [16]; the classic laryngeal mask airway (LMA) and the Combitube are the most extensively studied, but there are also reports on the use of the laryngeal tube. Supraglottic airway devices are easier to insert than a tracheal tube and, unlike tracheal intubation, they can generally be inserted without interrupting chest compressions [20]. None of the studies on the use of supraglottic airway devices during CPR have been powered adequately to study survival as a primary endpoint; instead, most researchers have studied insertion and ventilation success rates. Reported rates of successful ventilation during CPR with the classic LMA are very high for in-hospital studies (over 90 %) but generally less impressive (70 %) for out-of-hospital cardiac arrest [5]. The reason for the relatively disappointing results from the LMA in out-of-hospital cardiac arrest is not clear. Anecdotally, some prehospital providers report that the LMA is more prone than a tracheal tube to dislodgement but this observation is not supported by data. A Japanese study showed similar arterial blood gases in patients successfully resuscitated after out-of-hospital cardiac arrest when either an LMA or bag mask was used [21]. In this study, survival to hospital discharge, which was a secondary end point, was higher in the LMA group than in the bag-mask group (13.4 % versus 6.1 %; $p = 0.03$); however, this was a non-randomized study and included several confounders. Successful ventilation rates for the Combitube are in the range 70 – 90 % and all these studies have been in the out-of-hospital setting.

The laryngeal tube was introduced in 2001; it is known as the King LT airway in the United States. After just two hours of training, nurses successfully inserted a laryngeal tube and achieved ventilation in 24 of 30 (80 %) out-of-hospital cardiac arrests [22]. A disposable version of the laryngeal tube (LT-D) is available and was inserted successfully by paramedics in 92 out-of-hospital cardiac arrests (85 on the first attempt and 7 on the second attempt) [23].

The characteristics of the I-gel and the Supreme LMA (SLMA) suggest that both these devices may be useful for airway management during CPR. The cuff of the I-gel is made of thermoplastic elastomer gel (styrene ethylene butadene styrene) and does not require inflation; the stem of the I-gel incorporates a bite block and a narrow esophageal drain tube. It is very easy to insert, requiring only minimal training and a laryngeal seal pressure of 20–24 cmH_2O can be achieved [24, 25]. Use of the I-gel during cardiac arrest has been reported but more data on its use in this setting are awaited [26, 27]. The SLMA is a disposable version of the ProSeal LMA. Studies in anesthetized patients indicate that it is relatively easy to insert and laryngeal seal pressures of 24–28 cmH_2O can be achieved [28–30]. Data on the use of the SLMA during cardiac arrest are awaited.

Ventilation during CPR

Excessive ventilation rates are common during CPR [31] and the increase in intrathoracic pressure reduces coronary perfusion pressure [32]. Many animal cardiac arrest studies have shown no survival benefit with the addition of ventilation. A limitation of these studies is that the airways of the animals are generally patent, even when they are supine, which will enable chest compressions alone to generate some ventilation [33, 34]. Although supine, unconscious humans will generally have an obstructed airway (unless the airway is supported) in the early stages of cardiac arrest, gasping will enable significant ventilation and is associated with higher survival rates. A recent study documented gasping in 33 % of patients who had an EMS-witnessed cardiac arrest [35]. If airway patency can be assured, chest compressions might generate ventilation in human cardiac arrest; however, at least one clinical study has shown that chest compressions generate only very low tidal ventilation after prolonged cardiac arrest [36].

Passive Oxygen Insufflation

Investigators from the Sarver Heart Center have introduced the concept of 'minimally interrupted cardiac resuscitation' to their EMS [37]: tracheal intubation is delayed until three cycles of 200 compressions and rhythm analysis have been completed – during this time an oral airway is inserted and oxygen is given by a non-rebreather face mask, enabling passive delivery of oxygen during compressions; if the initial rhythm is ventricular fibrillation, 200 chest compressions are given before the first shock, followed by 200 post-shock chest compressions; finally, intravenous epinephrine is given within 10 minutes of EMS arrival. Ventilation is included in the minimally interrupted cardiac resuscitation strategy but it is de-emphasized in comparison with conventional CPR. Compared with historical controls, this group has reported significantly better survival rates with minimally interrupted cardiac resuscitation [37]. The contribution of passive oxygen insufflation to these outcomes has been analyzed retrospectively and reported separately [38, 39] (**Fig. 1**). After witnessed ventricular fibrillation/ventricular tachycardia out-of-hospital cardiac arrest, adjusted neurologically intact survival was higher for passive ventilation (39/102; 38.2 %) than for bag-mask ventilation (31/120; 25.8 %) (adjusted odds ratio [OR] 2.5; 95 % CI 1.3–4.6); however, there was no difference in survival in those with non-shockable rhythms or with unwitnessed ventricular fibrillation/ventricular tachycardia.

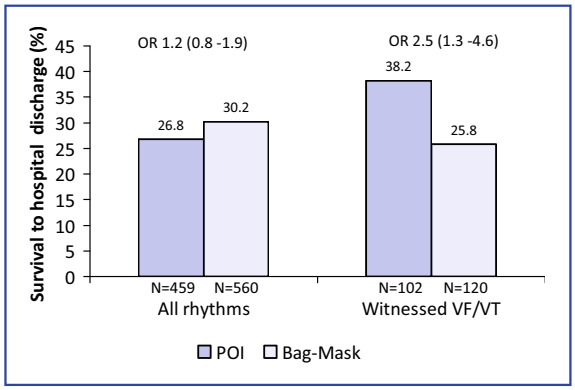

Fig. 1. Neurologically intact survival to hospital discharge after initial airway management with either passive oxygen insufflations (POI) or bag-mask ventilation. VF: ventricular fibrillation; VT: ventricular tachycardia. OR: odds ratio. Data from [38].

Mouth-to-mouth Ventilation

Laypersons and healthcare professionals are reluctant to do mouth-to-mouth ventilation (rescue breathing), partly because of fears of infection, but also because it is unpleasant [40]. Mouth-to-mouth ventilation is associated with a significantly increased risk of regurgitation compared with no CPR or compression-only CPR [2]. By teaching laypeople to perform compression-only CPR, rates of bystander CPR and survival may be increased. In comparison with conventional CPR, compression-only CPR is easier to learn.

In at least six studies in which EMS personnel observed and documented the technique of bystander resuscitation (none, compression-only, or conventional CPR), similar survival rates were achieved when bystanders delivered compression-only CPR instead of conventional CPR [41–46]. In all these studies, any CPR was associated with a higher survival rate compared with no CPR. The American Heart Association has published an Advisory Statement encouraging bystanders to "at a minimum – activate their community emergency medical response system (e.g., call 911) and provide high-quality chest compressions by pushing hard and fast in the center of the chest, minimizing interruptions..." [47]. This statement did not recommend that we abandon completely teaching laypeople how to perform mouth-to-mouth ventilation but it is difficult to reconcile the need for simplicity while at the same time addressing the needs of those who have a cardiac arrest that is not from a cardiac cause. Approximately 65–80 % of out-of-hospital EMS-treated cardiac arrests are of primary cardiac etiology. Those with asphyxial cardiac arrests or where response times are long will need early ventilation if they are to have any chance of surviving [48]. The solution might be to provide citizen CPR training in two stages: All laypeople are taught compression-only CPR initially; the second stage would enable some laypeople to be taught mouth-to-mouth ventilation [49]. This 'hot topic' will be addressed by the participants at the 2010 Consensus Conference on CPR Science [50].

Conclusion

Tracheal intubation during CPR should be attempted only by those highly skilled in the technique; healthcare professionals who are not highly skilled in this interven-

tion would be better to use a supraglottic airway devices or bag-mask. During CPR, excessive ventilation is harmful. Passive oxygen insufflation eliminates the negative hemodynamic effects of positive pressure ventilation but more data are required before this technique can be adopted for routine use. Chest compression-only CPR by bystanders may result in the same or better outcomes than bystander CPR that includes both rescue breathing and chest compressions but this is probably only true for cardiac arrest of cardiac etiology (sudden, witnessed collapse) and where response times are short.

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The Role of Gasping in Resuscitation

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III

Introduction

Gasping is a physiologic 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 [1–13]. Scientists have defined a gasp formally in nomenclature consensus processes as "an abrupt, sudden, transient inspiratory effort" [13] and it has been described in the published literature since 1812 [11]. The classic gasping that occurs after sudden cardiac arrest is also sometimes referred to as "agonal breaths" or "agonal respirations" [1, 3–6, 9]. However, the term agonal breathing may also be used by some when referring to a broader variety of respiratory efforts or conditions [12, 14]. Agonal breathing may, therefore, refer to various kinds of abnormal breathing observed at the time of clinical death, during certain types of stroke, or in progressive respiratory failure when rapid breathing reverts to slower and often shallow breaths [6, 11, 12, 14]. Classic gasps, according to strict definition, however, are usually sudden, abrupt, and much brisker and larger than normal respiratory efforts [13].

Though somewhat related, the typical gasping that frequently occurs after sudden cardiopulmonary arrest should be distinguished from 'death rattles' often described in cancer patients or the toxic gasping seen with certain poisonings [15–17]. Classic gasps (or any other type of agonal breathing) 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 [1, 3, 5, 6, 7, 9, 18]. 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 ventricular fibrillation or ventricular tachycardia [1, 6, 7, 9]. 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 [7]. 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 presenting with ventricular fibrillation. 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 may also simply mean the individual organism with the global ischemic insult, be it human or animal, was better developed to tolerate

anoxia. At the same time, as will be analyzed in the following discussion, gasping itself may also be an active and independent factor in the ability to achieve successful resuscitation [3, 10, 19–23].

In this chapter, the role of gasping in resuscitation will be considered in both sudden cardiac arrest and traumatic hemorrhage circumstances. We will also examine new ways in which gasping may be used in certain clinical settings to detect cardiac arrest and thus begin earlier intervention. Finally, we will examine ways in which gasping might be used to augment resuscitative efforts.

The Frequency of Gasping in Global Ischemic Events

Several studies have indicated that gasping does not occur in every sudden cardiac death patient [1, 7, 9]. Despite a relatively rapid response and a high frequency of basic cardiopulmonary resuscitation (CPR) being performed by bystanders in the community studied, one early investigation found that the rate of "agonal respirations" (as detected by dispatchers) was only 40 % overall and just 55 % in cases in which the bystander witnessed the cardiac arrest [1]. Though the incidence of agonal breaths for unwitnessed arrest was clearly much lower (16 %), the detection of gasping in only about half of the witnessed cases would indicate that it is not a universal event in sudden out-of-hospital cardiac arrest. Likewise, in a more recent similar study, though the presence of gasping was significantly higher in cases of witnessed ventricular fibrillation compared to other presenting EKG findings, the frequency was still only 18.4 % [7].

On the other hand, the methodology used in these studies depended largely on descriptions given to (or sounds heard by) dispatchers over the telephone. It is possible that direct observations of all patients, starting at the actual moment of cardiac arrest, would yield a higher frequency of agonal respirations detected. In a just published investigation designed specifically to identify agonal breathing in a prospective fashion, the investigators did indeed find many more cases of gasping, but they still did not find patients meeting those criteria in all cases of cardiac arrest [9]. Data are lacking regarding the frequency of gasping in moribund trauma patients such as those who are experiencing fatal or near-fatal hemorrhage. It is not well-known if gasping is a typical response or if it occurs more frequently in specific subcategories of patients as seen in non-traumatic cardiac arrest. In certain animal models of untreated fatal hemorrhage, gasping is observed uniformly [10]. However, unlike the sudden onset of ventricular fibrillation with instantaneous cessation of all circulatory function in an otherwise well-oxygenated organism, in the clinical setting of severe injury, gasping might occur somewhere along a continuum of circulatory impairment. Factors may include not only the severity of the circulatory compromise and how rapidly it develops, but also comorbid conditions such as traumatic brain injury that may directly affect the brainstem or be associated with relevant spinal cord injury.

There are other difficulties in analyzing the true frequencies of gasping in either traumatic or non-traumatic circulatory demise. One problem is related to how one defines a gasp or other forms of agonal respiratory effort and another is the observation that gasping may be confounded by the rapid initiation of therapy [6, 7]. For example, in severe traumatic injury, if endotracheal tube placement and manual ventilation is initiated rapidly and done so prior to the onset of full circulatory compromise in a hemorrhaging patient, the person's stimulus to inspire may be sup-

pressed physiologically by the provision of assisted rescue breathing, particularly when overzealous ventilation is applied (as commonly occurs).

The Meaning of Gasping in Global Ischemic Events

The finding of agonal respirations in patients with ventricular fibrillation clearly indicates that they are not, for the most part, the sequelae of a primary respiratory disturbance, a neurovascular event, or any underlying arterial hypoxia, but rather a physiological response stimulated primarily by the sudden loss of circulation. While ventricular fibrillation can indeed occur secondary to an underlying hypoxic event or other insults, it generally is due to a sudden cardiac dysrhythmia in a person who has a normal circulation prior to the event, no prior difficulty breathing or signs of respiratory distress, and rapid recovery to consciousness and often normal breathing when treated immediately [24–26]. The point here is that gasping is a special event triggered by a sudden loss of circulation to the brain [11, 12].

Nevertheless, the fact that the available data still show an association of gasping (or any kind of agonal respirations) in only half of the witnessed cases in one study or less than 20 % of the witnessed cases of ventricular fibrillation in another investigation, indicates that gasping does not routinely occur as a result of a sudden loss of circulation [1, 7]. Furthermore, in cardiac arrest cases that occurred after EMS arrival, one recent investigation showed that only a third of cases had 'gasping' witnessed by EMS crews [7]. Whether the arrests after EMS arrival represented a different physiology or etiology than pre-arrival arrests was not analyzed in the study and, specifically, there was no delineation of the relative percentage of cases of ventricular fibrillation or other physiological factors in the reported results [7]. It is known that the clinical course of ventricular fibrillation that occurs after EMS arrival is associated with poor survival if vital signs have been or become unstable. However, in those cases of ventricular fibrillation after arrival that are associated with good systemic circulation (and often only accompanied by chest pain) prior to a sudden arrest, patients generally fare extremely-well, particularly with the immediate intervention provided by the EMS crews already on-scene [27]. Therefore, the presentation of gasping in EMS-witnessed arrest may be affected by (or associated with) these kinds of factors. At the same time, however, immediate interventions such as rapid defibrillation by EMS crews in these EMS-witnessed events may also preclude the onset and observation of gasping. Classic gasping may not appear immediately at the time of collapse from the sudden circulatory arrest, but may start soon thereafter, and frequently within the first minute [1, 3, 7, 10–12, 14, 21, 28]. Depending on the species, the individual, any concurrent resuscitative efforts, and the underlying etiology of the circulatory compromise (or anoxic insult), gasping may continue for just a few minutes or much longer, if it occurs at all [1, 3, 7, 11, 12, 14, 21, 28]. In animals with well-performed CPR and no ventilation, gasping can continue for many minutes, though these unique respiratory efforts may not be adequate to support oxygenation for as long a period or if paralysis or sedation is induced [28, 29].

While gasping may persist for many minutes, its duration is variable [1, 3]. It makes intuitive sense that, as time passes, in a low flow, low perfusion (or no-perfusion) state, the less than normal flow of oxygen to the brainstem, spinal column, and respiratory apparatus would lead to weaker and fewer gasps [1]. Nonetheless, in the first few minutes after a cardiac arrest, gasps are not only more likely to occur, but

they are likely to be larger and stronger in nature at that time. Accordingly, in the early minutes after a sudden cardiac arrest, the presence of gasping may indeed play a critical role in resuscitation.

The Unique Physiology of Sudden Circulatory Collapse

Although sudden cardiac arrest rapidly leads to global ischemia, it is not usually the cause. The bloodstream and most body tissues, including much of the heart itself, are well-oxygenated when a person suddenly experiences ventricular fibrillation [30]. The primary disorder is generally a sudden collapse of the circulation secondary to an isolated erratic electrical rhythm in the heart's electrical system, not respiratory insufficiency or a cerebral lesion. With less than adequate circulation provided by basic CPR techniques, blood flow from the thorax is not as strong and oxygen is not delivered rapidly to the tissues for consumption [31]. As a result, near normal systemic arterial oxygen saturations may persist for several minutes following sudden cardiac arrest such as that occurring with ventricular fibrillation [4, 28, 31, 32]. If anything, in a situation not involving traumatic brain injury or intracerebral hemorrhage, the brain may even benefit from hypoventilation (elevations in $PaCO_2$) in a low flow state [33].

If there is little need to support systemic arterial oxygenation in the early stages of cardiac arrest, there is also little need to attempt to rapidly remove CO_2 from the body during periods of pulselessness, regardless of etiology [4, 31, 34]. With typical chest compressions, cardiac output may fall to less than 15 % of baseline and this hemodynamic compromise will result in a dramatic reduction in total body oxygen delivery [34–36]. In such severe low flow states, there is, as a result, a complementary pronounced reduction in total body CO_2 production. In turn, there is little need to attempt to remove it as there is much less blood flow returning back to the lungs to facilitate pulmonary removal of the gas [34, 36]. Even if metabolism of residual tissue oxygen continued (or even accelerated) in certain organs, such as the heart and brain, during the immediate first few minutes following sudden circulatory arrest, many of these cellular activities eventually shut down or dramatically diminish. Even when there is a temporary persistence of metabolic activity, basic CPR is not the most optimal form of circulation. As a result of the dramatically diminished circulation, excess CO_2 may simply accumulate in those tissues and not be carried away and returned to the lungs. Overall, total body cardiac output and the return blood flow back to the lungs still remains severely compromised and excretion of the CO_2 cannot occur regardless of respiratory interventions [34, 36].

One could increase end-tidal CO_2 production (reflective of better blood flow back to the lungs) perhaps with higher quality and minimally-interrupted chest compressions which will result in an increase in cardiac output and pulmonary blood flow. However, until there is restoration of near-normal spontaneous circulation, substantially less ventilation will be needed using current methodologies. Nevertheless, it should still be remembered that whenever new CPR adjuncts are employed that truly augment total body blood flow, more ventilation may be needed. In essence, one should keep in mind the general rule of thumb that ventilation should match perfusion. If total body cardiac output and pulmonary circulation is severely depressed, there is little perfusion of the lungs and, therefore, clear futility in attempting to eliminate CO_2, particularly because there will be little need to do so with the concomitant attenuation of total body CO_2 production.

Although the need to excrete CO_2 using standard basic CPR techniques generally will remain low throughout those low perfusion conditions, systemic arterial oxygen saturation still requires maintenance of the inflation (or re-inflation) of certain dependent lung zones subject to alveolar closure [19, 37]. Considering the lung compressing force of vigorous chest compressions and progressive lung deflation due to absence of spontaneous breathing in many cases, red blood cell oxygen desaturation eventually becomes a problem. While supplemental oxygen and assisted ventilation may provide some aid, the extent and number of deflated lung units is the major concern in terms of maintaining (or restoring) adequate pulmonary oxygenation (saturation of red blood cells) and systemic arterial oxygen tension [37]. The pivotal concern for most clinicians is to determine the point at which assisted lung inflation (i.e., alveolar recruitment) may be required and, when that time comes, what respiratory rate and tidal volume should be delivered [4].

This concern also becomes more pressing because interruption of chest compressions to provide rescue breaths can have serious deleterious effects in terms of maintaining coronary artery perfusion, the main factor in achieving return of spontaneous circulation [31, 32]. This observation has led many investigators to rely on minimally interrupted chest compressions even to the extent that ventilations are eliminated altogether, even after the first few minutes following sudden cardiac arrest – or any kind of arrest for that matter [31, 38–40]. In this line of thinking, it could be argued that on-going, uninterrupted delivery of oxygen to the tissues (by maintaining uninterrupted chest compressions and no ventilations) is better, even if it results in a lower oxygen saturation and low arterial oxygen tension. In other words, constant delivery of some level of oxygen, even if relatively desaturated, is better than only an intermittent flow of erythrocytes, even when they are 100 % oxygen-saturated. Even if oxygen carrying capacity is higher with intermittent rescue breaths, total oxygen delivery may be significantly higher if flow is maintained. Indeed, pulmonary function in terms of arterial oxygenation may actually be more compromised by overall diminishments in cardiac output, thus defeating the purpose of the rescue breaths [31, 34, 36].

Previously, assisted breathing with mouth-to-mouth ventilation always had been emphasized as a critical component of traditional bystander CPR training, but some investigators have pointed out that there are other potential sources of oxygenation and ventilation during cardiac arrest and the performance of CPR [31]. One mechanism is the thoracic squeeze and recoil process during the chest compressions of CPR. During chest compressions, air is expelled from the thorax during the downstroke phase. Then, to some degree, air is passively inhaled during the elastic recoil of the chest wall, assuming an open airway is present [29]. This technique may work to some extent for the purposes of removing CO_2, but it may not maintain adequate oxygenation, particularly in absence of spontaneous respiratory activity.

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, spontaneous respirations, in the form of agonal or gasping breaths, commonly occur (as previously described) in both animals and humans during the early minutes following sudden cardiac arrest [1–14, 31]. 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. This hypothesis is logical considering the fact that gasps are most often observed in witnessed collapses and non-asystole presentations [1, 7, 9]. Also, in theory, gasping

may be preserved for longer periods of time with early, effective and minimally interrupted basic CPR [28, 31, 40]. 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 [19–23]. 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 % in the non-gaspers. But while the 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 also are a number of animal studies with data that support the concept that gasping independently, by itself, improves survival chances as well.

Gasping as an Independent Factor for Improving Survival

While these spontaneous gasping ventilations eventually deteriorate due to the less than optimal perfusion of the brain and respiratory muscles during 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 [19–23]. 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 physiological reasons. First, they 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 [2, 3, 10–14, 19]. 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, with a greater percentage of each breath going toward alveolar ventilation (and a lesser percentage to dead space), more CO_2 is cleared as compared to typical normal resting breaths [31, 37].

In addition, these unique and extraordinary inspiratory efforts can often generate significantly enhanced negative intrathoracic pressures, thus significantly augmenting venous return to the heart and, in some cases, diminishing intracranial pressure as well [10, 19–23]. In fact, in one experimental study, gasping significantly increased carotid blood flow during untreated cardiac arrest in a pig model of ventricular fibrillation [21]. Accordingly, 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 important, 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 [41]. 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 as well [21–24, 31, 41].

Several experimental models have documented that animals can maintain adequate ventilation (removal of CO_2) for as long as twelve minutes following sudden arrest with ventricular fibrillation when chest compressions only are employed [2, 28, 29]. This observation reinforces the notion that gasping breaths and chest compressions can maintain an adequate degree of ventilation during cardiac arrest [31]. Likewise, animal models also demonstrate that adequate oxygenation (red cell saturation) can be maintained, at least for several minutes with chest compressions-only after sudden cardiac arrest, especially if paralytics are not involved [2, 28, 29, 31]. In essence, gasps may allow for very effective ventilation (removal of CO_2) for very long periods of time. Again, this effect is non-existent (and thus not effective) if paralytics are involved and perhaps certain sedatives as well [29].

Assisted ventilation would, theoretically, be more of a priority in asphyxial circumstances because the cardiac arrest is presumably the result of a significant and progressive interval of tissue hypoxia. Also, there is concern that certain patients may not be able to gasp or have the ability to overcome a relaxed or even fully-occluded airway. Nevertheless, one animal study compared six minutes of standard CPR (including assisted ventilation with a patent airway) to chest compression-only CPR with a totally occluded airway and found no difference in 24-hour survival between the two groups [43]. Although arterial blood gases were not as good when the airway was occluded, hemodynamic parameters remained significantly better with compression-only CPR. This observation suggests that, despite poorer saturation, overall oxygen delivery to the tissues may be matched by the improved flows attained with uninterrupted compressions [43]. While this study was not a true model of a hypoxic etiology because ventricular fibrillation was induced initially and then the endotracheal tube was clamped, it did demonstrate that compression-only CPR can be effective for the first few minutes, even if there is no active use of assisted ventilation in a cardiac arrest precipitated by ventricular fibrillation. Moreover, other experimental models have demonstrated reasonable lung inflation despite a mostly occluded airway during gasping [44]. As discussed in the following section, attempting to breathe against an occluded (or even partially occluded) airway may actually have significant positive hemodynamic effects that may benefit the patient during resuscitation.

Improved Airflow, Blood Flow, or Both?

The previous discussion about airway occlusion is very poignant and relevant to the discussion of the potential benefits of gasping. One question concerning 'no ventilation CPR' has been whether or not to attempt to open the airway. With an obstructed airway, the patient takes a rather abrupt, deep respiratory effort, yet ambient air cannot easily rush in to equalize the pressure in the chest. In essence, the thorax creates and sustains a slightly better vacuum (negative intrathoracic pressure) that should result in even more venous return, augmented cardiac output, heightened aortic pressure and eventually enhanced coronary and cerebral perfusion [10, 19–23]. Ironically, if the blood is still oxygenated after a sudden cardiac arrest, a partially occluded airway may theoretically enhance resuscitation chances because it generates more negative intrathoracic pressure and, therefore, enhances blood flow during CPR conditions.

Occluded airway or not, ventilation is not really needed during the first few minutes after cardiac arrest and clinical trials indeed support this concept. In a random-

ized clinical trial of 'chest compression only' instructions provided by emergency call center dispatchers (versus instructions using the traditional 'A-B-C' CPR technique), the chest compression-only CPR group did well in this early phase of cardiac arrest when most agonal breaths are expected to be occurring [45]. The study demonstrated a higher rate of performance of CPR by the on-scene laypersons with chest compressions alone, presumably because more of them were able to follow the simpler instructions versus traditional instructions that also involve airway establishment and mouth-to-mouth breathing. In addition, the chest compressions were not only less interrupted, but they were also started much earlier because the emergency medical dispatchers were able to deliver chest compression-only CPR instructions over the phone in significantly less time [45]. While these variables may be the key reasons for the increased survival found in the study, it is also speculated that the additional physiological benefits of gasping during this early phase of the arrest likely played an immeasurable, but significant role for many of the survivors [4, 7, 9]. 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 is better sustained. In turn, this will theoretically prolong the period of gasping and its additional positive physiological benefits [10, 19–23].

As discussed previously, despite the relatively infrequent rate of agonal respirations (breaths usually greater than 10 seconds apart), this form of ventilation generates a larger sized tidal volume and its very abrupt nature, provides, in many cases, more than adequate respiration gas exchange [2, 3]. This observation makes particular sense when one considers the very low systemic blood flow situation of cardiac arrest in which very little ventilation (CO_2 excretion) is generally feasible or needed. Gasping also involves the more physiological mechanism of creating lung inflation by 'pulling' open many of the dependent lung zones just superior to the diaphragm in a very specific manner that inflates a very specific inter-laced architecture of lung matrix. This mode of ventilation is likely to be more efficient and effective than the tidal volumes that are delivered using mouth-to-mouth ventilation or other positive pressure techniques that attempt to 'push' the lung zones open. Positive pressure techniques are more likely to maldistribute the delivered tidal volume into zones of lesser resistance and not the dependent lungs normally pulled open by the diaphragm and the other respiratory musculature [31].

Accordingly, gasps, as a form of spontaneous respiratory effort, are probably not only more efficient in terms of gas exchange, but they are also clearly preferred in terms of enhancing venous return and circulation as a whole [4, 19–23]. 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 cardiovascular deterioration such as that occurring when the peripheral vasculature begins to lose tone from under-perfusion [46]. When vascular tone is rapidly lost, coronary perfusion is diminished because of a declining aortic pressure and resuscitation chances diminish as well.

Using Gasps to Avoid the Detriments of Positive Pressure Breaths

According to the previous discussion, intermittent mouth-to-mouth breaths or any other rescue breaths using positive pressure may not only inhibit venous return and

create less effective breaths in terms of gas exchange, they may further diminish critical blood flow and pressure heads to the peripheral vasculature and the respiratory apparatus alike. Paradoxically, by stopping to breathe into the patient, a more rapid deterioration of gasping may occur. In turn, this traditional CPR scenario may lead overall to less effective gas exchange, less effective circulation, and thus earlier cardiovascular collapse. Again, recent research indicates that uninterrupted compressions may very well be applicable, even beyond the first few minutes [40]. 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 function through the gasping process (when present).

Accordingly, international standards for dispatchers who provide CPR instruction over the telephone to bystanders at the scene now emphasize compression-only CPR in their protocols, particularly in the first few minutes after a sudden cardiac arrest with no obvious precipitating cause for the arrest [4]. More recently, these same international consensus groups are also adopting protocols involving the identification of agonal breaths to detect cardiac arrest and persons who need initiation of basic CPR [9]. This approach has also become a topic in recent training materials for laypersons learning basic CPR techniques.

Better Detection of Cardiac Arrest Using Gasps

Several studies have confirmed that many persons with out-of-hospital cardiac arrest may not receive CPR by bystanders because the bystanders mistake gasping for 'normal' breathing. Based on studies of conversations between emergency medical dispatchers and on-scene witnesses, it appears that many bystanders believe that the patient is showing signs of life because they are 'breathing' when, indeed, they are actually making a gasping effort [9, 47, 48]. As a result, many patients may miss the opportunity to receive basic CPR while EMS responders are en-route to the scene not knowing it will be a cardiac arrest (**Fig. 1**).

Recently, however, techniques have been devised to identify gasping over the telephone, and, in turn, to detect persons who are actually in a state of circulatory arrest [9]. In the four-month follow-up period after implementation of a new protocol to detect gasps, 100 more patients were found by dispatchers to meet criteria for not breathing normally compared to the preceding eight months [9]. In previous investigations evaluating the factors that impeded dispatcher-assisted CPR, investigators found that the dispatcher-assisted CPR instructions were omitted in 64 % of cases because the patient was reported as having "signs of life", most likely attributed to agonal respirations [7, 47, 49].

In essence, the rapid identification of agonal breaths appears to be a very useful tool for detecting cardiac arrest and, based on study findings, a highly specific one as well. In the agonal breath detection study, it was clear that agonal breaths were always ten or more seconds apart and 'normal' (non-gasping) breathing always had less than a five-second interval between the spontaneous breaths [9]. It was a dramatic delineation, making the detection of agonal breaths (versus a 'normal breath') very reliable.

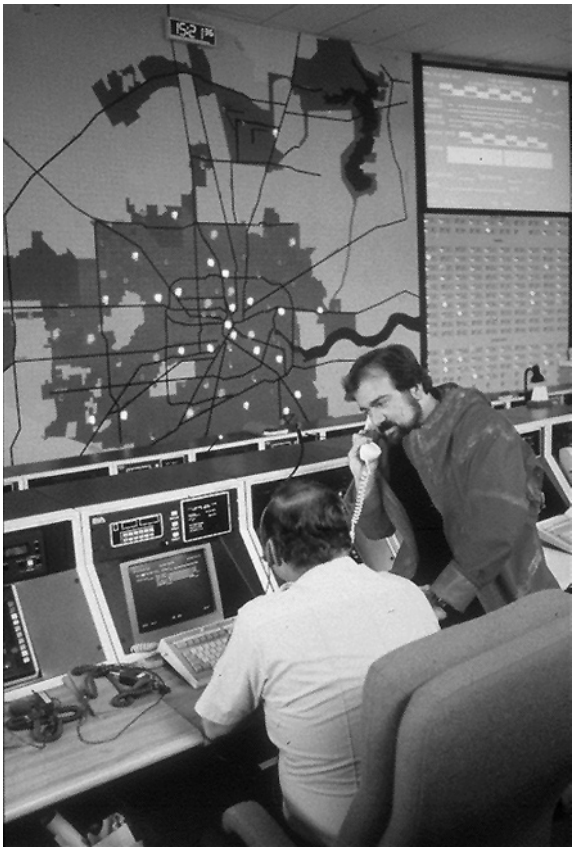

Fig. 1. As emergency medical services crews are responding to an unconscious person, emergency medical dispatch offices now have protocols for rapid identification of the presence of gasps (agonal respirations) over the telephone. In turn, these procedures increase the detection of cardiac arrest at the scene of an emergency, particularly when bystanders are unsure of whether or not to perform basic cardiopulmonary resuscitation (CPR). As a result, dispatchers can then instruct the bystanders how to initiate chest compressions in a large number of cases in which the life-saving technique previously might not have been performed prior to arrival of professional responders.

The Role of Gasping in Trauma Care and Infant Resuscitation

The detrimental hemodynamic effects of intermittent positive pressure breaths may be even more profound in severe hemorrhage situations and particularly in moribund conditions and states of severe hypovolemia [41]. The use of endotracheal intubation and delivery of tidal volumes of air, even at 'normal' ventilatory rates, may even lead to iatrogenic demise of the patient [41]. In such very tenuous patients, if positive pressure breaths could be avoided altogether, it would certainly be preferred. Accordingly, as in the discussion on cardiac-oriented resuscitation, gasping could indeed play an important role in resuscitation of the massively bleeding patient or even the patient with severe head injury, not only in terms of avoiding the deleterious effects of positive pressure breathing, but also to enhance cerebral blood flow and diminish intracranial pressure [10, 22]. In a rat model of untreated fatal hemorrhage, not only did all rats gasp and do so with great vigor, but, on average, they also enhanced cerebral blood in a very compelling manner (> 50 % from the baseline compared to 4 % of baseline following the hemorrhage) [10]. Even in trauma, despite the traditional concern over protecting the airway, outcomes may be better with no applied positive pressure ventilations and allowing gasps to help improve both respiration and circulation.

Relevant to infants, a recent review article of both experimental and clinical data indicated that gasping might be "auto-resuscitative" in infants, noting that almost all infants with sudden infant death syndrome had documented gasping [50].

Creating Gasps for Those Who Do Not Do So

The positive resuscitative effects of gasping are becoming more and more evident, but, again, not all patients make these unique respiratory efforts. One consideration is to artificially create a "super-gasp", not only for those who do not make gasping efforts at all, but also to sustain and enhance the gasp effects in those who are already gasping, through external interventions such as a phrenic nerve stimulator [51]. Even those who are already gasping might benefit if the stimulator could induce a stronger gasp in a person whose respiratory efforts are beginning to fade during resuscitation.

Conclusion

Gasping and other forms of agonal respiratory efforts may not only have positive prognostic value for those with global ischemic events, but they also likely serve as an adjunctive resuscitative intervention for both cardiac arrest and severely injured patients. Gasping is more of a physiologically sound mode of ventilation when compared to the traditional use of positive pressure breathing. Gasps may, therefore, even be more efficient and effective than traditional mouth-to-mouth rescue breathing and other positive pressure ventilatory techniques. Indeed, recent data demonstrate that gasping can enhance pulmonary gas exchange (oxygenation and ventilation) as well as circulation by enhancing venous return and, in turn, cardiac output, aortic pressures, coronary artery perfusion, and cerebral blood flow. Recent studies designed to identify gasping over the telephone at emergency dispatch offices have dramatically increased the ability of dispatchers to detect persons with cardiac arrest. In turn, dispatchers can now prompt earlier performance of chest compressions in a large number of cases in which the life-saving technique might not have been performed until arrival of professional responders. Such studies may provide a model for the future relevant training of laypersons, EMS responders and other medical personnel.

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Recent Concepts in Burn Resuscitation

D.J. Dries and W.J. Mohr

III

Introduction

The burn-injured patient is unique in resuscitation requirements, metabolic stress, pattern of complications, and determinants of outcome [1]. This chapter highlights the literature focused on those aspects of care which are unique to burn centers and the burn-injured patient and contribute in important ways to outcome.

Contemporary discussion of burn resuscitation begins with the Parkland formula proposed by Baxter and coworkers in the 1960s [2]. Reviews of recent experience with burn resuscitation suggest that treatment objectives and fluids administered in the approach recommended by the Parkland group are frequently exceeded [3]. What is contemporary thinking about initial fluid administration in the setting of burn injury? The American Burn Association (ABA) has recently presented a statement which begins to answer this question [4]. The Parkland Burn Center recently published a report on the use of the Parkland formula in the institution where it originated [5]. The military, faced with the complex logistics of austere conditions and long distance transport, has instituted a number of new treatment strategies and is beginning to examine outcomes. North American burn centers, including our own, are revising treatment protocols to reduce resuscitation volume with encouraging initial results.

Resuscitation Perspectives

Fluid administration in the setting of burn injury, monitoring of efficacy, and consensus recommendations are included in recent work published in the *Journal of Burn Care & Research* [6]. Blumetti and coworkers from the University of Texas Southwestern in Dallas provide a 35 year retrospective and commentary on the present state of the Parkland formula [7]. This standard for burn resuscitation has recently been criticized in multiple studies and in a recent editorial review by Saffle, pointing out that patients frequently receive greater amounts of fluid than predicted [8]. Saffle presents an example of resuscitation excess from his experience and suggests a resuscitation program incorporating feedback, communication requirements, and clinical targets (**Fig. 1**). The accuracy and practicality of the Parkland formula are open to question.

Blumetti et al. conducted a retrospective analysis of burn patients treated at Parkland Memorial Hospital Burn Center during a 15 year period from 1991 to 2005 [7]. Included were adults with burns covering > 19 % total body surface area (TBSA). In this adult group, adequate fluid resuscitation was defined as a urine output of 0.5 to

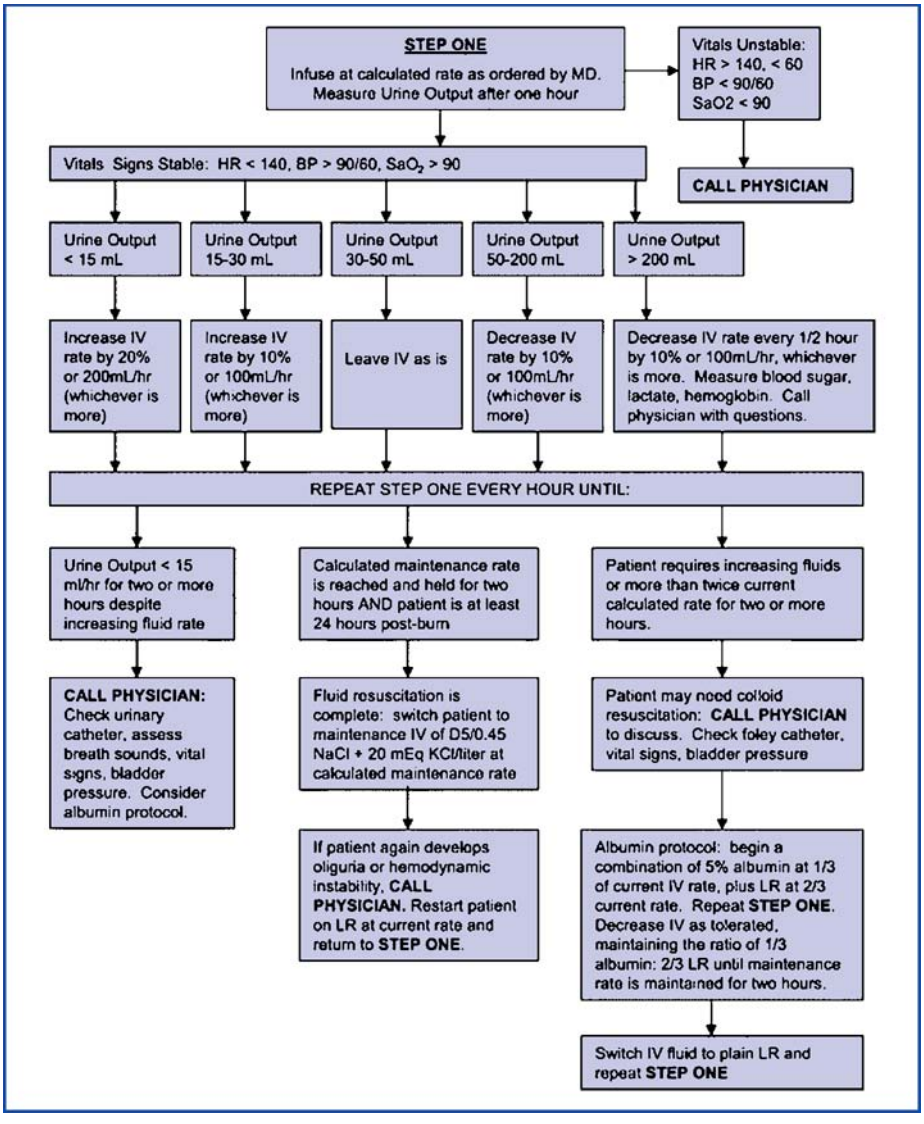


Fig. 1. Protocol for fluid resuscitation of adult burn patients. In response to requests from nursing, this protocol was developed to permit nursing staff to manage fluid resuscitation of acute burn patients. Initial fluid rates are calculated by the Parkland formula. Nurses begin hourly infusion, measure urine output and adjust fluids according to patient response. Development of unstable vital signs, inadequate response to fluids or persistently high fluid requirements prompts a call to the physician. A pathway to begin colloid replacement exists for patients who display increasing fluid requirements or develop evidence of torso compartment syndrome. From [8] with permission

1.0 ml/kg/h. Overresuscitation was defined as a urine output > 1.0 ml/kg/h. In a review of nearly 500 patients, 43 % received adequate resuscitation based on urine output criteria; 48 % were overresuscitated. There were no differences in complication rates or mortality according to over- versus adequate resuscitation. Patients were evaluated for inhalation injury with bronchoscopy. Contrary to reports from other centers, the amount of fluid required for adequate resuscitation based on target urine output was not different in patients with inhalation injury as opposed to those without this insult. Although Ivy and colleagues [9] demonstrated that intra-abdominal hypertension and abdominal compartment syndrome commonly occurred in burn patients with volume resuscitation in excess of 250 ml/kg, the Parkland data reported here noted a 1 % incidence of abdominal compartment syndrome even in burns exceeding 40 % TBSA where resuscitation volumes exceeded 250 ml/kg. In summary, even in the home of the Parkland formula, actual burn resuscitation frequently does not meet the standard set forth by this clinical strategy. Patients commonly received higher fluid volumes than predicted by the Parkland formula. The Parkland team recommended an emphasis on calculated formula volumes only as a guide to initial resuscitation and the use of careful titration to urine output as the most important intervention.

Can Metabolic Markers Guide Resuscitation and Help Predict Outcomes?

The United States Army Institute of Surgical Research at Fort Sam Houston, Texas, examined the value of arterial blood gas data in addition to standard parameters considered predictive of burn outcome such as: Total burn size, patient age, and presence of inhalation injury [10]. Driven by recent concern regarding efficacy of traditional formula-based burn resuscitation, this group sought to examine the value of arterial blood gas data in determining outcome after burn resuscitation. In 162 patients, all of whom were receiving percussive ventilation, these authors sought to determine whether metabolic acidosis during the first two days after burn injury, as measured by arterial-base excess, was associated with increased mortality. A second objective was to determine whether a decrease in oxygenation during the first two days after burn injury was associated with increased mortality. Oxygenation as measured by the alveolar-arterial gradient ($AaDO_2$) could be affected by the presence of inhalation injury or pulmonary edema in the setting of excessive burn resuscitation. Incremental logistic regression analysis was performed to examine the additional information provided by oxygenation data and base excess in these patients.

In the group of patients studied, the mean TBSA burn was 37.2 % and the mean age of study patients was approximately 42 years. Thirty-four percent of patients did not survive to hospital discharge. When epidemiologic data were examined, nonsurvivors were older, had larger TBSA burns and a greater incidence of inhalation injury than survivors. Infection was the leading cause of death in hospital accounting for 47 % of mortality. Resuscitation failure, however, accounted for 20 % of deaths. Thirteen percent of patients ultimately had care withdrawn due to the magnitude of the injury.

The principle finding in this study was that mean arterial base excess (negatively), and mean alveolar $AaDO_2$ (positively), averaged during the first two days after burn, were independently associated with the rate of mortality after burn injury along with burn size, patient age, and the presence of inhalation injury. When

incremental predictive accuracy of a regression model including acid base and oxygenation data was examined, however, inclusion of arterial blood gas variables did not improve predictive accuracy.

These data parallel the literature concerning the utility of base excess and lactate during resuscitation of patients with nonthermal trauma [11–13]. Studies in patients without burn injury confirm that lower base excess is associated with reduced mean arterial pressure (MAP) and increased fluid resuscitation volume. A worsening base excess during resuscitation was associated with ongoing hemorrhage, increased mortality and severity of injury. While a close relationship between base excess and lactate has been assumed during shock and resuscitation, recent studies suggest that lactate levels obtained during resuscitation out perform base excess in prediction of outcome and that lactate levels sometimes bear little relationship to the base excess. This is because in the setting of shock and resuscitation, changes in base excess may reflect processes other than lactic acidosis. Such processes may include impairment of renal function, changes in protein and phosphate buffer systems, and hyperchloremic acidosis secondary to large volume saline resuscitation.

Other authors have suggested that a series of values for either base excess or lactate obtained over the course of resuscitation provides more powerful prediction of mortality than a single, initial determination [13]. In this retrospective work, arterial blood gas data were obtained at variable time points after injury. Thus, the impact of trends in either oxygenation or base excess cannot be evaluated. Despite the lack of association between mean base excess and survival in this study, we continue to follow base excess closely during burn resuscitation and consider a value less than –6 as suggestive of end organ ischemia. Patients with persistent low base excess should be viewed as candidates for efforts to improve perfusion. Alveolar arterial oxygen gradient is also a weak predictor of mortality. Mortality in the setting of relative hypoxia may relate to effects of smoke inhalation, development of acute lung injury (ALI) secondary to resuscitation or a synergistic impact of administered fluids on lungs injured by exposure to products of combustion.

Surrogate parameters for adequacy of resuscitation were discussed in additional reports from civilian centers in the United States. Jeng and coworkers focused on wound perfusion as a key factor promoting progression of burn depth and questioned whether parameters, such as tissue and gastric PCO_2, could provide more immediate data on efficiency of resuscitation than measurement of urine output and MAP [14]. Four patients with severe life-threatening burns (median 58 % TBSA) and shock were enrolled in this study. All patients were adults with percent TBSA burns > 40 %. Time between burn injury and arrival at the burn center was < 2 hours and patients were admitted directly to the burn center with admission mean arterial pressure < 70 mmHg. Patients with concomitant electrical injury, trauma or lack of consent within 24 hours were excluded. Patients were resuscitated to maintain oxygenation (> 90 % saturation), urine output (30–50 ml/hr) and MAP (> 70 mmHg). In these patients with large burns, crystalloid volumes used in the first 24 hours were very high, averaging 16.8 ml/kg/% TBSA burn, vastly exceeding the Parkland formula predictions. Even with this massive fluid administration, cyclic changes were noted in burn wound pH, PCO_2, PaO_2, gastric PCO_2, gastric PO_2, arterial pH or base deficit. When the resuscitation parameters described above were compared to laser Doppler imaging, a standard used in this study to evaluate burn perfusion, changes in gastric PCO_2, burn wound pH and burn wound PCO_2 mimicked the changes in laser Doppler-measured burn perfusion. Tissue resuscitation parameters

showed statistically significant changes in perfusion 4 hours after the start of resuscitation while urine output did not change until 2 hours later. Remarkably, when burn wound perfusion was improved by interventions based on tissue parameters, the change did not translate into a measureable variation in hourly urine output. Use of tissue tonometry at both gastric and burn wound sites provided more rapid recognition of changes in resuscitation effectiveness. It is important to note that the impact of these interventions on outcome cannot be demonstrated in this limited data set.

Batchinsky and coworkers at the U.S. Army Institute of Surgical Research with collaboration from the University of Turku in Finland investigated heart rate variability and its relationship to cardiovascular regulation after burn injury [15]. Investigators have noted, in other settings of cardiovascular stress, that loss of R to R interval complexity is seen. These investigators demonstrated abnormally low R to R interval complexity during early post-burn resuscitation in a series of 13 patients with mean TBSA burns of 36 %. All of these patients survived resuscitation. Progress through resuscitation was associated with improvement in R to R interval complexity and improved end organ support. Nonlinear and frequency domain electrocardiogram (EKG) analysis was employed. These results mimic those of other investigators studying trauma resuscitation, particularly the group from Vanderbilt University [16].

Military Resuscitation Experience (Tables 1 and 2)

Burns are frequent in military conflicts, comprising 10 % of casualties. Of these, nearly 20 % of burns are categorized as severe (involving > 20 % TBSA) and require marked intravenous resuscitation [17, 18]. Twenty-first century conflict presents unique challenges associated with global evacuation of burned soldiers, frequently during the first 24 to 48 hours after burn injury as acute resuscitation is ongoing. The presence of smoke inhalation injury, occurring in 5 % to 15 % of patients with severe burns also increases fluid requirements. Frequently, the critical first days of burn resuscitation of war wounded are managed by physicians and nurses who are not specialized in burn care with priorities focused on stabilization and evacuation to sites for definitive treatment. Providing guidance and standardizing practice became a challenge leading to the evolution of a consistent military approach to burn resuscitation.

Delayed or inadequate resuscitation is well known to produce suboptimal tissue perfusion with end organ failure and, in severe cases, death. Fluid resuscitation after severe burns is intended to replace loss of intravascular volume sufficient to maintain tissue perfusion during the 48-hour period of increased capillary leak and relative hypovolemia, but at the lowest physiologic cost. Patients with severe burns, particularly if combined with extensive soft tissue trauma, inhalation injury or electrical insults will require administration of increased amounts of fluids to prevent burn shock. In some cases, resuscitation failure will occur due to limits in cardiovascular reserve and adverse host response.

Growing attention has been paid in the military to the consequences of over resuscitation. This parallels work which has been widely disseminated in the civilian sector of the international burn community. The military now describes resuscitation morbidity as a constellation of complications including abdominal compartment syndrome, airway edema causing obstruction, extremity compartment syndromes, and pulmonary edema. Resuscitation volumes approximating 16 liters dur-

Table 1. Recommendations for difficult fluid resuscitation. From [18] with permission

At 12–18 h postburn, calculate the projected 24 h resuscitation if fluid rates are kept constant. If the projected 24 h resuscitation requirement exceeds 6 ml/kg/% TBSA, then the following steps are recommended:

1. Initiate 5 % albumin early as described previously in the Emergency War Surgery Handbook.
2. Check bladder pressures every 4 h.
3. If urine output (UOP) < 30 ml/h, strongly consider the placement of a pulmonary artery (PA) catheter to guide resuscitation with specific pulmonary capillary wedge pressure (PCWP) and mixed venous saturation (SvO_2) goals. (Goal PCWP 10–12, SvO_2 65 %–70 %). If PA catheter placement is not practical, then consider monitoring central venous pressures (CVP) from a subclavian or internal jugular line along with central venous ($ScvO_2$) saturations. (Goal CVP 8–10, $ScvO_2$ 60 %–65 %).
   a) If CVP or PCWP not at goal, then increase fluid rate.
   b) If CVP or PCWP at goal, then consider vasopressin 0.04 units/min to augment mean arterial pressure (MAP) (and thus UOP) or dobutamine 5 mcg/kg/min (titrate until SvO_2 or $ScvO_2$ at goal). Max dose of dobutamine is 20 mcg/kg/min.
   c) If both CVP or PCWP and SvO_2 or $ScvO_2$ at goal, then stop increasing fluids (EVEN if UOP < 30 ml/hr). The patient should be considered hemodynamically optimized and the oliguria is likely a result of established renal insult. Some degree of renal failure should be tolerated and expected. Continued increases in fluid administration despite optimal hemodynamic parameters will only result in "resuscitation morbidity", that is oftentimes more detrimental than renal failure.
4. If the patient becomes hypotensive along with oliguria (UOP < 30 ml/hr), then follow the hypotension guidelines.
5. Every attempt should be made to minimize fluid administration while maintaining organ perfusion. If UOP > 50 ml/hr, then decrease the fluid rate by 20 %.

After 24 h, lactated Ringer's infusion should be titrated down to maintenance levels and albumin continued until the 48 h mark.

Table 2. Hypotension guidelines. From [18] with permission

The optimal minimum blood pressure for a burn patient must be individualized. Some patients will maintain adequate organ perfusion (and thus have adequate urine output [UOP]) at MAPs less than 70 mmHg. True hypotension must be correlated with UOP. If the MAP is not adequate (generally < 55 mmHg) to maintain the UOP goal of at least 30 m/h, then the following steps are recommended:

1. Start with vasopressin 0.04 units/min drip (Do Not Titrate).
2. Monitor central venous pressure (CVP) (Goal 8–10).
3. If CVP not at goal, then increase fluid rate.
4. If CVP at goal, then add Levophed (norepinephrine) 2–20 mcg/min.
5. If additional pressors are needed, consider the placement of a pulmonary artery (PA) catheter to guide resuscitation with specific pulmonary capillary wedge pressure (PCWP) and SvO_2 goals (Goal PCWP 10–12, SvO2 65 %–70 %). These patients may be volume depleted, but a missed injury should be suspected.
   a) If PCWP not at goal, then increase fluid rate.
   b) If PCWP at goal, then consider dobutamine 5 mcg/kg/min (titrate until SvO_2 at goal). Max dose of dobutatmine is 20 mcg/kg/min.
   c) If hypotension persists, look for missed injury.
   d) Consider adding epinephrine or neosynephrine as a last resort.
6. If the patient is exhibiting catecholamine-resistant shock, consider the following diagnoses.
   a) Missed injury and ongoing blood loss.
   b) Acidemia. If pH < 7.20, then adjust ventilator settings to optimize ventilation (Target PCO_2 30–35). If despite optimal ventilation, patient still has a pH < 7.20, consider sodium bicarbonate administration.
   c) Adrenal insufficiency. Check a random cortisol and start hydrocortisone 100 mg every 8 hours.
   d) Hypocalcemia. Maintain ionized calcium > 1.1.

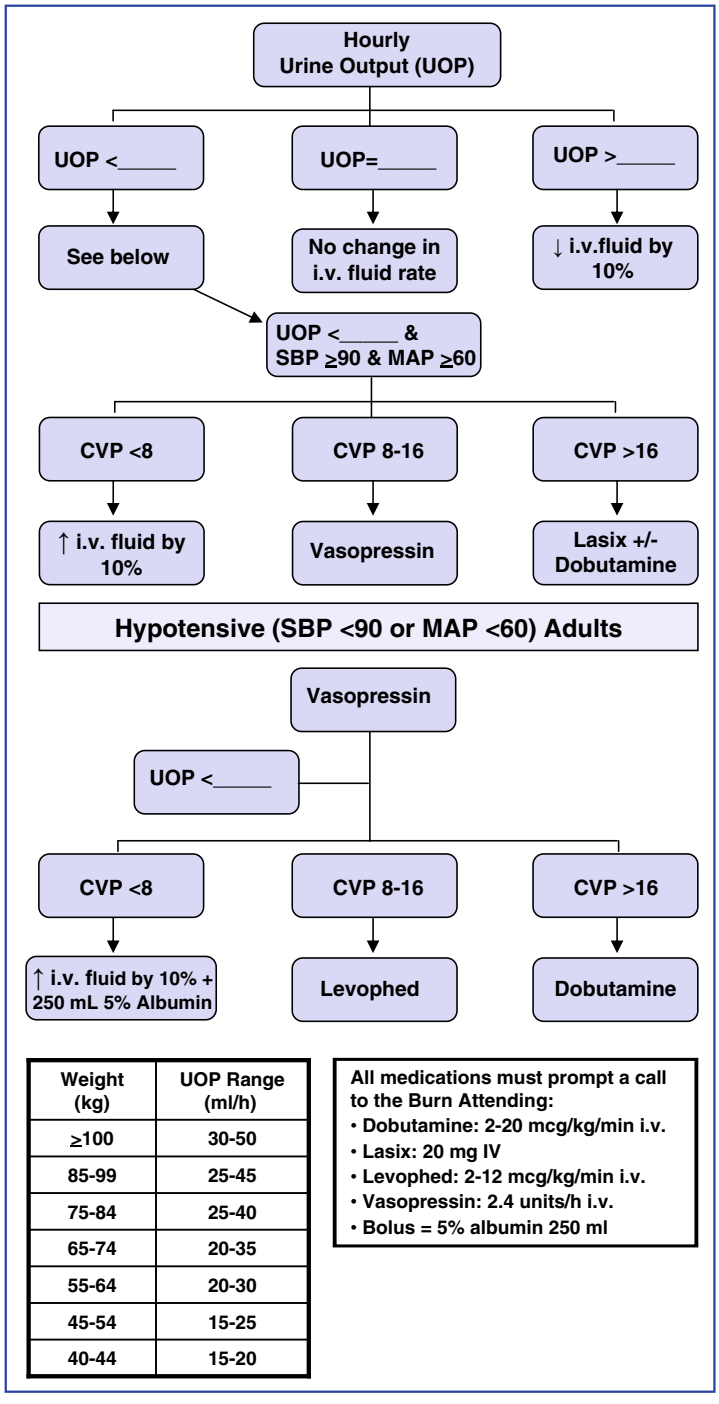
ing a 12 hour period in a 70 kg man appear to reach the threshold for development of abdominal compartment syndrome [19]. Multiorgan consequences of abdominal compartment syndrome have been well described. Renal failure, intestinal ischemia, respiratory compromise, and death follow if appropriate treatment is not initiated in a timely fashion. Even adequate treatment of abdominal compartment syndrome is frequently accompanied by significant morbidity. Mortality for decompressive laparotomy for abdominal compartment syndrome in burn injured patients has been reported to be 60 – 100 % [9, 17, 20].

A number of solutions designed to address the resuscitation problem in burn injury may be considered for civilian practice, particularly where significant time and distance is involved in referral of the patient. Guidelines created for management of hemorrhagic shock in the field use easily accessible clinical endpoints such as mentation and palpable radial pulses to decrease or stop infusion of intravenous fluids. While a standard pre-hospital guideline for severe burns (> 20 % TBSA) has not been developed, paramedics in the field are instructed to obtain peripheral access and initiate resuscitation with lactated Ringer's solution using similar endpoints. Some military units carry colloid solutions such as hetastarch in place of crystalloids in an attempt to reduce the weight of intravenous fluid transported while maintaining the ability to replace lost volume in injured soldiers. As hetastarch is a large molecular weight colloid, it may have advantages under conditions of increased microvascular permeability as seen in burn injuries. In the field, colloids may be both an excellent solution to packing constraints imposed by battlefield conditions, as well as an effective resuscitation fluid sparing excessive volume infusion.

Current military protocols establish field and transport parameters for use of vasopressin, dobutamine, and norepinephrine for situations in which the burn injured, multiple trauma patient may develop hypotension or decreased urine output despite adequate fluid administration. Before implementation of these guidelines, 13 % of soldiers with > 20 % TBSA burns underwent decompressive laparotomies for abdominal compartment syndrome prior to reaching definitive care in the United States. With implementation of this standard approach to burn/shock resuscitation, decompressive laparotomy for abdominal compartment syndrome has been essentially eliminated [18]. Examination of these burn resuscitation protocols reveals more aggressive implementation of vasoactive drugs, previously unheard of in surgical resuscitation. In more recent experience with the standard burn resuscitation protocol, documented use of vasoactive drugs (48 % in the protocol group and 34 % in the control group) was associated with a significant increase in survival (OR, 6.309; CI 1.466 – 27.137; $p = 0.013$). As Chung and coworkers write, "fluid begets more fluid" [21]. Conservative fluid administration may reduce the risk of resuscitation failure [21 – 23].

Nurse-driven Resuscitation

In our institution, we define the goals of initial resuscitation for our burn patients as adequate volume administration to prevent acute renal failure, maintain tissue perfusion, and avoid complications of abdominal or extremity compartment syndromes. Three obstacles preventing us from controlling fluid administration were inconsistent reduction of intravenous fluid rates when adequate urine output was present, frequent use of boluses of crystalloids, and the practice of waiting 24 hours after burn injury to employ colloids. A nurse-driven resuscitation protocol was developed to address these issues (**Fig. 2**). With computerized order sets, this proto-



Weight (kg)	UOP Range (ml/h)
≥100	30-50
85-99	25-45
75-84	25-40
65-74	20-35
55-64	20-30
45-54	15-25
40-44	15-20

All medications must prompt a call to the Burn Attending:
- **Dobutamine: 2-20 mcg/kg/min i.v.**
- **Lasix: 20 mg IV**
- **Levophed: 2-12 mcg/kg/min i.v.**
- **Vasopressin: 2.4 units/h i.v.**
- **Bolus = 5% albumin 250 ml**

Fig. 2. Sample adult resuscitation protocol for Burn Center Regions Hospital St. Paul, MN. Urine output (UOP) target is set by weight. Central venous pressure (CVP), urine output and vital signs guide the administration of fluid and vasoactive drugs. SBP: systolic blood pressure; MAP: mean arterial pressure.

col provides guidelines for nurses at the bedside to use in titration of initial burn resuscitation.

The nurse-driven resuscitation protocol was implemented in June 2007 as a point of care change in our burn center. The Parkland formula was employed to identify initial intravenous fluid administration rate. The rate of intravenous fluid administration is adjusted according to protocol using hourly urine output, which we consider the best endpoint of resuscitation presently available. No crystalloid boluses are administered. Colloid administration is initiated once total crystalloid infusion reaches 100 ml/kg (approximately 40 % of the identified threshold for abdominal compartment syndrome in adult burn patients) or at 24 hours after burn injury to prevent over resuscitation. Adults with > 20 % TBSA burns and children with > 15 % TBSA burns were retrospectively reviewed for 24 months prior to and 20 months after initiation of the nurse-driven resuscitation protocol. Patients who died prior to 72 hours after burn injury and those arriving at the burn center greater than 24 hours after injury were excluded.

In our initial study period, 56 patients were evaluated (38 in the non-protocol or control group and 18 in the nurse-driven resuscitation protocol group). There were 13 pediatric patients (11 in the protocol group and 2 in the nurse-driven resuscitation protocol group). The majority of the patients suffered flame injuries (79 %). Other patients suffered scald (17 %) and electrical (4 %) injuries. With implementation of nurse-driven resuscitation protocol, a 37 % decrease in the amount of fluid given in the first 24 hours was seen [24]. Among patients with inhalation injury, there was a decrease in total 24 hour fluid resuscitation volume and a reduction in average hospital charges per day. There were nine deaths in the non-protocol group and none in the nurse-driven resuscitation protocol group. Four of the deaths were attributed to multiple organ failure while two patients had support withdrawn. Hospital length of stay and charges, ventilator utilization, incidence of compartment syndromes and maintenance of renal function all trended toward improvement in the nurse-driven resuscitation protocol group. While these data are preliminary, we note that the nurse-driven resuscitation protocol has been widely and enthusiastically accepted by burn center staff and it provides a means by which resuscitation is consistently administered at the bedside. Our preliminary experience, similar to that in the military, suggests that lower volume, carefully titrated fluid administration may be associated with improved outcomes.

Consensus Statements

A consensus statement has been released from the *American Burn Association* regarding burn/shock resuscitation [6]. Notably, no 'standards' for the approach to the resuscitation of burn injured patients exist from contemporary data. A number of 'guidelines' are supported by evidence of lesser strength.

Based on the strength of present evidence, there is no consensus regarding optimal fluid composition, rate of fluid administration, and the role of colloid. No resuscitation parameters specific to individual patient fluid needs are better than routine hemodynamic endpoints and adequate urine output. In any fluid program employed, practitioners must be compulsive in providing adequate fluids but avoiding excessive resuscitation.

Three additional points of clarification regarding burn resuscitation should be made. First, many patients, particularly with < 20 % TBSA burns may be candidates

for oral resuscitation as an intact gastrointestinal tract is tolerant of large amounts of fluid administration. Enteral resuscitation should be considered, particularly when resources are limited, an austere setting is encountered and the patient is able to tolerate oral intake. Second, invasive hemodynamic monitors, including central venous catheters and pulmonary artery catheters, have been employed to optimize burn resuscitation in a variety of prospective and retrospective studies. Patients with invasive central hemodynamic monitors tended to have far more fluid administered without improvement in outcome. While invasive monitoring may be indicated for patients with special comorbidity or patients who fail to respond to resuscitation prescriptions, a blanket statement in favor of this approach cannot be made. Third, antioxidant therapies show promise in reduction of burn resuscitation fluid requirements and edema formation in a variety of preclinical trials. Unfortunately, patient data are limited and multicenter prospective validation has not been attempted.

Conclusion

Historical reservations about under-resuscitation have led to a clear trend toward over-resuscitation in the setting of burn injury. Multiple civilian and military groups are investigating resuscitation protocols which, for the first time, make use of vasoactive drugs as well as limiting crystalloids and providing earlier administration of colloids to support early (48 hours) resuscitation following burn injury. While conclusive data are not yet available, there is no evidence of increased complications with tighter control on resuscitation and preliminary data support improved organ system outcome.

A variety of metabolic parameters has been investigated to further guide the resuscitation process. Retrospective reviews of blood gas data fail to disclose better prognostic information than is contained in traditional parameters such as burn size, age, and the presence/absence of inhalation injury. An intriguing global measure of resuscitation success is heart rate variability which is under investigation by a number of groups. Tissue specific parameters such as wound pH and PCO_2 may be more sensitive than urine output and changes in vital signs to indicate effectiveness of resuscitation. At present, however, use of tissue tonometry at burn wound sites has not been demonstrated to guide resuscitation more effectively than simple changes in vital signs and urine output.

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Intra-aortic Balloon Counterpulsation in Cardiogenic Shock

K. Werdan, M. Russ, and M. Buerke

III

Introduction

What can we expect from the implementation of an intra-aortic balloon counterpulsation pump (IABP) in a patient with shock (Fig. 1)? The conventional indication for IABP is cardiogenic shock of ischemic etiology. With the IABP in place in the thoracic aorta, inflation of the balloon in diastole and active deflation in systole induces higher perfusion pressures in the brain and the coronary arteries in diastole and unloads the diseased heart by reducing left ventricular afterload in systole. Of special relevance is the volume shifting of about 40 ml per beat by the IABP, increasing left ventricular ejection fraction and thereby cardiac output in the range of at best 1 l/min.

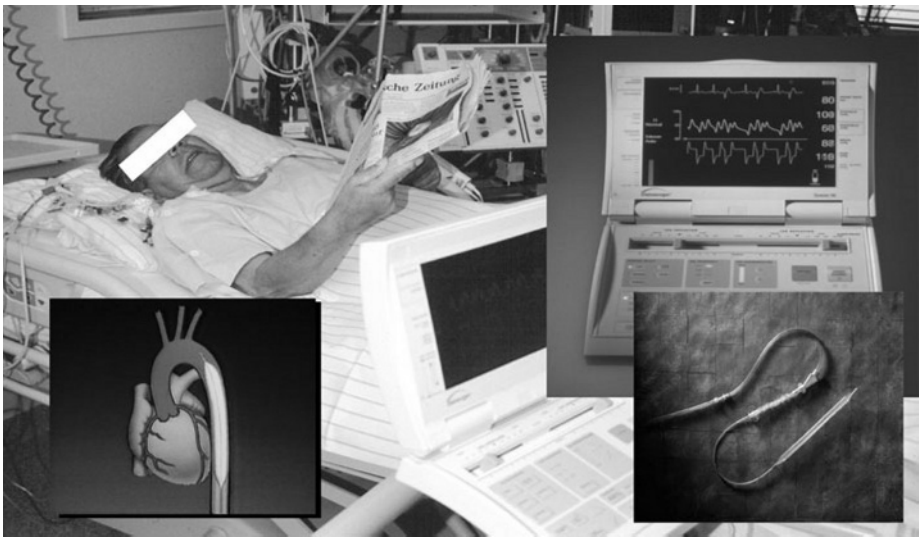

Fig. 1. Patient with myocardial infarction complicated by cardiogenic shock. After treatment with primary percutaneous coronary intervention the patient is still under adjunctive therapy with the intra-aortic balloon counterpulsation (IABP). Written permission obtained from the patient

What do the Guidelines tell Us and What about 'Real Life'?

The European STEMI (ST elevation myocardial infarction) guideline [1] states that IABP should be used in patients with myocardial infarction complicated by cardiogenic shock, with a recommendation level of grade I and an evidence level of grade C, for bridging till an interventional/surgical coronary intervention can take place. In patients with mechanical complications of myocardial infarction – ventricular septal defect and in most cases of acute mitral insufficiency – an IABP is also indicated to stabilize hemodynamic status.

The American STEMI guideline [2] recommends the use of IABP a) in STEMI patients with hypotension (systolic blood pressure less than 90 mmHg or 30 mmHg below baseline mean arterial pressure [MAP] who do not respond to other interventions (I/B); in STEMI patients with low output states (I/B); c) in STEMI patients as a stabilizing measure for angiography and prompt revascularization when cardiogenic shock is not quickly reversed with pharmacological therapy (I/B); d) in addition to medical therapy in STEMI patients with recurrent ischemic-type chest discomfort and signs of hemodynamic instability, poor left ventricular function, or a large area of myocardium at risk, as additional support to the urgently needed revascularization procedure (I/C); e) in STEMI patients with refractory polymorphic ventricular tachycardia to reduce myocardial ischemia (IIa/B); f) in STEMI patients with refractory pulmonary congestion (IIb/C); g) in STEMI patients with mechanical complications (acute mitral insufficiency due to papillary muscle rupture, ventricular septal rupture) for preoperative hemodynamic stabilization.

An IABP benchmark registry [3] presents the 'real life' of IABP applications and complications and includes a total of 5,495 patients with acute myocardial infarction. In 250 institutions worldwide, IABP implementations were documented between June 1996 and August 2001. In patients with myocardial infarction, cardiogenic shock was the most frequent indication (27.3 %), followed by hemodynamic support (27.2 %) during percutaneous coronary interventions (PCI), and support before high risk cardiac surgery (11.2 %), the latter indication – as shown recently [4] – shifting high-risk patients undergoing coronary bypass grafting into a lower-risk category. In 11.7 % of cases, mechanical complications following myocardial infarction were the indication, and in 10 %, refractory unstable post-infarction angina. Total mortality in patients with myocardial infarction was 20 %, and in patients with myocardial infarction complicated by cardiogenic shock it was 30.7 %. Severe complications of IABP insertion were seen in 2.7 % of cases, during a mean duration of IABP application of 3 days. Premature temination of IABP treatment was necessary in only 2.1 % of the patients.

Does Hemodynamic Improvement Improve Prognosis in Infarction-triggered Cardiogenic Shock?

In 5 – 10 % of all patients with myocardial infarction, cardiogenic shock develops in the acute phase, with a high mortality of at least 50 %, predominantly (80 %) as a result of left heart failure [5]. There is no doubt that cardiac pump failure due to coronary occlusion plays the dominant role in the early phase of shock. However, in prolonged shock states, development of multiple organ failure (MOF) due to impaired organ perfusion and due to the systemic inflammatory response syndrome (SIRS) determines the unfavorable prognosis. The relative importance of each of these components – cardiac impairment and failure, MOF and SIRS – becomes evi-

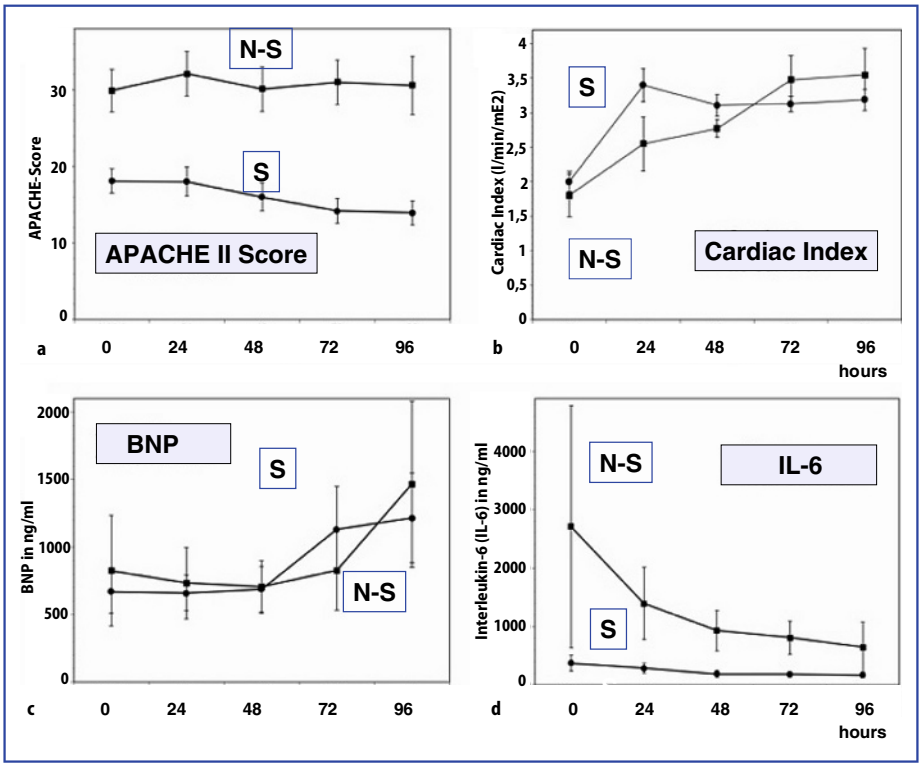

Fig. 2. The "IABP Shock" Trial [6]: What determines prognosis? Forty patients with myocardial infarction complicated by cardiogenic shock and treated with percutaneous coronary intervention (PCI) were prospectively randomized to receive or not additional hemodynamic support with IABP. In this figure, serial biomarker monitoring is presented for the 27 survivors (S) and for the 13 non-survivors (N-S) during the first 96 hours after having started treatment. APACHE II score represents severity of disease, cardiac index represents heart function, plasma B-type natriuretic peptide (BNP) represents pump failure, and serum interleukin (IL)-6 represents systemic inflammation. The values for APACHE II and for IL-6 were significantly different at all time points ($p < 0.05$) and cardiac index differed significantly at 24 hours ($p < 0.05$). BNP levels, however, were not different between the groups. Modified from [6] with permission.

dent when we look for the respective biomarkers in surviving versus non-surviving patients with myocardial infarction complicated by cardiogenic shock (**Fig. 2**; [6]). Surprisingly, cardiac index was higher in survivors only at 24 hours, and brain natriuretic peptide (BNP) levels did not differ at all. In contrast, serum interleukin (IL)-6 levels were significantly higher in survivors during the total period (96 hours). The most impressive difference between survivors and non-survivors was seen with the APACHE II score: Non-survivors had much higher initial values (29.9 ± 2.9), and the values even increased by 0.7 points to 30.6 ± 3.6 over the next 96 hours; in contrast, survivors had lower initial score values (18.1 ± 1.7), which further fell by 4.2 points to 13.9 ± 1.6. The fall in APACHE II score of > 4 points/96 hours in survivors reflects a considerable improvement in severity of MOF, with, as consequence, an improved prognosis. These findings are similar to those shown in a prospective manner in the Score-Based Immunoglobulin Therapy of Sepsis (SBITS) trial for patients with

severe sepsis and septic shock (APACHE II change from day 0 to day 4 in survivors (n = 385) was – 5.9 and in non-survivors (n = 238) was + 0.4 [7]).

Receiver operating characteristic (ROC) curves calculated for the initial biomarker values demonstrate the relative accuracy of these variables: APACHE II score 0.850; cardiac index 0.771; IL-6 0.769; BNP 0.502. Therefore, prognosis in patients with myocardial infarction complicated by cardiogenic shock is determined not only by hemodynamic impairment but also by systemic inflammation and even more by the severity of disease and development of MOF.

Effects of IABP on Hemodynamics, Systemic Inflammation and MOF in Infarction-triggered Cardiogenic Shock

As shown in **Fig. 2**, and discussed earlier, the prognosis of infarction-triggered cardiogenic shock is not only dependent on impaired hemodynamics, but also on

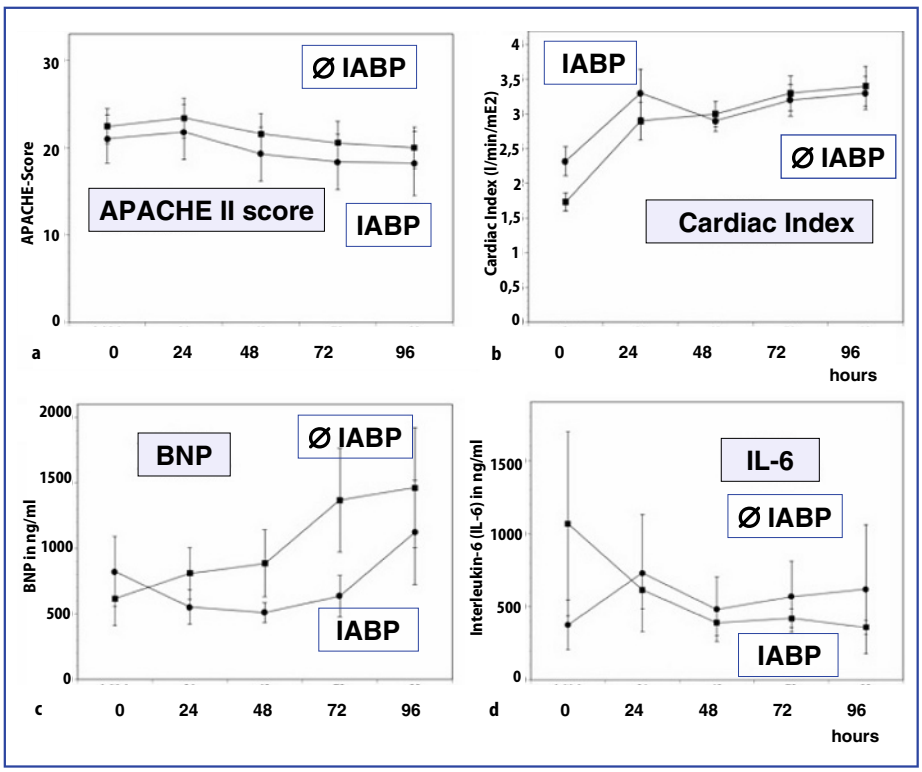

Fig. 3. The "IABP Shock" Trial [6]: Effects of adjunctive IABP therapy. Patients with myocardial infarction complicated by cardiogenic shock and treated by primary PCI were randomly assigned to receive (IABP, n = 19) or not (∅ IABP, n= 21) adjunctive support with IABP. In this figure, serial biomarker monitoring is presented during the first 96 hours after having started treatment. APACHE II score represents severity of disease, cardiac index represents heart function, plasma B-type natriuretic peptide (BNP) represents pump failure, and serum interleukin (IL)-6 represents systemic inflammation. Of all biomarker measurements, only BNP plasma levels at 48 and at 72 hours were significantly different between the groups ($p < 0.05$). Modified from [6] with permission.

shock-triggered systemic inflammation and the development of MOF. The question is whether IABP implementation can improve not only hemodynamics, but also this systemic inflammatory process finally resulting in MOF. This question was assessed by the prospective, randomized, monocenter, unblinded IABP Shock Trial [6], where we looked for the effects of early IABP therapy in 45 patients with infarction-triggered cardiogenic shock, all treated initially with primary PCI. The primary endpoint of the study was the effect of IABP on severity of disease (MOF) within the initial 96 hours, as measured by serial APACHE II scoring; secondary endpoints were the effects of IABP on cardiac output, BNP and IL-6 (**Fig. 3**). Complete data were available for 19 patients treated with IABP (IABP group) and for 21 patients without IABP (non-IABP group). Thirty-day mortality was 36.8 % in the IABP group and 28.6 % in the non-IABP group (p=n.s). The severity of disease (APACHE II score) was not improved in the IABP- compared to the non-IABP-group within the initial 96 hours, neither was cardiac index nor systemic inflammation (serum IL-6 levels). Only plasma BNP levels, at 48 and 72 hours, were significantly ($p < 0.05$) lower in the IABP patients.

What do these results tell us? In this randomized prospective trial – representative of a one-year population of patients with infarction-triggered cardiogenic shock treated in a medical intensive care unit (ICU) – we were unable to demonstrate a relevant beneficial effect of the adjunctive use of IABP. Although this trial was small, we can nevertheless conclude that the numbers needed to treat must be high concerning a possible benefit of IABP in these well-defined patients with infarction-triggered cardiogenic shock treated by primary PCI.

What Does a Meta-Analysis Tell Us?

In contrast to the numerous data from registries and non-controlled trials concerning the effects of IABP in infarction-triggered cardiogenic shock, the number of controlled trials with mortality as an endpoint are rare. A recently published meta-analysis [8] has summarized the available data:

In two separate meta-analyses, the authors looked for the effects of IABP on mortality in high-risk patients with STEMI (meta-analysis I) and in patients with STEMI complicated by cardiogenic shock (meta-analysis II). In meta-analysis I (**Fig. 4**) seven randomized trials (1,009 STEMI patients) were analyzed. Use of IABP in these patients did not reduce 30-day mortality or improve left ventricular ejection fraction; however patients treated with IABP had significantly higher complication rates, including strokes (+ 2 %) and bleeding (+ 6 %) (**Fig. 4**). Meta-analysis II (**Fig. 5**) included 9 cohorts of STEMI patients with cardiogenic shock (N = 10,529). In those patients treated with systemic thrombolysis, IABP was associated with an 18 % (95 % confidence interval 16 – 20 %; $p < 0.001$) decrease in 30-day mortality, albeit with significantly higher revascularization rates compared to patients without support. Contrariwise, in patients treated with primary PCI, IABP was associated with a 6 % increase (95 % confidence interval 3 – 10 %; $p < 0.0008$) in 30-day mortality.

This meta-analysis [8] yielded unexpected results. Consequently, we should rethink our concept of adjunctive IABP therapy in patients with myocardial infarction complicated by cardiogenic shock. First, we have to accept that in STEMI patients in general the use of IABP neither reduces 30-day mortality nor improves left ventricular ejection fraction, but increases the risk of stroke and of bleeding. Therefore, IABP cannot be recommended in general for high risk STEMI patients

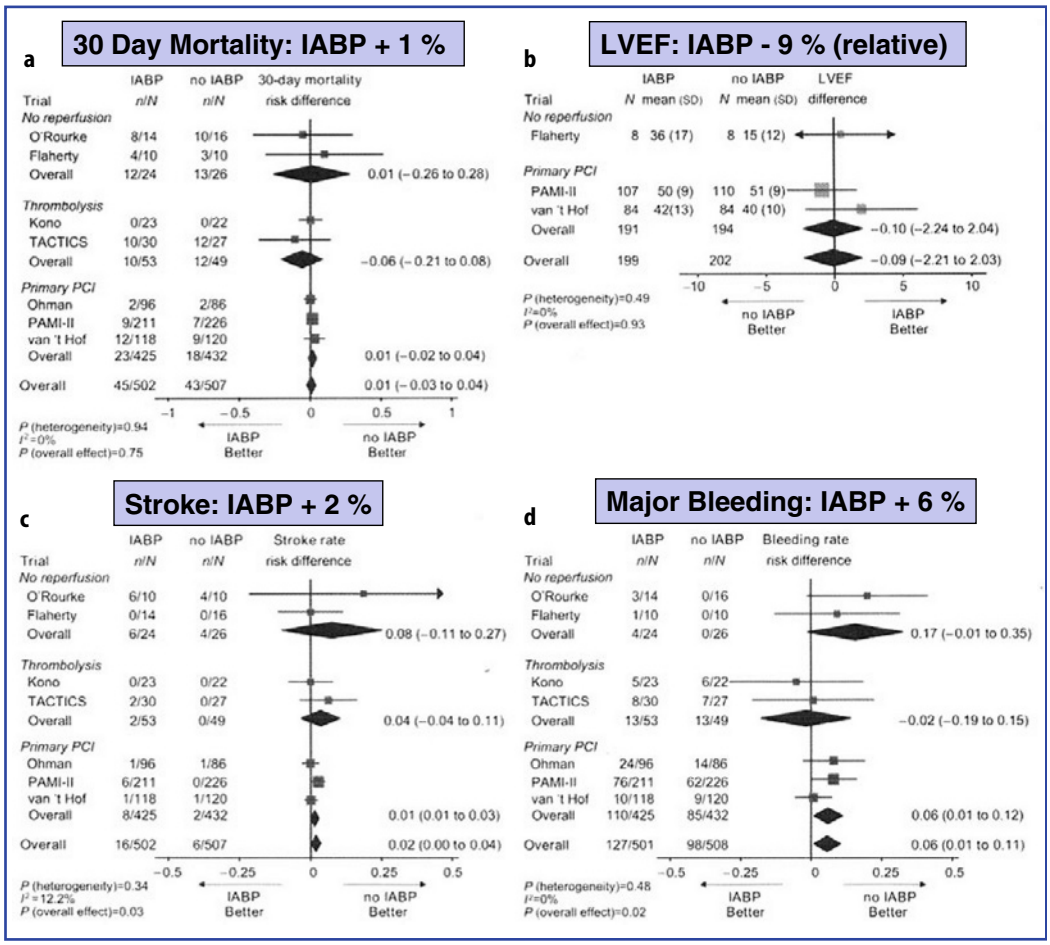

Fig. 4. Meta-analysis of randomized clinical trials of intraaortic balloon counterpulsation (IABP) therapy in patients with ST elevation myocardial infarction (STEMI). All meta-analyses show effect estimates for the individual trials, for each type of reperfusion therapy, and for the overall analysis. The size of each square is proportional to the weight of the individual trial. In panel **a**, the risk difference in 30-day mortality is shown; in panel **b**, the mean difference in left ventricular ejection fraction (LVEF); in panel **c** the risk difference in stroke; and in panel **d**, the risk difference in rate of major bleeding. PCI: percutaneous coronary intervention. Modified from [8] with permission.

without cardiogenic shock. Second, in patients with cardiogenic shock complicating STEMI, analysis is hampered by bias and confounding. What can be said is that the available observational data support IABP therapy adjunctive to thrombolysis. In contrast, observational data do not support IABP therapy adjunctive to primary PCI. To resolve these issues, we urgently need a multicenter, prospective, randomized IABP trial with mortality as an endpoint. Organization of such a study has been initiated in Germany and hopefully it will start in 2010.

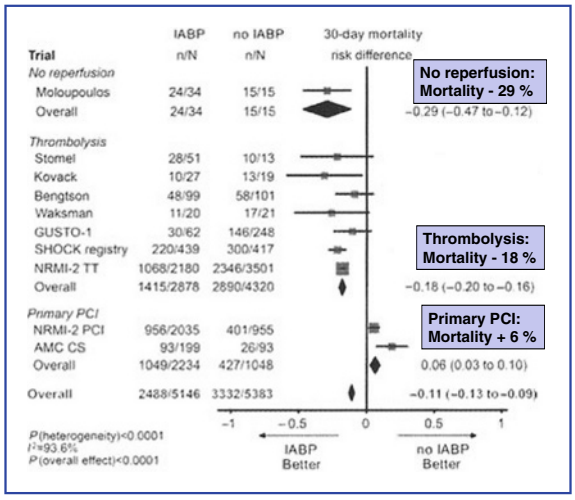

Fig. 5. Meta-analysis of cohort studies of intraaortic balloon counterpulsation (IABP) therapy in patients with ST elevation myocardial infarction (STEMI) complicated by cardiogenic shock. The risk differences in 30-day mortality for the individual studies, for each type of reperfusion therapy and for the overall analysis are given. The size of each square is proportional to the weight of the individual study. PCI: percutaneous coronary intervention. Modified from [8] with permission.

Beyond IABP: Do We Have Better Alternatives for the Treatment of Cardiogenic Shock?

A large number of surgically and percutaneously implantable left ventricular assist devices (LVAD) are available, providing better hemodynamic support for the patient than does IABP [9]. But improving hemodynamics is not everything! Coupling improvement in hemodynamics to a better prognosis is what is needed. So, the question arises as to whether this goal can be met by any of the short-term cardiovascular assist devices:

Impella® Pump

In a prospective randomized trial, 26 STEMI patients with cardiogenic shock and PCI intervention were treated adjunctively either with an Impella pump or with IABP [10]. Although cardiac index (primary endpoint) rose significantly more in the Impella group than in the IABP group (0.49 ± 0.46 vs. 0.11 ± 0.31 l/min/m^2, $p = 0.02$), 30-day mortality (one of the secondary endpoints) was identical in the two groups (46 %).

Extracorporeal Membrane Oxygenation (ECMO)

Eighty-one patients with refractory cardiogenic shock were treated adjunctively with pump-driven ECMO [11]. Hospital mortality was 42 %. At least one serious ECMO-related complication occurred in 57 % of patients. Independent predictors of ICU-mortality were: Device insertion under cardiac massage (odds ratio [OR] 22.68); 24 h urine output < 500 ml (OR 6.52); prothrombin activity < 50 % (OR 3.93), and female sex (OR 3.89). Quality of life one year after shock was less than that of matched healthy controls, but higher than that reported for patients on chronic hemodialysis, with advanced heart failure or after recovery from acute respiratory distress syndrome (ARDS). One third (16/44) of the patients had suffered from infarction-triggered cardiogenic shock; their 1-year-mortality was 31 %. A relatively simple, easy-to-apply pumpless ECMO device is the iLA Novalung [12].

Tandem Heart®

This device can pump up to 4 l/min. In 42 patients with infarction-triggered cardiogenic shock and primary PCI a Tandem Heart® or an IABP were used adjunctively in a randomized manner [13]. Hemodynamic improvement was much better in the Tandem Heart group than in the IABP group – e.g., cardiac output increase by 1.0 l/min from 3.5 to 4.5 vs increase by 0.3 l/min from 3.0 to 3.3 – but the 30-day-mortality was not significantly different (43 vs 45 %; p = 0.86). However, complications were considerably higher in the Tandem Heart® group (severe bleedings: n = 19 vs n = 8, p = 0.002; limb ischemia n = 7 vs n = 0, p = 0.09).

Assisted Extracorporeal Life-support in Adults with In-hospital Cardiac Arrest

Extracorporeal life-support as an adjunct to cardiac resuscitation has been associated with encouraging outcomes in patients with cardiac arrest. An important trial is that by Chen et al [14], which compared conventional cardiopulmonary resuscitation (CPR) and assisted extracorporeal life-support in adults with in-hospital cardiac arrest. From 975 resuscitated patients, 113 were enrolled in the conventional CPR group and 59 in the assisted extracorporeal CPR group. Patients in the assisted extracorporeal group had a significantly better outcome than those in the conventional CPR group in terms of hospital-survival (RR 0.51; 95 % confidence interval 0.35 – 0.74; p< 0.0001), 30-day mortality (RR 0.47; 0.28 – 0.77; p = 0.003), and one-year survival (RR 0.53; 0.33 – 0.83; p = 0.006).

These results [14] are very impressive, although the logistics and technology necessary are ambitious! A portable miniature version of extracorporeal life support is the Lifebridge® system [15] which can be brought to the patient for resuscitation. However, no randomized trial data are yet available for this specific system.

IABP versus Percutaneous LVAD in Cardiogenic Shock: A Meta-analysis

In comparing IABP and percutaneous LVAD in cardiogenic shock, effects on hemodynamic status and prognosis need to be evaluated, as has been done in a recent meta-analysis [16]. Three controlled trials compared the effects of IABP with LVAD systems (two trials using Impella® and one using the Tandem Heart®) in a total of 53 LVAD patients and of 47 IABP patients. The increase in cardiac index was greater in the LVAD patients than in the IABP group (+ 0.35 l/min/m^2); MAP increased to a greater extent (+ 12.8 mmHg) and pulmonary artery occlusion pressure (PAOP) decreased more (- 5.3 mmHg). However, 30-day-mortality in the LVAD group was not significantly different from 30-day mortality in the IABP group (RR 1.06). Concerning side effects, the incidence of limb ischemia was not significantly different; however, bleeding occurred 2.35-fold more often in the LVAD group.

We Should Change the Guidelines for IABP Use in Infarction-triggered Cardiogenic Shock!

In view of the data from the described meta-analysis [8], we believe we really do not have enough evidence to give a class I recommendation for the adjunctive use of IABP in all STEMI patients with cardiogenic shock, as has been made by the European [1] and the American [2] Cardiological Societies (see above). A German-Aus-

trian expert team are developing a guideline for infarction-triggered cardiogenic shock (Werdan et al., unpublished data] and took this meta-analysis into account to make the following recommendations:

- Adjunctive IABP therapy is indicated in cases of primary systemic thrombolysis in patients with infarction-triggered cardiogenic shock.
- Adjunctive IABP use can be considered in cases of primary PCI in patients with infarction-triggered cardiogenic shock; whether this will be helpful, is unclear.
- If an emergency PCI is not possible and the patient with infarction-triggered cardiogenic shock is treated with systemic thrombolysis, then an IABP should be inserted for hemodynamic stabilization and the patient should be transported to a PCI center.
- When a mechanical complication of myocardial infarction occurs – ventricular septal defect and acute severe mitral insufficiency – then IABP should be inserted for hemodynamic stablilization before the patient is transferred to cardiac surgery.
- Percutaneous LVAD can undoubtedly improve hemodynamics more than IABP. However, it has not yet been shown that this hemodynamic improvement results in a better prognosis. Therefore, no general recommendation for LVAD in refractory cardiogenic shock should be given (although this is the case in the European STEMI guidelines [1]); the decision to use a percutaneous LVAD should be made on an individual basis.
- In-hospital cardiac arrest has a very unfavorable prognosis. Assisted extracorporeal life-support may represent a real progress in resuscitating these patients, although the logistics and the technology are ambitious!

Intra-aortic Balloon Counterpulsation in Septic Shock?

In severe sepsis and septic shock, every second death is due to refractory cardiovascular shock [17]. Most intensivists would attribute this cardiovascular shock primarily to refractory vascular shock and not to myocardial depression: Septic shock typically presents as a hyperynamic, high cardiac output, low systemic vascular resistance (SVR) state. However, one quarter of adult patients and even more children with fluid refractory septic shock have a hypodynamic cardiovascular profile [18]. Furthermore, one would assume that the dramatic reduction in afterload seen in septic shock may trigger an even higher cardiac output than that seen under normal afterload conditions. With this in mind, it becomes obvious that 'septic cardiomyopathy' contributes more to the septic shock state than is often suggested: 40 % of patients have a cardiac output corresponding to only 60 – 80 % of the expected value, and in a further 40 % of the patients, cardiac output is even worse [19, 20]. Consequently, supporting the heart not only by inotropes but also by mechanical assist devices, like IABP, could be helpful to rapidly improve the deleterious shock state.

In an experimental model of septic shock, use of IABP as an adjunctive measure was studied thoroughly [18]. In this hypodynamic, mechanically ventilated canine sepsis model triggered by intrabronchial *Staphylococcus aureus* challenge, IABP therapy showed some beneficial effects: In the animals receiving the highest bacterial dose, IABP improved survival time by 23 hours – but not survival – and lowered SVR index as well as norepinephrine requirements. On the negative side was the increase in blood urea nitrogen and creatinine. The authors [18] claim that because

of their findings in this animal model, a randomized controlled trial of IABP therapy may be indicated in carefully selected patients with low cardiac output septic shock and a high risk of death. As cardiac function is similarly depressed in patients with Gram-positive and Gram-negative septic shock [21], this finding could apply to a broad spectrum of septic patients.

But what can we really expect from the use of an IABP in a patient with hypodynamic septic shock [22]? We have the results of Solomon and colleagues [18] on Gram-positive septic shock in dogs that showed some beneficial effects. In newborn lambs infected with group B streptococci, septic shock was improved by IABP as indicated by an increase in cardiac output and a decrease in pulmonary resistance [23]. On the other hand, in a porcine model of endotoxemic shock, IABP was of no benefit [24]. Clinical data are anecdotal and were published more than a quarter of a century ago [25–27], showing beneficial effects in patients with cold extremities and low cardiac output, but not in those with warm extremities and high cardiac output. Finally, an interesting patient group for the IABP approach may be patients with cardiogenic shock complicating myocardial infarction, superimposed by sepsis, amounting to 18 % of the total population [28, 29]. In nearly all of these patients, IABP has been applied, with a higher median duration of IABP in septic than in non-septic cardiogenic shock patients, but not with a greater number of complications [28].

How, at best, could IABP help us in treating our patients with septic shock? We should not expect a lowering of mortality by use of the IABP itself; this has not been shown yet, even for the best validated IABP indications. But what we could expect is a lowering of the dosages of potentially detrimental vasopressors and a prolongation of survival time [18]. This prolongation of survival time could be used to enable causal anti-sepsis therapy time to work. Knowing that prognosis depends on 'early goal directed therapy', we should start very early in the process, because IABP needs more than three and up to 24 hours to be fully effective [30]. We also need to watch carefully whether worsening of renal function under IABP may override any beneficial IABP effects. Although complications of IABP are rare, they may be higher in septic shock owing to coagulation problems due to septic disseminated intravascular coagulation.

However, the most important consideration when thinking about IABP therapy in septic shock is how to precisely define the patient with 'hypodynamic septic shock'. What we need is a quantitative description of the extent of myocardial depression and a quantitative description of the sepsis-induced reduction in afterload, as measured by the SVR. Only when we correlate cardiac output with the SVR, can we clearly estimate the 'real' extent of cardiac output reduction [19, 20]. The 'ideal' patient for IABP would be the septic patient with a highly depressed myocardial function and an SVR that is not severely reduced. We could control the success of IABP treatment by following the cardiac power index/output, which is of prognostic relevance in patients with cardiogenic shock [31]. Finally, if we are thinking about mechanical hemodynamic support in patients with septic shock, perhaps we should move beyond the narrow limits of IABP to percutaneous LVADs, like the Impella® pump, which are able to provide more efficient hemodynamic support than IABP. This approach seems reasonable in view of ongoing attempts in patients with cardiogenic shock (see earlier). Nevertheless, improved survival and not hemodynamic improvement is the final goal.

Conclusion

The use of IABP in the adjunctive treatment of cardiogenic shock is accepted even at the guideline level. However, the promise of IABP use as an evidence-based standard procedure is by no means fulfilled. This is especially the case when we consider IABP use in the large group of patients with myocardial infarction complicated by cardiogenic shock: Available low quality study evidence may favor IABP use when patients are treated with systemic thrombolyis, but in patients treated with primary PCI, IABP use may even be detrimental. Unfortunately, percutaneous LVADs – although hemodynamically more efficient than IABP – have not shown superiority over IABP with respect to prognosis. The recent STEMI guidelines concerning the use of IABP in patients with infarction-triggered cardiogenic shock need to be revised, and, furthermore, we need a randomized controlled IABP trial for these patients, with mortality as the primary endpoint.

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IV Inflammatory Responses in the Lung

Vascular Endothelial Growth Factor in Acute Lung Injury

V. D'Souza, R.C.A. Dancer, and D.R. Thickett

IV

Introduction

Increased permeability and interstitial and pulmonary edema are prominent features of acute lung injury (ALI)/acute respiratory distress syndrome (ARDS) [1]. Vascular endothelial growth factor (VEGF) and its receptors have been implicated in the regulation of vascular permeability in many organ systems, including the lung. Data extrapolated from other organs and animal experiments have suggested that over-expression of VEGF would, therefore, be harmful within the lung. Recent data, from animal models as well as from patients with ALI, have shown decreased levels of VEGF in the lung. It is clear that the regulation of pulmonary vascular permeability and the roles of VEGF expression in the lung are complex. In this chapter, we explore the literature looking at the expression and function of VEGF in animal models of ALI and in patients with ALI. Novel evidence points to a potential role of VEGF in promoting repair of the alveolar-capillary membrane during recovery from ALI. Pro-VEGF therapy may therefore have potential as a rescue therapy for alveolar epithelial damage in ALI.

Biology of VEGF

In order to interpret the evidence about VEGF in ALI, it is essential to understand its biology and relevant cellular effects. VEGF-A is a subgroup of the platelet derived growth factor family [2]. Other members are placenta growth factor (PLGF), VEGF-B, VEGF-C and VEGF-D. A number of VEGF-related proteins have also been discovered encoded by viruses (VEGF-E) and in the venom of some snakes (VEGF-F). The most studied member of the family is VEGF-A upon which this chapter will focus.

Alternate splicing of the VEGF-A gene leads to the generation of splice variants/isoforms of VEGF of differing sizes which are denominated by the number of amino acids in the protein (**Table 1**) [3]. The predominant isoform expressed within the lung and the circulation is VEGF165. The longer isoforms contain a heparin binding domain coded by exons 6 and 7 and are predominantly bound to the extracellular matrix, whereas the shorter molecules such as VEGF121 are freely soluble. Recently, a whole new class of inhibitory isoforms of VEGF which are anti-angiogenic, generated by alternate splicing of exon 8 [4], have been discovered but their expression and functional importance within the lung is unknown.

Table 1. Isoforms of vascular endothelial growth factor (VEGF)

Isoform	Size+	Coding exons	Properties
VEGF121	121	1–5,8	Soluble and secreted
VEGF145	145	1–6,8	Binds NRP2 but not NRP1
VEGF165	165	1–5,7,8	Main biologically active isoform, binds NRP1 and NRP-2
VEGF165b	165	1–5,7, alternative 8	Secreted inhibitory isoform*
VEGF183	183	1–5, short exon 6,7,8	Bound to ECM**
VEGF189	189	1–8	Bound to ECM**
VEGF 206	206	1–8 plus extra 6-encoded sequence	Bound to ECM**

+ amino acids; ECM: extracellular matrix; NRP: neuropilin; * $VEGF_{xxxb}$ inhibitory forms have been identified for the other VEGF isoforms; ** released from ECM by proteolytic cleavage into smaller forms.

VEGF Receptors

VEGF isoforms signal via the tyrosine kinase receptors, VEGFR-1 (also known as FLT-1) and VEGFR-2 (also known as KDR). These receptors were initially thought to be largely confined to the vascular bed (on endothelial cells), but studies in animal and human lung confirm expression in lung tissue on activated macrophages and respiratory epithelial cells, especially type II cells.

Most of the angiogenic activities of VEGF as well as its effects on vascular permeability are mediated by its receptor VEGFR-2. The proliferative and anti-apoptotic effects of VEGF on endothelial cells are also VEGFR-2 dependent. The function of VEGFR-1 is controversial with data suggesting that it acts as a decoy receptor, but it has been reported to have functional importance in some cell lines, e.g., monocyte chemotaxis. Isoforms of VEGF that express the amino acid sequence from exon 7 (e.g., VEGF165 but not VEGF121) also bind neuropilin 1 and neuropilin 2, which are expressed on endothelial cells. Such interactions enhance activation of VEGFR-2 and may account for the greater mitogenic activity of VEGF165 over VEGF121.

Cellular Source of VEGF within the Lung

VEGF expression has been found in perivascular cells in most human tissues. VEGF mRNA is highest in the spleen, kidney and the lung. Within the lung, mRNA expression is primarily located in epithelial cells and vascular smooth muscle cells with protein production believed to be highest by alveolar type II cells [5]. During acute inflammation, however, both neutrophils and macrophages can produce VEGF and contribute to its alveolar levels [6].

Cellular Actions of VEGF

The known effects of VEGF-A on primary human pulmonary cell lines are outlined in **Table 2**. Although studies have reported that VEGF increases vascular leakage, the cellular mechanisms underlying the hyperpermeability have not been fully eluci-

Table 2. The known effects of vascular endothelial growth factor (VEGF)-A on primary human pulmonary cell types.

Cell type	Biological function
Pulmonary artery endothelial cell	Proliferation [29] Increases permeability of monolayers *in vitro* [16] Anti-apoptotic [29]
Human adult small airway	Proliferation [30] Increases wound repair *in vitro* [30] Anti-apoptotic to FasL and oxidant species [30]
Human fetal alveolar type II cell	Increases choline incorporation in saturated phosphatidylcholine [31] Increases surfactant protein B (SP-B) mRNA (4 fold) [31] Slows transdifferentiation of type II cells into type I cells [31] Possible effect on proliferation (controversial) [7, 31]
Adult normal human type II cells	Proliferation in 50 % sub-confluent culture[1] Promotes wound repair *in vitro*[1] Increases SP-D but not SP-B secretion[1] Delays transdifferentation[1] Increases soluble RAGE production[1] No effect upon monolayer protein permeability *in vitro*[1] Anti-apoptotic to FasL but not oxidant species[1]
Human peripheral blood monocyte	Chemotaxis (mediated by VEGFR-1) [32]

[1] DR Thickett, unpublished data; RAGE: receptor for advanced glycation endproducts

dated. Contrary to the name, it has also become clear that VEGF is a growth factor for lung epithelial cells, as well as endothelial cells, causing proliferation, stimulating wound repair *in vitro* and protecting against oxidant injury and apoptosis.

VEGF as a Pathophysiological Driver of Acute Lung Injury?

The biological properties of VEGF, especially its effects upon capillary permeability, have led to the hypothesis that it has a predominantly injurious role in ALI. Many experiments *in vitro* have demonstrated upregulation of VEGF secretion by pro-inflammatory cytokines, such as interleukin (IL)-6 and tumor necrosis factor (TNF), which have been implicated in the pathogenesis of ALI [7]. Indeed adenoviral over-expression of VEGF in mice leads to non-cardiogenic pulmonary edema and increased pulmonary capillary permeability [8]. Unfortunately, the levels of VEGF induced in that model were not reported, and as such the overwhelming expression of VEGF in this model may not be representative of ALI in humans.

In a subsequent study, transgenic mice over-expressing VEGF developed pulmonary hemorrhage, alveolar remodeling, and macrophage accumulation as early as 2 weeks of age. Electron microscopy demonstrated abnormal alveolar capillary endothelium in the VEGF transgenic mice. Over expression of VEGF in the neonatal lung resulted in increased infant mortality compared to control animals [9]. In LPS-induced murine lung injury, immunostaining for VEGF increased early after challenge, associated with the recruitment of macrophages and neutrophils to the alveolar space [10]. Thus it seems that, in the earliest part of experimental lung injury, VEGF levels may be increased, and this may be associated with alveolar edema – at least in animals.

Not all animal studies support the pathophysiological role of VEGF as being harmful in ALI. Thus, recovery from hyperoxic lung injury in rabbits is associated with elevated alveolar VEGF levels [11]. VEGF plays a central role in IL-13 induced protection against hyperoxic lung damage in transgenic mice [12]. Intratracheal VEGF administration ameliorated the extent of lung inflammation and edema in LPS treated mice, an effect that was associated with reduced apoptosis in alveolar epithelial cells. These findings are compatible with the observed loss of alveolar tissue and an emphysema phenotype in mice chronically treated with the VEGFR-2 antagonist SU5416 [13]. In addition, intra-tracheal delivery of VEGF165 to neonatal transgenic mice deficient in hypoxia-inducing factor (HIF)-2α (who develop a fatal respiratory distress syndrome in the neonatal period and have low lung VEGF levels) protected them against developing respiratory distress in part by elevated surfactant protein production [14]. Thus, the role of VEGF in the pathophysiology of experimental ALI remains controversial and a major limitation for these studies is the lack of adequate animal models of human ALI.

VEGF Compartmentalization in Acute Lung Injury

It has been recognized that VEGF protein levels within epithelial lining fluid are around 10 ng/ml – approximately 500 times higher than normal plasma levels [15]. To date several studies have looked at protein levels of VEGF in bronchoalveolar lavage (BAL) fluid, epithelial lining/edema fluid, and plasma of patients with ALI [6, 16, 17]. Most, but not all, BAL fluid studies have demonstrated reduced VEGF levels – with a remarkably consistent relationship to the severity of lung injury. Epithelial lining fluid levels measured by bronchoscopic micro sampling demonstrated that VEGF levels were higher in survivors than non-survivors [18]. Thickett et al. demonstrated that resolution of lung injury was associated with a local upregulation of VEGF within the lung [6]. VEGF levels were also upregulated in the epithelial lining fluid of patients with ALI by day 4 of treatment with intravenous salbutamol [19].

In contrast, VEGF protein levels are elevated in the plasma of patients with ALI and sepsis [16]. Plasma VEGF levels from ALI patients were highest in those who died and decreased during recovery from lung injury [16]. However, the relationship between plasma VEGF and survival has not been confirmed in all studies [20], and reported plasma levels vary significantly between studies. This may in part be due to confounding effects of differing etiologies – since sepsis on its own is associated with elevated plasma VEGF levels [21].

Tissue Studies

The results of the BAL fluid and epithelial lining fluid studies are backed up by tissue studies which demonstrate reduced VEGF levels in whole lung homogenate from subjects with ARDS, with VEGF levels negatively correlating with the number of apoptotic endothelial cell counts by TUNEL staining [22]. Increased VEGF isoform expression (VEGF121, VEGF165 and VEGF189) has also been reported later in ARDS in comparison to both normal subjects and early ARDS [23]. A recent study further demonstrated upregulation of VEGFR1 and VEGFR2 on both sides of the alveolar-capillary barrier in later ARDS tissue [5], perhaps supporting an increased bioactivity of VEGF at these later stages of lung injury.

Regulation of VEGF Bioactivity

The mechanisms of the reduced VEGF levels seen in ALI are likely to be multifactorial – in part related to alveolar flooding, type II epithelial cell apoptosis, proteolytic degradation by proteases, as well as suppression of mRNA expression due to the effects of hyperoxia. Most inflammatory cytokines, which are known to be elevated in BAL fluid of ALI patients, stimulate VEGF expression in a variety of cultured cells and, consequently, do not explain the decrease in VEGF in BAL fluid of the ARDS patients [22]. VEGF bioactivity is further subject to functional regulation including by VEGF receptors and co-receptors. These receptors are themselves subject to functional regulation by oxygen tension and VEGF itself.

In addition, several soluble inhibitors which bind VEGF (sVEGFR-1, sVEGFR-2, alpha-2 macroglobulin) or its receptors (endostatin binds VGEFR-2) are elevated in the lung during ALI, therefore reducing the bioactivity of VEGF within the alveolar space [24, 25]. Given that cumulatively these proteins are present in much higher molar quantities than VEGF-A, it is likely that VEGF has little alveolar bioactivity once lung injury has developed.

Is there a Unifying Hypothesis for the Role of VEGF in Acute Lung Injury?

With increasing knowledge of the effects of VEGF within the lung it seems likely that the role of VEGF differs according to the stage of lung injury. At the earliest onset of ALI, differing insults such as bacterial wall products/lipopolysaccharide (LPS), and pro-inflammatory cytokines may stimulate the production and release of VEGF from alveolar type II cells, macrophages and neutrophils. This hypothesis is supported by recent reports of elevated VEGF in the BAL fluid of human volunteers after nebulized LPS challenge. In addition, peripheral tissue hypoxia associated with sepsis may increase circulating VEGF levels [21]. As such, the alveolar endothelial-epithelial barrier may be exposed to higher than normal concentrations of VEGF, which may promote a functional vascular leak and non-cardiogenic pulmonary edema (**Fig. 1**) [26]. As the lung injury persists or worsens, however, with the loss of type I and type II cells, alveolar protease release, and the influence of inhibitors/hyperoxic conditions, alveolar VEGF levels decrease. This effect is observed within 24 hours of onset of lung injury [25]. During recovery from lung injury, when type II cells begin proliferating to restore the alveolar epithelial barrier, VEGF production by these cells probably has an autocrine tropic effect as well as a paracrine effect upon endothelial cells to promote alveolar repair.

Conclusion

VEGF was originally described as a specific angiogenic and permeability-inducing factor and its function was considered to be specific for endothelial cells. However, emerging evidence has revealed that the VEGF/VEGFR system has many more biological roles and great complexity. The original hypothesis that VEGF was a foe in the pathogenesis of ALI was based in part upon extrapolation from the effects of VEGF upon other vascular beds. However, it is important to remember that unlike many vascular beds in which the endothelium is the tight barrier preventing tissue

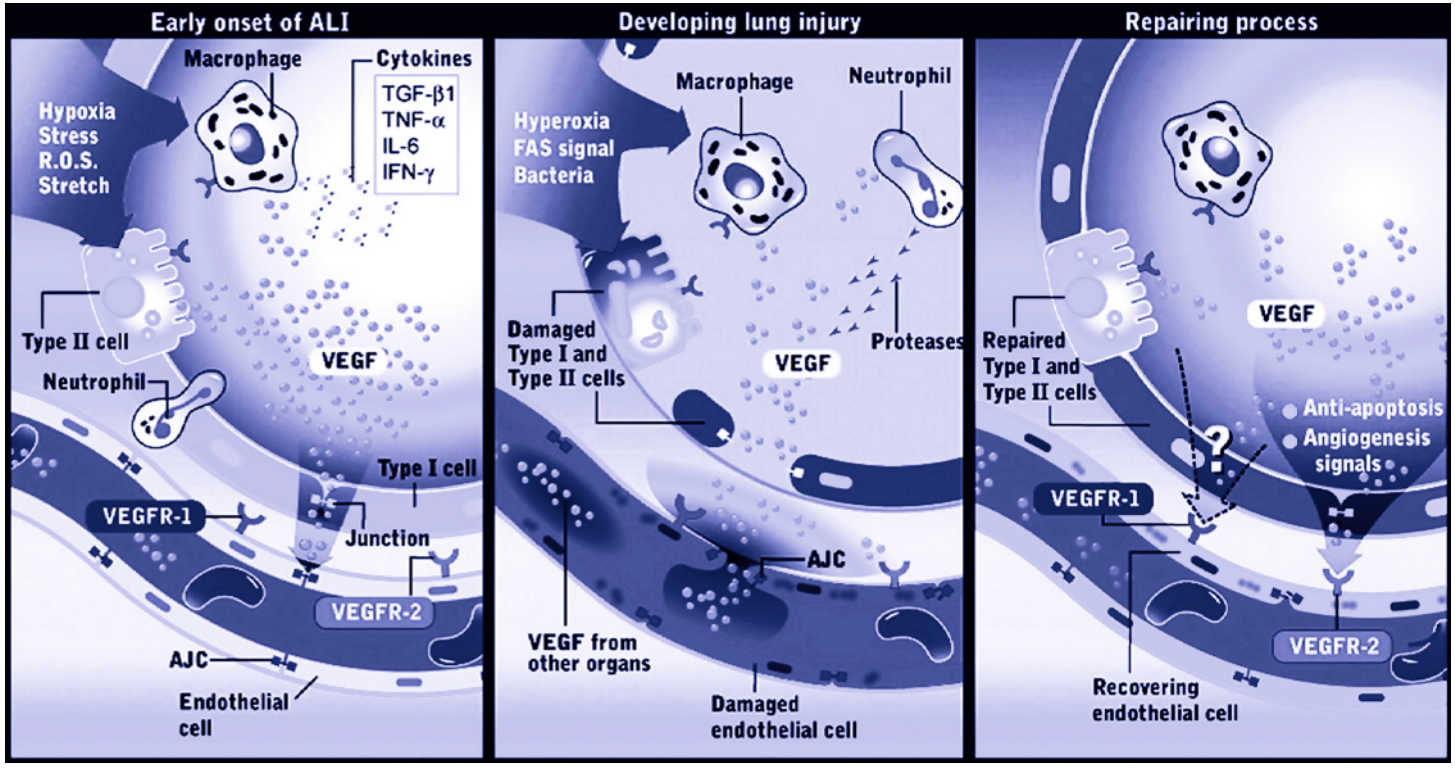

Fig. 1. Overall hypothesis of the role of vascular endothelial growth factor (VEGF) in acute lung injury (ALI). Early onset of ALI: VEGF levels are increased which promotes functional pulmonary edema. Developing lung injury: VEGF levels decrease due to epithelial damage, and loss of compartmentalization of VEGF may mean that VEGF "leaks out" into the circulation. Repairing process: During successful repair of alveolar epithelial damage, type I and type II cells are repaired, and VEGF production can increase again, which may contribute to the repair and angiogenesis by acting on VEGFR-2 on endothelial and alveolar epithelial cells. TNF: tumor necrosis factor; TGF: transforming growth factor; IL: interleukin; IFN: interferon; ROS: reactive oxygen species; AJC: adherens junction complexes. From [26] with permission.

edema, the lung has a dual endo-epithelial barrier. It is the alveolar epithelial barrier that forms the main barrier to alveolar flooding and adult human epithelial cells do not seem to increase permeability in response to VEGF. Indeed, considerable evidence now supports a beneficial role of VEGF within the lung, as its loss is associated with lung immaturity, pulmonary hypertension, emphysema, and the repair stage of ALI [27]. Thus, in conclusion, early in ALI, VEGF may lead to enhanced capillary permeability in active sites of inflammation. However, once the disease is initiated, lung levels of VEGF decrease, which may limit the ability of the alveolar epithelium to repair itself. Pro-VEGF therapy may, therefore, have potential as a rescue therapy for alveolar epithelial damage in ALI and warrants further study.

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Role of CD14 in Lung Inflammation and Infection

A. Anas, T. van der Poll, and A.F. de Vos

IV

Introduction

Toll-like receptors (TLR) on the surface of cells of the respiratory tract play an essential role in sensing the presence of microorganisms in the airways and lungs. These receptors trigger inflammatory responses, activate innate immune responses, and prime adaptive immune responses to eradicate invading microbes [1]. TLR are members of a family of pattern-recognition receptors, which recognize molecular structures of bacteria, viruses, fungi and protozoa (pathogen-associated molecular patterns or PAMPs), as well as endogenous structures and proteins released during inflammation (damage/danger-associated molecular patterns or DAMPs). To date, ten different TLR have been identified in humans and twelve in mice. TLR are expressed on all cells of the immune system, but also on parenchymal cells of many organs and tissues. The binding of a PAMP to a TLR results in cellular activation and initiates a variety of effector functions, including cytokine secretion, proliferation, co-stimulation or phagocyte maturation. To facilitate microbial recognition and to amplify cellular responses, certain TLR require additional proteins, such as lipopolysaccharide (LPS) binding protein (LBP), CD14, CD36 and high mobility group box-1 protein (HMGB-1). In this chapter, the role of CD14 as an accessory receptor for TLR in lung inflammation and infection is discussed. The central role of CD14 in the recognition of various PAMPs and amplification of immune and inflammatory responses in the lung is depicted in **Figure 1**.

CD14 was characterized as a receptor for bacterial endotoxin (LPS) in 1990, almost a decade before the discovery and characterization of TLR, and can be regarded as the first described pattern-recognition receptor [2]. The protein was first identified as a differentiation marker on the surface of monocytes and macrophages and was designated CD14 at the first leukocyte typing workshop in Paris in 1982. The genomic DNA of human CD14 was cloned in 1988 and the gene was later mapped to chromosome 5q23–31. Several polymorphisms have been found in the CD14 gene, of which nucleotide polymorphisms at position –159 and –1619 correlated with decreased lung function in endotoxin-exposed farmers [3].

The CD14 gene consists of two exons which code for a single mRNA that is translated into a protein of 375 amino acids. The CD14 protein is composed of eleven leucin-rich repeats, which are also found in TLR and which are important in PAMP binding. Moreover, the crystal structure of CD14 revealed that the protein has a 'horse-shoe' shape, similar to TLR4, and that LPS is bound within the pocket [4]. In contrast to TLR, however, CD14 lacks a transmembrane domain, and thus cannot initiate intracellular signal transduction by itself. The CD14 protein is processed in the endoplasmatic reticulum and expressed as a 55 kDa glycoprotein on the cell sur-

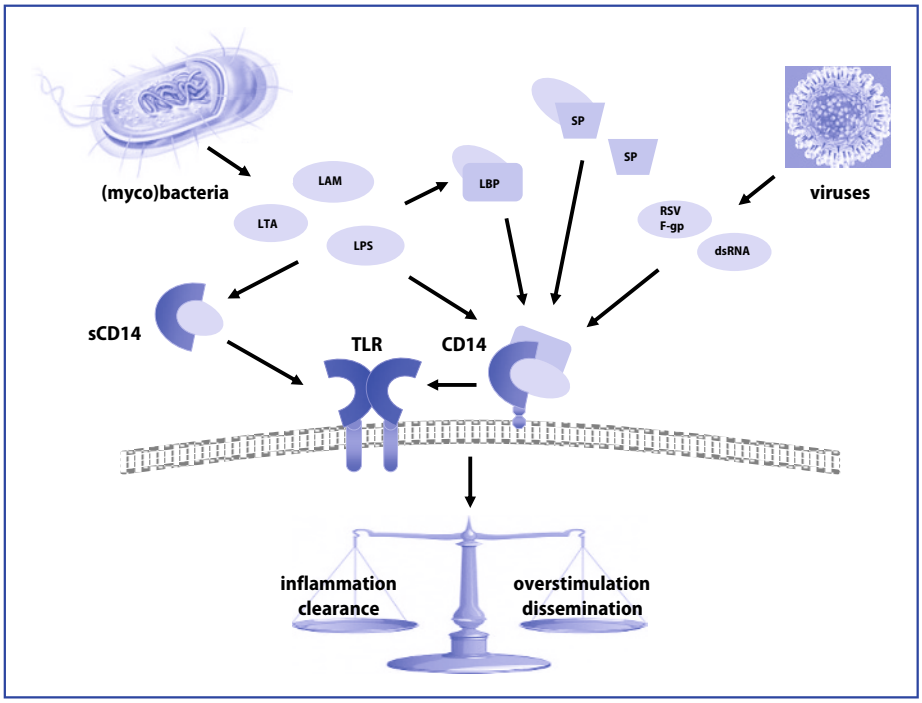

Fig. 1. Central role of CD14 in pathogen- and pathogen-associated molecular pattern (PAMP)-induced responses in the lung. CD14, which lacks an intracellular domain for signal transduction, is expressed on the surface of alveolar macrophages, infiltrating monocytes and neutrophils, and at lower levels also on epithelial and endothelial cells in the lung. CD14 recognizes and binds various structures from invading microbes, such as lipopolysaccharide (LPS) from Gram-negative bacteria, lipoteichoic acid (LTA) from Gram-positive bacteria, lipoarabinomannan (LAM) from mycobacteria, viral double stranded (ds) RNA and F glycoprotein (F-gp) from respiratory syncytial virus (RSV). CD14 subsequently transfers these bound components to Toll-like receptors (TLR) which than trigger cell activation. Binding of LPS to CD14 is regulated by additional accessory receptors in the lung, including LPS-binding protein (LBP) and a number of surfactant proteins (SP). Furthermore, soluble CD14 (sCD14) enhances LPS-induced activation of cells with low CD14 expression. Depending on the microbe and the PAMPs it expresses, CD14-amplified responses can either be beneficial to the host by induction of an adequate inflammatory and immune response to eradicate the invading microbe, or detrimental to the host by excessive inflammation and/or dissemination of the pathogen.

face via a glycosylphosphatidyl (GPI) anchor [5]. Like other GPI-anchored proteins, CD14 accumulates on the cell surface in microdomains known as lipid rafts, which are fairly rich in cholesterol and accumulate several kinases at the intracellular site. CD14 is expressed predominantly on the surface of 'myeloid' cells, such as monocytes, macrophages and neutrophils, but at lower levels also on epithelial cells, endothelial cells and fibroblasts.

In addition to being expressed as a GPI-anchored membrane protein, CD14 is also expressed in a soluble form (sCD14) [2]. sCD14 may result from secretion of the protein before coupling to the GPI anchor or from shedding or cleavage from the surface of monocytes. sCD14 is present in the circulation and other body fluids and levels of sCD14 in plasma increase during inflammation and infection. Since inter-

leukin (IL)-6 induces sCD14 expression in liver cells it is regarded as an acute phase protein. In bronchoalveolar lavage (BAL) fluid from patients with acute respiratory distress syndrome (ARDS), sCD14 levels were strongly increased and correlated with total protein levels and neutrophil numbers in the BAL fluid [6], suggesting that sCD14 contributes to the inflammatory process in the lung.

CD14 is a molecule with a wide range of functions. In addition to functioning as a pattern recognition receptor for a variety of microbial ligands, CD14 also acts as a receptor for endogenous molecules like intercellular adhesion molecule (ICAM)-3 on the surface of apoptotic cells, amyloid peptid, ceramide, and urate crystals. Ligation of CD14 by these ligands, except for apoptotic cells, mediates activation of inflammatory responses.

CD14 and the LPS Receptor Complex

LPS is the major constituent of the outer membrane of Gram-negative bacteria and is one of the most potent TLR ligands. CD14 together with LBP plays an essential role in binding of LPS to the TLR4/MD-2 complex [7]. LBP, which, among others, is present in the bloodstream and BAL fluid [8], binds to LPS aggregates and transfers LPS monomers to CD14. CD14 associates with TLR4/MD-2 and transfers the LPS monomer to this complex [7]. Likewise, sCD14 is able to mediate LPS-activation of cells with low membrane CD14 expression, such as epithelial and endothelial cells [9]. However, at high concentrations, LBP and sCD14 are also able to downregulate LPS-induced responses by transfer of LPS to lipoproteins for subsequent removal [10]. Recent data indicate that LPS is bound by MD-2 within the TLR4/MD-2 complex [11] and that subsequent conformational changes in TLR4 lead to reorganization of its cytoplasmic domain, enabling the recruitment of the adaptor proteins, myeloid differentiation primary-response protein 88 (MyD88) and TIR-domain-containing-adaptor-protein-inducing-interferon (IFN)-β (TRIF) [12]. These adaptors initiate signal transduction to the nucleus by activation of nuclear factor (NF)-κB and IFN regulatory transcription factor (IRF)-3, leading to the production of cytokines that regulate inflammatory cells [12]. In macrophages, TRIF-dependent signaling is essential for the expression of the majority of LPS-induced genes, including IFN-α/β.

Recently, it was reported that, in the absence of CD14, the TLR4/MD-2 complex can distinguish between different chemotypes of LPS [13]. Smooth LPS is synthesized by most Gram-negative bacteria and consists of three modules: The lipid A moiety, a core polysaccharide, and an O-polysaccharide of variable length (made up of 1 to over 50 monosaccharide units) [7]. Gram-negative bacteria that fail to add the core polysaccharide or the O-polysaccharide chain to the lipid A moiety produce 'rough' LPS, named after the rough morphology of the colonies these bacteria form. Lipid A, the bioactive part of both smooth and rough LPS, is responsible for most of the pathogenic effects in Gram-negative bacterial infections [7, 12]. Murine macrophages lacking CD14 secreted equal amounts of tumor necrosis factor-α (TNF) to macrophages expressing CD14 upon stimulation with rough LPS, but failed to secrete TNF in response to smooth LPS, an effect which was reversed by addition of sCD14 [13]. Moreover, macrophages lacking CD14 failed to secrete IFN-α/β in response to either rough or smooth LPS. These findings indicate that CD14 is required for activation of the TLR4/TRIF pathway by either smooth or rough LPS, and required for the activation of TLR4/MyD88 pathway by smooth but not by

rough LPS [13]. In addition to LPS, CD14 also facilitates TLR4 activation by other PAMPs including certain viral components [13, 14].

In the lung, binding of LPS to TLR4 is influenced by a number of surfactant proteins (SP), including SP-A, SP-C and SP-D [15]. These surfactants are able to influence the interaction between TLR4 and LPS by direct binding to LPS; i.e., SP-A binds to rough LPS and lipid A, but not to smooth LPS, SP-C also binds to rough LPS, and SP-D binds to both rough and smooth LPS. SP-A and SP-C binding to LPS inhibits TNF secretion by alveolar macrophages, whereas SP-D binding to LPS moderately enhances TNF secretion by alveolar macrophages. In addition, SP-A, SP-C and SP-D also bind to CD14 at the site which recognizes LPS. Strikingly, binding of SP-A to CD14 enhanced the binding of rough LPS and binding of SP-C to CD14 augmented binding of smooth LPS [15], whereas binding of SP-A to CD14 reduced binding of smooth LPS and binding of SP-D to CD14 decreased binding of both smooth and rough LPS. Furthermore, SP-D influences LPS-induced TNF secretion by alveolar macrophages by regulating matrix metalloproteinase-mediated cleavage of CD14 from the surface of these cells [16].

Together, these findings suggest that LPS recognition in the lung and subsequent induction of inflammatory immune response is a complexly regulated process.

CD14 and other Pattern Recognition Receptors

In addition to LPS-induced activation of TLR4, CD14 also amplifies a number of TLR-dependent responses triggered by other bacterial PAMPs, including peptidoglycan, lipoteichoic acid (LTA) and lipoarabinomannan (LAM) [17–19].

Peptidoglycan is an essential cell wall component of virtually all bacteria. Peptidoglycan is a polymer of N-acetylglucosamine and N-acetylmuramic acid, cross-linked by short peptides. Breakdown products of peptidoglycan are recognized by different classes of pattern-recognition receptors [19]. Polymeric soluble peptidoglycan is recognized by TLR2 on the surface of cells, and the interaction of peptidoglycan with TLR2 triggers MyD88-dependent activation and nuclear translocation of NF-κB, and subsequently the transcription and secretion of cytokines. Muramyl dipeptide and γ-D-glutamyl-meso-diaminopimelic acid, which are low-molecular weight breakdown fragments of peptidoglycan, are recognized by intracellular pathogen recognition receptors, nucleotide-binding oligomerization domain containing (Nod)2 and Nod1, respectively [19]. Ligand binding to these receptors triggers interaction with the receptor-interacting protein kinase, RIP2, which activates NF-κB. Of these peptidoglycan breakdown products, only polymeric peptidoglycan binds to CD14, and CD14 enhances polymeric peptidoglycan-induced TLR2 activation. The low molecular weight fragments of peptidoglycan, like muramyl dipeptide, do not bind to CD14, do not induce cell activation through CD14 and also do not interfere with the binding of polymeric peptidoglycan to CD14 [19]. Furthermore, unlike LPS, peptidoglycan bound to sCD14 is not able to activate epithelial and endothelial cells with low membrane CD14 expression.

LTA is a constituent of the cell wall of Gram-positive bacteria, anchored on the outer face of the cytoplasmic membrane and commonly released during growth and antibiotic therapy. Like polymeric peptidoglycan, LTA induces NF-κB activation and cytokine secretion in a TLR2-dependent manner. LTA is recognized by LBP and CD14, and these accessory receptors both enhance LTA-induced cell activation [18]. Presumably in a similar manner, CD14 also enhances TLR2-dependent cellular acti-

vation by LAM derived from the cell-wall of mycobacteria. LAM derived from slowly growing virulent mycobacteria like *Mycobacterium tuberculosis* and *M. leprae* is capped with mannose (ManLAM), whereas LAM from avirulent and fast growing mycobacterial species is uncapped (AraLAM). Strikingly, AraLAM from avirulent mycobacteria is much more potent in inducing TNF secretion by macrophages than ManLAM from virulent mycobacterial strains [12]. AraLAM-, but not ManLAM-induced TNF secretion by monocytes and macrophages was largely CD14-, TLR2- and MyD88-dependent [17].

Recently CD14 was also found to enhance the innate immune response triggered by the TLR3 ligand poly(I:C), a synthetic mimic of double stranded RNA [20]. TLR3 together with TLR7 and TLR8 are regarded as sensors for viral infection, since these receptors recognize viral nucleic acids, like single and double stranded RNA. The potentiating effect of CD14 on TLR3 activation resulted from increased uptake of poly(I:C) and intracellular delivery to the compartment where TLR3 resides [20]. Taken together, these findings suggest that CD14 plays an important role in the induction and amplification of inflammatory responses evoked by a wide variety of pathogens.

Role of CD14 in LPS- and LTA-induced Lung Inflammation

The contribution of CD14 to TLR ligand-induced lung inflammation has been investigated in several animal studies (**Table 1**). Intratracheal administration of LPS did not significantly induce TNF release and neutrophil accumulation in the lungs of rabbits, unless LPS was complexed with LBP [21] or the animals were subjected to mechanical ventilation [22]. Intratracheal instillation of anti-CD14 antibodies together with LPS/LBP or intravenous pretreatment with anti-CD14 or anti-TLR4 antibodies before mechanical ventilation markedly reduced these inflammatory responses [21, 22]. Despite a reduction in lung neutrophil number, intravenous anti-CD14 treatment of rabbits exposed to LPS and subjected to ventilation did not cause a decrease in lung chemokines, including CXCL8 (IL-8), growth related oncogene (GRO) and monocyte chemoattractant protein (MCP)-1, whereas anti-TLR4 treatment did lower the level of GRO moderately and of CXCL8 significantly [22]. These findings reveal that LPS alone does not cause significant lung inflammation in rabbits and suggest that additional accessory signals are required. Whether mechanical ventilation induces increased release of LBP or release of (endogenous) DAMPs which potentiate the LPS-induced response remains to be determined.

In contrast to rabbits, administration of LPS alone to lungs of naive mice induced severe pneumonitis, irrespective of the manner of LPS delivery (inhalation or intratracheal or intranasal instillation) or the source of LPS (*Escherichia coli* or *Acinetobacter baumannii*). Using antibody-treated and gene-deficient mice, CD14 was found to be critically involved in the development of LPS-induced lung inflammation [23–26]. A study with CD14-deficient mice and TLR4 mutant mice (lacking a functional TLR4) showed that LPS-induced vascular leakage, neutrophil infiltration, nuclear translocation of NF-κB. The release of cytokines (TNF and IL-6) and chemokines (CXCL1 and CXCL2) in the lung was completely dependent on these pattern recognition receptors [24]. Similar observations were made by others using mice treated intravenously with anti-CD14 antibodies [23] and by our group using CD14-deficient and TLR4-deficient mice [25]. Furthermore, intratracheal treatment of CD14-deficient mice with sCD14 restored the inflammatory response to the level

Table 1. Effect of CD14 'neutralization' in lung inflammation and lung infection

Inciting ligand/pathogen	Animal model*	Effect of CD14 'neutralization' in the lung**	Ref.
LPS (*E. coli* +LBP)	rabbit αCD14	↓↓neutrophil influx, ↓↓cytokines	21
LPS (*E. coli* +ventilation)		↓↓neutrophil influx, ~chemokines	22
LPS (*E. coli*)	mouse αCD14	↓neutrophil influx, ↓vascular leakage, ↓NF-κB activation	23
LPS (*E. coli*)	mouse $CD14^{-/-}$	↓↓neutrophil influx (reversed by sCD14), ↓↓cytokines (restored by sCD14), ↓↓chemokines, ↓↓vascular leakage	24, 26
LPS (*A. baumannii*)		↓↓neutrophil influx, ↓↓cytokines	25
LTA (*S. aureus*)	mouse $CD14^{-/-}$	~neutrophil influx, ↓cytokines, ↓chemokines	28
LTA (*S. pneumoniae*)		↓neutrophil influx, ~cytokines, ~chemokines	29
nontypeable *H. influenza*	mouse $CD14^{-/-}$	↓↓clearance, ↓↓(early) ↑↑(late) neutrophil influx, ↓↓(early) ↑↑(late) cytokines	30
A. baumannii	mouse $CD14^{-/-}$	↓↓clearance, ~neutrophil influx, ~cytokines (↑↑dissemination)	25
E. coli	rabbit αCD14	↓↓clearance, ~neutrophil influx, ~cytokines, ~chemokines (↓↓systemic responses)	32
B. pseudomallei	mouse $CD14^{-/-}$	↑↑clearance (reversed by sCD14), ↓neutrophil influx (reversed by sCD14), ~cytokines (↑↑systemic clearance (reversed by sCD14)) (↓↓mortality)	40
S. pneumoniae	mouse $CD14^{-/-}$	↑↑clearance (reversed by sCD14), ↓↓neutrophil influx, ↓↓cytokines, ↓↓chemokines (↓↓ dissemination (reversed by sCD14)) (↓↓mortality (reversed by sCD14))	41
M. tuberculosis	mouse $CD14^{-/-}$	~clearance, ↓↓cellular infiltration, ~/↑cytokines (↓↓mortality)	44
Influenza A	mouse $CD14^{-/-}$	↑/~clearance, ~lymphocyte recruitment and activation, ~neutrophil influx, ~cytokines	50

* αCD14: anti-CD14 antibody treatment; $CD14^{-/-}$: CD14-gene deficient
** ↓(↓): (strongly) reduced; ~: unaltered; ↑(↑): (strongly) increased
LPS: lipopolysaccharide; LTA: lipoteichoic acid

present in wild-type mice, whereas treatment with wild-type alveolar macrophages restored the neutrophil infiltration of the lung but not pulmonary TNF release [26]. Moreover, treatment with wild-type alveolar macrophages also restored neutrophil infiltration in the lung of LPS-exposed TLR4-deficient mice [27]. These findings indicate that sCD14, and CD14 and TLR4 on the surface of alveolar macrophages contribute to the development of LPS-induced lung inflammation. However, when a high dose of LPS was administered to the lungs of mice, acute lung inflammation was absent in mice lacking functional TLR4, but only partially reduced in CD14 deficient mice [24]. Thus, LPS-induced lung inflammation is entirely dependent on TLR4 and, depending on the dose of LPS, also on the presence of CD14 in the lung.

Our group determined whether CD14 also contributes to the development of lung inflammation induced by LTA, a TLR2 ligand from the cell wall of Gram-positive bacteria [28, 29]. Lung inflammation induced by *Staphylococcus aureus* LTA was completely dependent on TLR2, but independent of LBP and only moderately

dependent on CD14 expression. As compared to wild-type mice, *S. aureus* LTA-induced neutrophil influx was unchanged in CD14-deficient mice, whereas TNF and CXCL2 release in the lung were partially reduced [28]. Strikingly, however, pulmonary inflammation was also greatly diminished in TLR4-deficient mice, as well as in mice deficient for platelet activating factor receptor (PAFR), a known receptor for LTA on epithelial cells. Similarly, lung inflammation induced by *Streptococcus pneumoniae* LTA, which is less potent compared *S. aureus* LTA, was also completely dependent on TLR2 expression. However, in contrast to *S. aureus* LTA, neutrophil infiltration of the lung was moderately reduced in CD14-deficent mice treated with pneumococcal LTA, whereas TNF and CXCL2 release in the lung was unchanged [29]. Moreover, pneumococcal LTA-induced lung inflammation was moderately diminished in TLR4-deficient mice. Thus, despite the amplifying effect on LTA-induced TLR2-mediated responses in vitro, CD14 contributes minimally to lung inflammation induced by LTA. The unexpected contribution of TLR4 to LTA-induced lung inflammation may result from DAMPs generated during the inflammatory process in the respiratory tract.

Role of CD14 in Lung Infection

In line with the findings that CD14 contributes to LPS-induced lung inflammation in mice, a number of studies have shown that CD14 is essential for the host defense response in the lung against Gram-negative bacteria, such as nontypeable *Haemophilus influenzae*, a possible cause of community acquired pneumonia, and *A. baumannii* and *E. coli*, which are frequent inducers of nosocomial pneumonia (**Table 1**). Nontypeable *H. influenzae* expresses the TLR4 ligands LPS and lipooligosaccharide on its cell wall, as well as several TLR2 ligands, including lipoproteins and porins. Previously, we found that activation of alveolar macrophages by nontypeable *H. influenzae* depended on expression of TLR4, TLR2, and CD14 [30]. Moreover, bacterial clearance after intranasal infection with nontypeable *H. influenzae* was markedly reduced in CD14-deficient and TLR4-deficient mice, as well as in TLR2-deficient mice at later stages of the disease [30]. Interestingly, despite impaired bacterial clearance in CD14-deficient and TLR4-deficient mice, the inflammatory response in the lung was strongly reduced in TLR4 deficient mice, but elevated in CD14 deficient mice. Similar observations were made with encapsulated *H. influenzae* in TLR4-mutant mice [31]. Furthermore, clearance of nontypeable *H. influenzae* was also significantly impaired in MyD88-deficient mice, but not in mice lacking functional TRIF [30]. In a similar manner, CD14 was involved in the host defense response against *A. baumanii* [25]. CD14-deficient mice, like-TLR4-deficient mice, suffered from impaired bacterial clearance in the lungs and enhanced bacterial dissemination after intranasal infection with *A. baumannii*. However, unlike TLR4-deficient mice, CD14-deficient mice developed similar inflammatory responses compared to wild-type mice. These findings suggest a role for CD14 in anti-bacterial responses against nontypeable *H. influenzae* and *A. baumannii*. Although the role of TLR4 (and TLR2) in phagocytic killing is controversial, it is unknown whether CD14 is involved in such processes. The role of CD14 in *E. coli*-induced pneumonia was determined in anti-CD14 antibody treated rabbits. Intravenous anti-CD14 antibody treatment of rabbits inoculated with *E. coli* by bronchial instillation, resulted in decreased bacterial clearance from the lungs, but had no effect on neutrophil infiltration or cytokine release in the lungs [32]. However, anti-CD14 treatment pro-

tected against sustained hypotension and reduced the levels of nitrate and nitrite in the blood. The contribution of CD14 to *E. coli*-induced pneumonia has not been investigated in mice, whereas the role of the other components of the LPS receptor complex (TLR4, MD-2, MyD88, TRIF) has been determined using gene-deficient or mutant mice. Although analysis of bacterial clearance after intranasal infection of TLR4-mutant mice with *E. coli* produced inconsistent results [33], lack of MD-2 or TRIF resulted in impaired bacterial clearance after *E. coli* instillation in the lungs [34, 35]. Moreover, *E. coli*-induced neutrophil accumulation and cytokine release was significantly reduced in mice devoid of functional TLR4, MD-2, MyD88 or TRIF [33–35]. These findings indicate that signaling through the TLR4 receptor complex is essential in the host defense response against *E. coli*, and suggests that CD14 may contribute to these *E. coli*-induced responses.

To our knowledge, it is unclear whether CD14 contributes to host defense against *Pseudomonas aeruginosa*, a frequent cause of nosocomial pneumonia, and *Burkholderia cepacia*, a prevalent Gram-negative bacterium, together with *P. aeruginosa*, in patients with cystic fibrosis. Recently, it was found that both TLR4 and TLR5 are critical in the host response to *P. aeruginosa* and that TLR4-deficient mice were not susceptible to intratracheal *P. aeruginosa* infection unless a bacterial mutant devoid of flagellin production was used [36]. A similar approach is required to determine a role for CD14 in *Pseudomonas*-induced pneumonia. It is plausible that CD14 also contributes to the host response against *B. cepacia*, since LPS from this bacterium signals through TLR4 and anti-CD14 antibodies dramatically inhibited *B. cepacia*-induced chemokine secretion by lung epithelial cells [37]. Whether CD14 contributes to host defense response against *Klebsiella pneumoniae*, a known cause of nosocomial pneumonia, also remains to be determined, but data from our study with TLR4-mutant mice indicate that signaling through TLR4 is essential for successful clearance of this bacterium [38].

In contrast to the essential role of pulmonary TLR4 and CD14 in the host defense response against most Gram-negative bacteria, we found that TLR4 was not involved and CD14 played a remarkable detrimental role in the host response to *B. pseudomallei*, the causative organism of melioidosis (the most common cause of community-acquired sepsis in Southeast Asia) [39, 40]. CD14-deficient mice infected intranasally with *B. pseudomallei* were protected from mortality, accompanied by enhanced bacterial clearance in the lung, blood and liver, and reduced cellular infiltration in the lung [39], whereas the course of disease in TLR4-deficient mice was indistinguishable from wild-type mice [40]. Moreover, intranasal administration of sCD14 to CD14-deficient mice partially reversed the phenotype into that of wild-type mice [40]. Interestingly, these findings in *B. pseudomallei*-infected CD14-deficient mice strongly resemble our previous results found with TLR2-deficient mice, and are in line with the observation that *B. pseudomallei* expresses an atypical LPS which signals through TLR2 [39]. Whether CD14 interacts with TLR2 in *B. pseudomallei*-induced responses, and by which mechanism these receptors facilitate the growth and dissemination of *B. pseudomallei* after intranasal infection remains to be determined.

In the model for *S. pneumoniae*-induced pneumonia, we observed an unexpected detrimental role for CD14 in the innate host defense response. *S. pneumoniae*, a Gram-positive bacterium and the single most frequent pathogen causing community-acquired pneumonia, induces severe lung inflammation and sepsis in wild-type mice after intranasal instillation. Strikingly, CD14-deficient mice were protected against pneumococcal pneumonia, presumably as a result of reduced bacterial

spread to the circulation and reduced lung inflammation [41]. In contrast, TLR2-deficient and TLR4-mutant mice were not protected against pneumococcal pneumonia [38, 42], but in fact TLR2 seemed redundant for efficient bacterial clearance and TLR4-mutant mice were more susceptible to pneumonia, accompanied by impaired bacterial clearance. However, as in CD14-deficient mice, lung inflammation was also reduced in pneumococci-infected TLR2-deficient mice [42]. Since intrapulmonary treatment with sCD14 rendered CD14-deficient mice equally susceptible to *S. pneumoniae* as wild-type mice [41], these results suggest that *S. pneumoniae* abuses (s)CD14 in the lung to cause invasive respiratory tract infection. Interestingly, the phenotype of CD14 deficient mice strongly resembled the phenotype of mice deficient for PAFR [43], a receptor for phosphoryl choline from the pneumococcal cell wall which facilitates pneumococcal invasion of cells. Further studies are required to determine whether CD14 serves as a chaperone in the presentation of *S. pneumoniae* to the PAFR so that the phosphoryl–PAFR-mediated invasion is facilitated.

Since *M. tuberculosis* expresses a number of molecules, such as lipoproteins, which activate immune cells in a CD14-dependent manner, we and others investigated whether CD14 also contributed to the host immune response in mice with lung tuberculosis [44]. Although initially after intranasal infection of wild-type and CD14-deficient mice no differences in bacterial loads, cell infiltration and release of most cytokines in the lung were found [44, 45], at later time points (> 20 weeks after infection) CD14-deficient mice were protected from mortality presumably as a result of a reduced inflammatory response in the lungs [44]. These findings are completely opposite to the results from *M. tuberculosis*-infected TLR2-deficient and TLR4-mutant mice, which suffered from reduced bacterial clearance, chronic inflammation, increased cellular infiltration of the lungs and reduced survival [46–48]. The mechanism underlying the detrimental effect of CD14 in the host response against *M. tuberculosis* remains to be established.

In addition to its role in (myco)bacterial infections, CD14 may also play a role in the pulmonary host response against respiratory syncytial virus (RSV), the most common cause of lower respiratory tract disease in infants and young children worldwide, and influenza A virus, a cause of pneumonia in very young children, the elderly and immunocompromised patients. The envelop F glycoprotein from RSV and certain influenza A virus components activate macrophages in a CD14-dependent manner [14, 20]. Experiments with wild-type and TLR4-mutant mice infected intranasally with RSV showed that viral clearance was reduced in the absence of functional TLR4 [14], due to impaired natural killer (NK) cell migration and function and impaired cytokine secretion. Recently, it was found that TLR2 and TLR6 are also involved in recognition of RSV [49]. Whether CD14 contributes to these TLR-mediated immune responses against RSV remains to be determined. Using CD14-deficient mice, we demonstrated that CD14 played a minimal role in influenza A virus-induced pneumonia [50]. During the entire course of disease, viral loads were slightly reduced in CD14-deficient mice, but this did not result from improved lymphocyte recruitment or lymphocyte activation, or consistent changes in pulmonary cytokines [50]. Thus, despite the fact that influenza A expresses ligands that require CD14 for immune cell activation [20], CD14 seems redundant in the host defense reponse against influenza A virus.

Conclusion

CD14 plays a central role in the lung in the recognition and binding of a variety of (myco)bacterial and viral components, and in the amplification of subsequent host responses. The studies discussed in this chapter indicate that the contribution of CD14 to the pulmonary host defense responses may range from beneficial to detrimental, depending on the microbe and the PAMPs it expresses. Interfering with CD14-LPS or CD14-LTA interactions reduced lung inflammation. Interference with CD14-pathogen interactions, however, did not have a significant effect on *M. tuberculosis* or influenza A virus infection, resulted in reduced clearance of nontypeable *H. influenzae*, *E. coli* or *A. baumannii* in the lung, but enhanced clearance (and reduced dissemination) of *B. pseudomallei* or *S. pneumoniae*. The latter observation indicates that certain pathogens may abuse CD14 in the lung to cause invasive disease. Whether CD14 is a suitable target for intervention in these latter infectious diseases and/or in aberrant inflammatory responses during pneumonia requires further study.

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V Mechanical Ventilation

Measurement of Functional Residual Capacity during Mechanical Ventilation

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Introduction

Functional residual capacity (FRC) is defined, in classical physiology, as the volume of gas remaining in the lungs at the end of expiration. In other words, FRC is the volume at which the elastic recoil pressure of the chest wall equals that of the lung and, at FRC, the system is in equilibrium. If the mechanical properties of the system change, FRC will change as well: For example, if lung compliance decreases, elastic recoil pressure will increase, and FRC will decrease so that a new equilibrium with the elastic recoil pressure of the chest wall is reached. Moreover, if a fraction of the alveoli collapse or are flooded (as frequently occurs in the setting of acute lung injury [ALI]) this will also result in a decrease in FRC. On the other hand, if at end-expiration the airway pressure is kept above the atmospheric one by application of a positive-end expiratory pressure (PEEP), the system will reach a different equilibrium (i.e., FRC) at a higher lung volume, which is usually termed the end-expiratory lung volume (EELV, which corresponds to the FRC in the presence of PEEP, although in this chapter we will use the term FRC for FRC and EELV). The action of PEEP can, moreover, determine the re-opening of previously collapsed alveoli (recruitment). In this case, the increase in FRC will be greater than expected, because the system will shift to a different pressure-volume curve (**Fig. 1**). For this reason, FRC appears to be a very promising tool for monitoring lung recruitment.

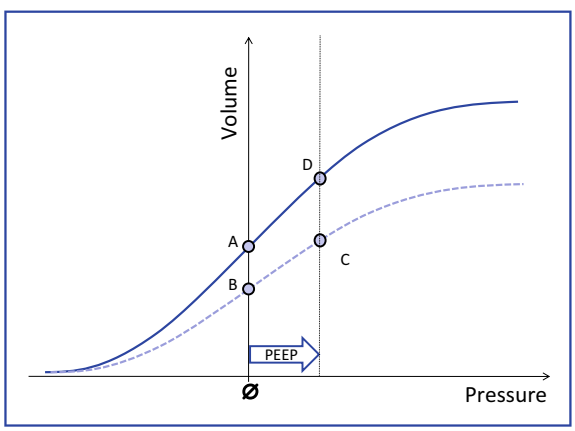

Fig. 1. The figure displays the pressure-volume curve of the respiratory system on an arbitrary scale. The functional residual capacity (FRC) is the volume at which the system is at equilibrium and does not generate any pressure (A). If the mechanical properties of the system change, such as in the case of decreased compliance (dashed line), the FRC will decrease as well (B). The application of positive end-expiratory pressure (PEEP) can increase the FRC (C), usually termed, in the presence of PEEP, the end-expiratory lung volume (EELV). Moreover PEEP can promote the recruitment of previously collapsed alveoli. In this case the increase in FRC will be greater that what would be expected from the pressure volume curve (D).

Methods for FRC Measurement During Mechanical Ventilation

In classical physiology and in pneumology, FRC is measured in awake, non-intubated, spontaneously breathing subjects by means of whole body plethysmography or by techniques based on dilution of a gaseous tracer. In mechanically ventilated and intubated patients, whole body plethysmography is not feasible for obvious reasons, but several techniques based on dilution of a tracer have been described and tested. The purpose of this chapter is certainly not to describe each of these techniques, which basically rely on the same theoretical background, with different engineering approaches. We will rather focus on a number of the most recently described approaches and on those most likely to be available, currently or in the near future. In addition, we will briefly describe techniques based on entirely different approaches, such as computed tomography (CT) and respiratory inductive plethysmography. Finally a cautiously comprehensive list of the methods so far described in the literature is provided in **Table 1**.

Closed Circuit Techniques

Closed circuit techniques are based on the dilution of an inert gas as a tracer in the lungs of the patient, so that the volume of distribution can be computed from the final concentration of the gas. A definite advantage of closed circuit techniques is that, since the measurement of the tracer is performed at the end of the mixing procedure, in a supposedly steady-state condition, there is no need for a real time (or 'fast') gas analyzer.

The 'classical' helium dilution technique has been variously modified for patients being mechanically ventilated [1–4]. Most of these techniques required quite bulky instrumentation, but Patroniti et al. [5] described in detail an extremely simple dilution technique based on helium. During an end-expiratory pause at PEEP, a flexible connector, inserted between the circuit Y and the patient's endotracheal tube, was occluded by a clamp. The flexible tube was then connected to a balloon filled with 1.5 l of a gas mixture of known helium concentration in oxygen. After releasing the clamp, the operator delivered at least 10 tidal volumes to the patient by rhythmically compressing the balloon to dilute the helium gas mixture with the gas contained in the patient's lungs (**Fig. 2**). At the end of this procedure, the balloon was clamped off the circuit, and the patient was reconnected to the ventilator. The concentration of helium in the balloon was then measured. Since the mass of helium at the beginning and at the end of the procedure is the same (due to the extremely low solubility of helium in the blood):

$$Ci \cdot Vi = Cf \cdot Vf$$

where Ci and Cf are the initial and final concentrations of helium, and Vi and Vf are the initial and final volumes of distribution for helium. Since Vf = Vi + FRC, the equation can be rearranged as follows:

$$FRC = (Vi \cdot Ci/Cf) - Vi.$$

The technique showed good repeatability, with 95 % confidence interval limits for agreement of –191 and +141 ml. The authors also tested the accuracy of the technique by comparing it with quantitative CT scan (see below about this technique): Although helium dilution underestimated FRC by 14 % on average, the measurements obtained by the two techniques were tightly correlated (r = 0.941) with "clini-

Table 1. The table enlists studies proposing and/or validating new methods for measuring functional residual capacity in patients undergoing mechanical ventilation. Studies performed in and/or methods devised for a pediatric population are labeled as (P)

Study	Technique
Hewlett, 1974 [37]	Helium dilution (closed-circuit)
Suter, 1974 [7]	Helium dilution (closed-circuit)
Heldt, 1978 [1]	Helium dilution (closed-circuit)
Hedenstierna, 1979 [40]	Nitrogen washout
Ozanne, 1981 [42]	Argon and nitrogen dilution
Paloski, 1981 [17]	Nitrogen washout
Weaver, 1981 [4]	Helium dilution (closed-circuit)
Mitchell, 1982 [24]	Oxygen washin
Ibanez, 1983 [2]	Helium dilution (closed-circuit) Multi-breath nitrogen washout
Mentz, 1984 [45] (P)	Multiple gas rebreathing
Jonmaker, 1985 [10]	Sulfur-hexafluride washout
Larsson, 1987 [11]	Sulfur-hexafluride washout
Hoffman, 1989 [47]	Inductive pletismography
East, 1990 [9]	Sulfur-hexafluride washout
Imanaka, 1990 [48]	Argon washout
Werchowski, 1990 [49]	Inductance plethysmography
Valta, 1992 [29]	Inductance plethysmography
Fretschner, 1993 [21]	Multi-breath nitrogen wash-out
Macnaughton, 1994 [3]	Helium dilution (closed-circuit)
Schulze, 1994 [13] (P)	Sulfur-hexafluride washout
Miller, 1995 [38] (P)	Multi-breath nitrogen washout
Hentschel, 1997 [16] (P)	Multi-breath nitrogen washout
Uhlig, 1997 [39]	Laser monitor
Fujino, 1998 [41]	Argon washout
Hammer, 1998 [14] (P)	Nitrogen washout
Neumann, 1998 [30]	Inductance plethysmography
Wrigge, 1998 [19]	Nitrogen washout
Riou, 1999 [43] (P)	Four mathematical models
Eichler, 2002 [44]	Oxygen washout
Schibler, 2002 [46] (P)	Sulfur-hexafluride and nitrogen wash-in/washout with ultrasonic flowmeter
Patroniti, 2004 [5]	Helium dilution and computed tomography
Olegard, 2005 [22]	Nitrogen wash-in/washout
Weismann, 2006 [25]	Oxygen wash-in/washout
Brewer, 2007 [28]	CO_2 rebreathing
Di Marco, 2007 [8]	Helium dilution
Maisch, 2007 [26]	Oxygen wash-in/washout
Heinze, 2008 [15]	Nitrogen wash-in/washout
Patroniti, 2008 [27]	Nitrogen wash-in/washout
Chiumello, 2008 [6]	Nitrogen wash-in/washout, helium dilution and computed tomography
Bikker, 2009 [23] (P)	Nitrogen wash-in/washout

cally acceptable" limits of agreement (LOA – 373 and +438 ml). The main limitation of the technique consists of the ability for the diluted helium to reach a uniform concentration in the FRC, despite ventilation heterogeneities. Indeed, underestimation of helium increased with the amount of hyperinflated tissue (usually receiving less ventilation). Moreover oxygen consumption and carbon dioxide (CO_2) production might alter the total volume during the mixing procedure. A frequent criticism

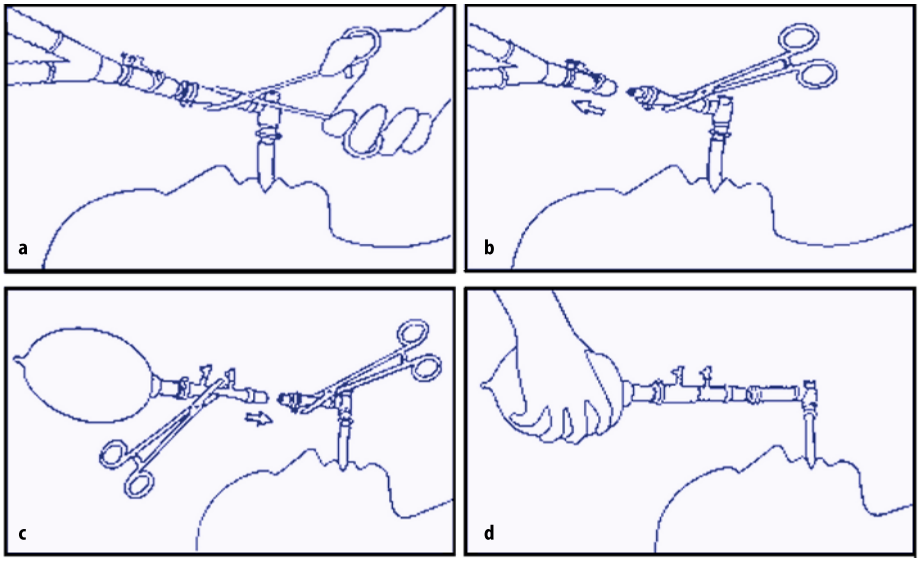

Fig. 2. Simplified helium dilution technique. During an end-expiratory pause, a flexible tube, inserted between the circuit Y and the patient's endotracheal tube, is clamped (panel a) and the Y connector is disconnected from it (panel b). The flexible tube is then connected to a balloon containing 1.5 liters of a gas mixture of helium (13.44 %) in oxygen (panel c). The patient is then ventilated by rhythmical compressions of the balloon, in order to dilute the helium mixture (panel d). From [5] with permission.

of this technique is that FRC changes during the mixing procedure, since PEEP is lost at the release of the clamp (as the helium bag is at atmospheric pressure), while the tidal volume delivered to dilute helium may promote alveolar recruitment; however, the total volume of the system (i.e., Vi + FRC), unless there are leaks, does not change throughout the mixing procedure, but is simply redistributed in a different proportion among the bag and the lungs. The initial results from Patroniti et al. [5] have been replicated by others, confirming that FRC values obtained by helium dilution are tightly correlated with those obtained by CT scan, although the degree of underestimation increases with increasing lung volumes [6].

In line with previous investigators [1, 4, 7] Di Marco and coworkers [8] used a "bag-in-the-box" system to perform helium dilution with the proposed advantage of avoiding the loss of PEEP and maintaining the ventilatory assistance as delivered by the mechanical ventilator to the patient. In such a system, the bag containing helium is enclosed in a rigid box. The ventilator pressurizes the box and the pressure is transmitted to the bag, ventilating the patient and diluting the helium; alternatively, the box can be by-passed using a switch and the ventilator connected directly to the patient. The system, after *in vivo* validation showed high accuracy, was applied during pressure-controlled and pressure-support ventilation, without major changes in the respiratory pattern and with good reproducibility of the results. However, whether the additional equipment required by the "bag-in-the-box" system offers an actual improvement of the technique as opposed to a "simple" bag system is debatable.

Open Circuit Wash-in/washout Procedures

Wash-in/washout techniques require a step variation in the inspiratory concentration of a tracer gas: The wash-in (if the tracer concentration is increased) or washout in the ensuing period of ventilation, until a new steady state is reached, allows the measurement of FRC as the ratio between the mass of exhaled (or inhaled) tracer gas and the change in concentration. For example, if 150 ml of the gas X is washed out from the lung bringing the concentration from 8 to 0 %, the FRC will be 160/(0.08 – 0)= 1875 ml. The key problem with these systems is that, since the mass of the dilution tracer is instantaneously measured as the product of concentration and flow, a perfect synchrony between these two signals is required. This is jeopardized by the response time of the sensor and (when using a sidestream analyzer) by the delay due to the transport time of the sampled gas and several efforts have been devoted to deal with this issue.

For several years sulfur hexafluride (SF6), an inert and insoluble gas, has been used as a tracer for washout with good results [9 – 13], although this approach never really made it into clinical practice since it requires an additional tank in the ventilator and a dispensing device that delivers the tracer gas in proportion to the instantaneous inspiratory flow so that the inspiratory concentration is held constant.

For this reasons, nitrogen washout received considerable interest and application in a number of different variants [2, 14 – 20]. In 1993, Fretschner and coworkers [21], in probably the only study pioneering the possibility of actually carrying out the wash-in/washout technique at the bedside, proposed a technique based on nitrogen washout and wash-in. The technique was based on a 30 % step change (from 70 to 100 %) in FiO_2 and on the measurement of the amount of nitrogen washed out to reach a new steady state. The authors did not measure nitrogen concentration (FN_2) directly but used $FN_2 = 1 - FCO_2 - FO_2$, where FCO_2 and FO_2 are the CO_2 and oxygen concentrations, respectively. While the FCO_2 was directly measured by means of a fast mainstream analyzer yielding a signal synchronous with that of the flow, the signal for FO_2 was obtained by a slower sidestream (and thus carrying a delay) analyzer. Ingeniously, assuming that the 'true' oxygen signal had to be congruent with the CO_2 signal, the authors were able to correct for the delay in the FO_2 signal. This technique showed excellent accuracy in an *in vitro* test ($FRC_{measured} = 1.03 \times FRC_{reference} + 23$ ml, $r^2 = 0.957$); the reproducibility of the technique in mechanically ventilated patient was also clinically acceptable with a mean bias of –2.7 ± 14 %.

Some years later, Wrigge and coworkers [19] used a sidestream mass spectrometer to directly measure FN_2 during nitrogen washout over a short period of ventilation with an FiO_2 of 1; the authors used a dynamic correction of the sampling delay, taking into account the effect of the gas viscosity on the rate of gas sampling; moreover a correction was made to take into account the amount of N_2 washed out from the body. The authors demonstrated that the assumption of 'constant' delay yields large estimation errors and that the difference between two repeated measures increased with increasing baseline FiO_2. The same group has also shown that, as expected, the reproducibility of the technique decreases in the presence of irregular flow patterns (e.g., during airway pressure-release ventilation [APRV] with superimposed spontaneous breathing as opposed to continuous positive airway pressure [CPAP]) [20].

More recently, in order to avoid the synchronization problems, Olegard et al. [22] focused on the *alveolar* N_2 exchange, calculated from inspiratory and end-tidal plateau gas concentrations of O_2 and CO_2 measured by sidestream analyzers. First, the

fraction of tidal *alveolar* ventilation (i.e., which participates in gas exchange, V_{TA}) was computed as:

$$V_{TA} = \frac{V_{CO_2}}{F_{ETCO_2}} \cdot \frac{1}{RR},$$

where V_{CO_2} is CO_2 production, F_{ETCO_2} is the CO_2 end-tidal fraction, and RR is respiratory rate. The breath by breath alveolar nitrogen exchange was then computed as:

$$V_TN_2 = (F_1N_2 \cdot V_{TA}) - (F_{ET}N_2 \cdot V_{TA})$$

where F_1N_2 and $F_{ET}N_2$ are the inspiratory and the end-tidal N_2 fraction, respectively, while V_{TA} is the tidal alveolar ventilation. Finally, FRC was computed (as in any other wash-in/washout technique) as the ratio between the amount of nitrogen exchanged (sum of the nitrogen exchange of each tidal volume) and the difference in inspiratory N_2 concentration between start and end of washout. For those who like formulas:

$$FRC = \frac{\sum V_TN_2}{F_1N_{2ini} - F_1N_{2end}}$$

where $F_1N_{2ini} - F_1N_{2end}$ is the difference in inspiratory N_2 concentration between start and end of washout. Calculations were based on a period of three time constants, when 95 % of the wash-in/washout was completed. The authors proposed that a 10 % change in FiO_2 would be sufficient to obtain appropriate measurements. An *in vitro* study showed a very high precision of the measured values, while, in mechanically ventilated patients, the limits of agreement for measurement obtained with a 10 % and a 30 % variation in FiO_2 were −365 and +347 ml. No external validation was used in patients. This technique has recently been embedded in a commercial ventilator (Engstrom Carestation, GE Healthcare), hopefully facilitating the spread and clinical use of FRC data. Chiumello et al. [6] compared the FRC measurements obtained with the Engstrom Carestation with those obtained from the CT scan in 30 mechanically ventilated patients. The measurements were tightly correlated ($r^2 = 0.89$); Engstrom Carestation tended to overestimate results, compared to CT values, by an average of 93 ml. The limits of agreement between the techniques were, however, quite narrow, being within −50 and 236 ml. The technique has also been applied in children: Although no external reference was used, a tight correlation with child's age, weight and height was shown, indirectly suggesting data reliability [23].

Dieter Weismann and colleagues [24] reappraised and improved a technique (originally proposed by Mitchell et al. [25]) based on the wash-in/washout of oxygen after a change in FiO_2 (10 % is sufficient, although 20 % is recommended). The core of the technique is basically a software (LUFU) installed on a personal computer. The LUFU continuously acquires airflow, volume and airway pressure from the digital output of a commercial ventilator (Evita 4, Draeger, for which it was specifically developed); there is thus no further need for an additional spirometer or an analog/digital converter, with a great simplification of the technique. A fast sidestream paramagnetic sensor is used to measure oxygen concentration, the data from which are recorded by the same software. The authors developed an elegant algorithm to synchronize this signal with the airflow (reconstructing the oxygen concentration at the Y-piece), taking into account not only the viscosity of the sampled gas, but also the swings in airway pressure, which heavily affect the gas sampling speed. These computations are performed by the LUFU software, which displays a value of the

FRC after each breath and stops the measurement when the ventilated volume is greater than eight times the FRC. In the first *in vitro* studies, the technique was tested in a number of different ventilatory settings, and provided very reliable and reproducible results. Maisch and coworkers [26] compared the results obtained by LUFU with those of whole body plethysmography in spontaneously breathing healthy and lung-diseased volunteers: The limits of agreement between the two techniques were quite broad ranging from –43 % to 19 % in healthy and –39 % to 32 % in diseased subjects. More encouraging results were reported by Patroniti et al. [27], who applied the LUFU technique in patients undergoing mechanical ventilation. These authors enrolled 20 patients undergoing controlled mechanical ventilation (4 volume-controlled and 16 pressure-controlled) and 16 patients receiving assisted spontaneous breathing (2 patients on APRV, 10 on pressure-support ventilation [PSV], and 4 on CPAP). In this population, the technique proved safe and easy to apply at the bedside; its reproducibility was clinically acceptable, with 95 % confidence intervals of approximately ± 9 % and ± 15 % during controlled and assisted mechanical ventilation, respectively, similar for the wash-in and washout phases. In the subgroup of patients undergoing controlled mechanical ventilation, the authors compared the results obtained by LUFU with those obtained by the previously described helium dilution [5]; again, the 95 % confidence intervals were clinically acceptable being around ± 17 %.

Nitrogen and oxygen wash-in/washout techniques are both affected by errors arising from the shift of oxygen between alveolar gas and blood, although sophisticated algorithms have been devised to avoid this effect. For this reason the FRC value should always be derived as the average of a wash-in and a washout maneuver.

After nitrogen and oxygen, CO_2 also received some attention: A method based on CO_2 rebreathing has been proposed [28], relying on the 'CO_2 wash-in' signals during the onset of a partial CO_2 rebreathing maneuver that is performed using a CO_2 rebreathing non-invasive cardiac output monitor (NICO, Novametrix); we will not describe the computation in detail, but basically the technique computes the amount of CO_2 that 'disappears' in the first breath of rebreathing, assuming that it is diluted in the FRC. The computation includes a correction factor (0.45) for stores of CO_2 in the lungs other than FRC, such as blood and tissue. Although the method is undoubtedly ingenious, the appropriateness of this factor in all clinical conditions (e.g., lung edema, increased or decreased lung perfusion) is questionable. Nevertheless, when compared to nitrogen washout in an animal model, the correlation coefficient was high (r^2 0.89), with a bias of –77 ml and 95 % limits of agreement of ± 276 ml.

Respiratory Inductive Plethysmography

Respiratory inductive plethysmography is based on two coils of wire enclosed in elastic bands encircling the abdomen and the rib cage. Changes in the cross sectional areas of the rib-cage and abdomen due to respiratory motions alter the self induction of the coils. This signal is read by the device and converted into volume after an appropriate calibration. Thus, in order to obtain reliable measurements of volume, a calibration of the signal with a known volume (e.g., the tidal volume insufflated by the respirator) is necessary; moreover respiratory inductive plethysmography is not suitable for obtaining *absolute* FRC values, but rather the *changes* induced by ventilatory settings (e.g., PEEP increase, recruitment maneuvers) [29]. Neumann et al. [30] compared the measurement of PEEP-induced changes in FRC

by respiratory inductive plethysmography and nitrogen washout in a group of post-operative, chronic obstructive pulmonary disease (COPD), and ALI patients. The authors found that only 46 % of measurements were within a ± 20 % range; accuracy was particularly low in COPD patients. In addition, the authors confirmed the presence of a considerable drift in the signal (averaging 25 ± 29 ml), with marked patient-to-patient variability, hindering the use of respiratory inductive plethysmography for following the evolution of FRC over time.

A similar approach has recently been described for electrical impedence tomography [31].

Computed Tomography Scan

The CT scan is an excellent tool to measure both volume and density. The density of each voxel in the lung depends linearly on the relative amount of air (with a density of –1000 Hounsfield units [HU]) and tissue or water (with a density of 0 HU), according to the formula:

Gas fraction = (CT + 1000) / 1000.

For example, a voxel with a density of –700 HU is constituted by 70 % of gas; if its volume is 10 mm^2 that voxel contains 0.7 × 10 mm^2 of gas. Performing a CT scan of the whole thorax during an end-expiratory pause, the FRC can be computed as the sum of the gas volume contained in each voxel of the lungs (or as the product of the average gas fraction and total volume of the lung). Literature data support CT as an accurate estimate of both whole and gas volume of the lungs [32]. Results have been obtained in models [33, 34], isolated lung [35], and animal studies [36], as well as in healthy subjects and in patients affected by restrictive or obstructive disease [33, 34].

As opposed to the techniques based on gas tracers, CT scan measures the 'anatomical' residual capacity (i.e., the total gas volume in the lung, be it ventilated or not), which in the presence of regions of gas trapping, can be quite different from the 'functional' residual capacity; apart from this proviso, and although certainly not suitable for 'routine' measurements, the authors of this chapter believe that CT scan is probably still the most solid (although probably not 'gold') standard for FRC measurement in mechanically ventilated patients.

Conclusion

The volume of gas within the lung, coupled ideally with the transpulmonary pressure, is a most important parameter to evaluate the pathophysiology of the respiratory system. It can be used to tailor tidal volume, to evaluate recruitment and changes in specific elastance. Unfortunately, FRC measurement has been restricted for too long, although various techniques have been available for decades. The recent inclusion of automatic measurement capability into clinical ventilators may finally promote the FRC into the clinical scenario, providing promise of an important contribution to our understanding of pathological conditions, and, hopefully helping increase standards of care.

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New and Conventional Strategies for Lung Recruitment in Acute Respiratory Distress Syndrome

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

V

Introduction

Mechanical ventilation is a supportive and life saving therapy in patients with acute lung injury (ALI)/acute respiratory distress syndrome (ARDS). Despite advances in critical care, mortality remains high [1]. During the last decade, the fact that mechanical ventilation can produce morphologic and physiologic alterations in the lungs has been recognized [2]. In this context, the use of low tidal volumes (V_T) and limited inspiratory plateau pressure (Pplat) has been proposed when mechanically ventilating the lungs of patients with ALI/ARDS, to prevent lung as well as distal organ injury [3]. However, the reduction in V_T may result in alveolar derecruitment, cyclic opening and closing of atelectatic alveoli and distal small airways leading to ventilator-induced lung injury (VILI) if inadequate low positive end-expiratory pressure (PEEP) is applied [4]. On the other hand, high PEEP levels may be associated with excessive lung parenchyma stress and strain [5] and negative hemodynamic effects, resulting in systemic organ injury [6]. Therefore, lung recruitment maneuvers have been proposed and used to open up collapsed lung, while PEEP counteracts alveolar derecruitment due to low V_T ventilation [4]. Lung recruitment and stabilization through use of PEEP are illustrated in **Figure 1**. Nevertheless, the beneficial effects of recruitment maneuvers in ALI/ARDS have been questioned. Although Hodgson et al. [7] showed no evidence that recruitment maneuvers reduce mortality or the duration of mechanical ventilation in patients with ALI/ARDS, such maneuvers may be useful to reverse life-threatening hypoxemia [8] and to avoid derecruitment resulting from disconnection and/or airway suctioning procedures [9].

The success and/or failure of recruitment maneuvers are associated with various factors: 1) Different types of lung injury, mainly pulmonary and extra-pulmonary origin; 2) differences in the severity of lung injury; 3) the transpulmonary pressures reached during recruitment maneuvers; 4) the type of recruitment maneuver applied; 5) the PEEP levels used to stabilize the lungs after the recruitment maneuver; 6) differences in patient positioning (most notably supine vs prone); 7) use of different vasoactive drugs, which may affect cardiac output and the distribution of pulmonary blood flow, thus modifying gas-exchange.

Although numerous reviews have addressed the use of recruitment maneuvers to optimize ventilator settings in ALI/ARDS, this issue remains controversial. While some types of recruitment maneuver have been abandoned in clinical practice, new, potentially interesting strategies able to recruit the lungs have not been properly considered. In the present chapter we will describe and discuss: a) Definition and factors affecting recruitment; b) types of recruitment maneuvers; and c) the role of variable ventilation as a recruitment maneuver.

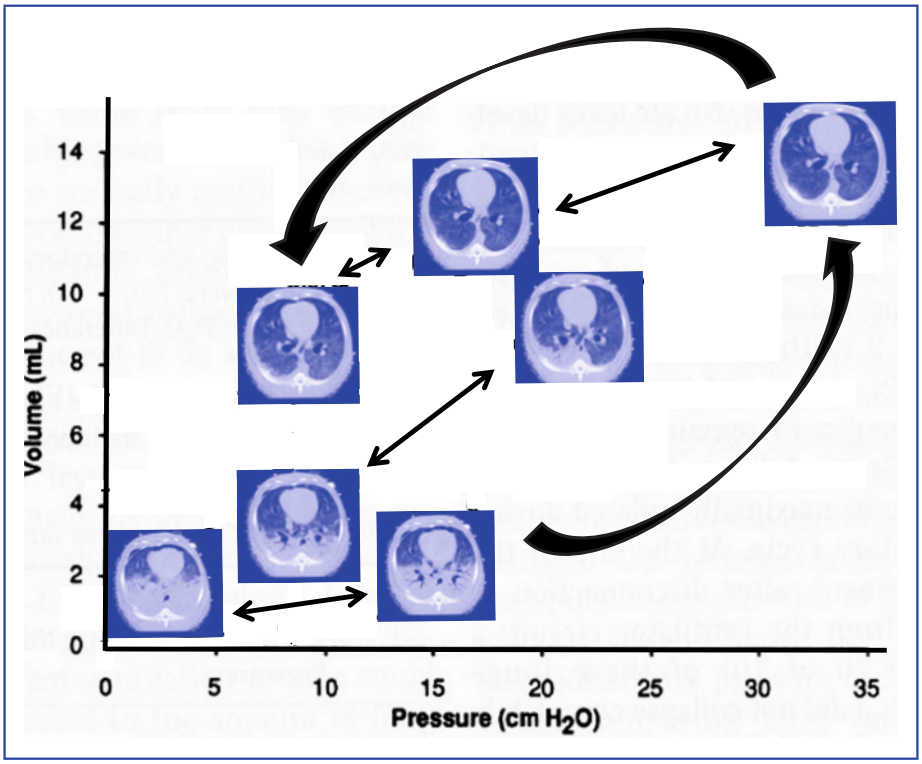

Fig. 1. Computed tomography images of oleic acid-induced acute lung injury in dogs at different inspiratory and expiratory pressures. Note the improvement in alveolar aeration at end-expiration after the recruitment maneuver. Large arrows represent inspiration and expiration. Double-ended arrows represent the tidal breathing (end-expiration and end-inspiration). Adapted from [4].

Definition and Factors Affecting Recruitment Maneuvers

Recruitment maneuver denotes the dynamic process of an intentional transient increase in transpulmonary pressure aimed at opening unstable airless alveoli, which has also been termed alveolar recruitment maneuver. Although the existence of alveolar closure and opening in ALI/ARDS has been questioned [10], the rationale for recruitment maneuvers is to open the atelectatic alveoli, thus increasing end-expiratory lung volume, improving gas exchange, and attenuating VILI [11]. However, recruitment maneuvers may also contribute to VILI [11, 12], with translocation of pulmonary bacteria [13] and cytokines into the systemic circulation [14]. Furthermore, since recruitment maneuvers increase mean thoracic pressure, they may lead to a reduction in venous return with impairment of cardiac output [15].

Various factors may influence the response to a recruitment maneuver, namely: 1) The nature and extent of lung injury, and 2) patient positioning.

Nature and Extent of Lung Injury

The nature of the underlying injury can affect the response to a recruitment maneuver. In direct (pulmonary) lung injury, the primary structure damaged is the alveolar epithelium resulting in alveolar filling by edema, fibrin, and neutrophilic aggregates. In indirect (extrapulmonary) lung injury, inflammatory mediators are released from extrapulmonary foci into the systemic circulation leading to microvessel congestion and interstitial edema with relative sparing of intra-alveolar spaces [16]. Therefore, recruitment maneuvers should be more effective to open atelectatic lung regions in indirect compared to direct lung injury. Based on this hypothesis, Kloot et al. [17] investigated the effects of recruitment maneuvers on gas exchange and lung volumes in three experimental models of ALI: Saline lavage or surfactant depletion, oleic acid, and pneumonia, and observed improvement in oxygenation only in ALI induced by surfactant depletion. Riva et al. [18] compared the effects of a recruitment maneuver in models of pulmonary and extrapulmonary ALI, induced by intratracheal and intraperitoneal instillation of *Escherichia coli* lipopolysaccharide, with similar transpulmonary pressures. They found that the recruitment maneuver was more effective for opening collapsed alveoli in extrapulmonary compared to pulmonary ALI, improving lung mechanics and oxygenation with limited damage to alveolar epithelium. Using electrical impedance and computed tomography (CT) to assess lung ventilation and aeration, respectively, Wrigge et al. [19] suggested that the distribution of regional ventilation was more heterogeneous in extrapulmonary than in pulmonary ALI during lung recruitment with slow inspiratory flow. However, this phenomenon and the claim that recruitment maneuvers are useful to protect the so called 'baby lung', i.e., the lung tissue that is usually present in ventral areas and receives most of the tidal ventilation, has been recently challenged. According to Grasso et al. [20], recruitment maneuvers combined with high PEEP levels can lead to hyperinflation of the baby lung due to inhomogeneities in the lung parenchyma, independent of the origin of the injury (pulmonary or extrapulmonary).

Recently, we assessed the impact of recruitment maneuvers on lung mechanics, histology, inflammation and fibrogenesis at two different degrees of lung injury (moderate and severe) in a paraquat ALI model [21]. While both degrees of injury showed comparable amounts of lung collapse, severe ALI was accompanied by alveolar edema. After a recruitment maneuver, lung mechanics improved and the amount of atelectasis was reduced to similar extents in both groups, but in the presence of alveolar edema, the recruitment maneuver led to hyperinflation, and triggered an inflammatory as well as a fibrogenic response in the lung tissue.

Patient Positioning

Prone positioning may not only contribute to the success of recruitment maneuvers, but should itself be considered as a recruitment maneuver. In the prone position, the transpulmonary pressure in dorsal lung areas increases, opening alveoli and improving gas-exchange [22]. Some authors have reported that in healthy [23], as well as in lung-injured animals [24], mechanical ventilation leading to lung overdistension and cyclic collapse/reopening was associated with less extensive histological change in dorsal regions in the prone, as compared to the supine position. Although the claim that body position affects the distribution of lung injury has been challenged, the development of VILI due to excessively high V_T seems to be delayed during prone compared to supine positioning [25].

The reduction or delay in the development of VILI in the prone position can be explained by different mechanisms: (a) A more homogeneous distribution of transpulmonary pressure gradient due to changes in the lung-thorax interactions and direct transmission of the weight of the abdominal contents and heart [22], yielding a redistribution of ventilation; (b) increased end-expiratory lung volume resulting in a reduction in stress and strain [25]; and (c) changes in regional perfusion and/or blood volume [26]. In a paraquat model of ALI, the prone position was associated with a better perfusion in ventral and dorsal regions, a more homogeneous distribution of alveolar aeration which reduced lung mechanical changes and increased end-expiratory lung volume and oxygenation [27]. In addition, the prone position reduced alveolar stress but no regional changes were observed in inflammatory markers. Recruitment maneuvers also improved oxygenation more effectively with a decreased PEEP requirement for preservation of the oxygenation response in prone compared with supine position in oleic acid-induced lung injury [28]. Those findings suggest that the prone position may protect the lungs against VILI, and recruitment maneuvers can be more effective in the prone compared to the supine position.

Types of Recruitment Maneuver

A wide variety of recruitment maneuvers has been described. The most relevant are represented by: Sustained inflation maneuvers, high pressure controlled ventilation, incremental PEEP, and intermittent sighs. However, the best recruitment maneuver technique is currently unknown and may vary according to the specific circumstances.

The most commonly used recruitment maneuver is the sustained inflation technique, in which a continuous pressure of 40 cmH_2O is applied to the airways for up to 60 sec [8]. Sustained inflation has been shown to be effective in reducing lung atelectasis [29], improving oxygenation and respiratory mechanics [18, 29], and preventing endotracheal suctioning-induced alveolar derecruitment [9]. However, the efficacy of sustained inflation has been questioned and other studies showed that this intervention may be ineffective [30], short-lived [31], or associated with circulatory impairment [32], an increased risk of baro/volutrauma [33], a reduced net alveolar fluid clearance [34], or even worsened oxygenation [35].

In order to avoid such side effects, other types of recruitment maneuver have been developed and evaluated. The most important are: 1) incrementally increased PEEP limiting the maximum inspiratory pressure [36]; 2) pressure-controlled ventilation applied with escalating PEEP and constant driving pressure [30]; 3) prolonged lower pressure recruitment maneuver with PEEP elevation up to 15 cmH_2O and end-inspiratory pauses for 7 sec twice per minute during 15 min [37]; 4) intermittent sighs to reach a specific plateau pressure in volume or pressure control mode [38]; and 5) long slow increase in inspiratory pressure up to 40 cmH_2O (RAMP) [18].

Impact of Recruitment Maneuver on Ventilator-induced Lung Injury

While much is known about the impact of recruitment maneuvers on lung mechanics and gas exchange, only a few studies have addressed their effects on VILI. Recently, Steimback et al. [38] evaluated the effects of frequency and inspiratory pla-

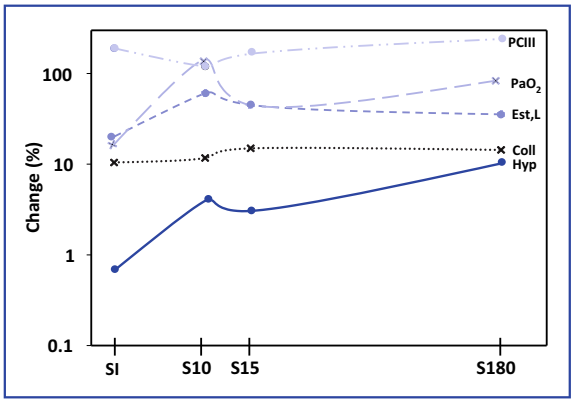

Fig. 2. Percentage of change in static lung elastance (Est,L), oxygenation (PaO_2), fractional area of alveolar collapse (Coll) and hyperinflation (Hyp), and mRNA expression of type III procollagen (PCIII) from sustained inflation (SI) and sigh at different frequencies (10, 15 and 180 per hour) to non-recruited acute lung injury rats. Note that at low sigh frequency, oxygenation and lung elastance improved, followed by a reduction in alveolar collapse and PCIII. Adapted from [38].

V

teau pressure (Pplat) during recruitment maneuvers on lung and distal organs in rats with ALI induced by paraquat. They observed that although a recruitment maneuver with standard sigh (180 sighs/hour and Pplat = 40 cmH_2O) improved oxygenation and decreased $PaCO_2$, lung elastance, and alveolar collapse, it resulted in hyperinflation, ultrastructural changes in alveolar capillary membrane, increased lung and kidney epithelial cell apoptosis, and type III procollagen (PCIII) mRNA expression in lung tissue. On the other hand, reduction in the sigh frequency to 10 sighs/hour at the same Pplat (40 cmH_2O) diminished lung elastance and improved oxygenation, with a marked decrease in alveolar hyperinflation, PCIII mRNA expression in lung tissue, and apoptosis in lung and kidney epithelial cells. However, the association of this sigh frequency with a lower Pplat of 20 cmH_2O worsened lung elastance, histology and oxygenation, and increased $PaCO_2$ with no modifications in PCIII mRNA expression in lung tissue and epithelial cells apoptosis of distal organs. **Figure 2** illustrates some of these effects. We speculate that there is a sigh frequency threshold beyond which the intrinsic reparative properties of the lung epithelium are overwhelmed. Although the optimal sigh frequency may be different in healthy animals/patients compared to those with ALI, our results suggest that recruitment maneuvers with high frequency or low plateau pressure should be avoided. Theoretically, a recruitment maneuver using gradual inflation of the lungs may yield a more homogeneous distribution of pressure throughout the lung parenchyma, avoiding repeated maneuvers and reducing lung stretch while allowing effective gas exchange.

Riva et al. [18] compared the effects of sustained inflation using a rapid high recruitment pressure of 40 cmH_2O for 40 sec with a progressive increase in airway pressure up to 40 cmH_2O reached at 40 sec after the onset of inflation (so called RAMP) in paraquat-induced ALI. They reported that the RAMP maneuver improved lung mechanics with less alveolar stress. Among other recruitment maneuvers proposed as alternatives to sustained inflation, RAMP may differ according to the time of application and the mean airway pressure.

Recently, Saddy and colleagues [39] reported that assisted ventilation modes such as assist-pressure controlled ventilation (APCV) and biphasic positive airway pressure associated with pressure support Ventilation (BiVent+PSV) led to alveolar recruitment improving gas-exchange and reducing inflammatory and fibrogenic mediators in lung tissue compared to pressure controlled Ventilation. They also showed that BiVent+PSV was associated with less inspiratory effort, reduced alveo-

lar capillary membrane injury, and fewer inflammatory and fibrogenic mediators compared to APCV [39].

The Role of Variable Ventilation as a Recruitment Maneuver

Variable mechanical ventilation patterns are characterized by breath-by-breath changes in V_T that mimic spontaneous breathing in normal subjects, and are usually accompanied by reciprocal changes in the respiratory rate. Time series of V_T and respiratory rate values during variable mechanical ventilation may show long-range correlations, which are more strictly 'biological', or simply random (noisy). Both biological and noisy patterns of variable mechanical ventilation have been shown to improve oxygenation and respiratory mechanics, and reduce diffuse alveolar damage in experimental ALI/ARDS [40, 41]. Although different mechanisms have been postulated to explain such findings, lung recruitment seems to play a pivotal role.

Suki et al. [42] showed that once the critical opening pressure of collapsed airways/alveoli was exceeded, all subtended or daughter airways/alveoli with lower critical opening pressure would be opened in an avalanche. Since the critical opening pressure values of closed airways as well as the time to achieve those values may differ through the lungs, mechanical ventilation patterns that produce different airway

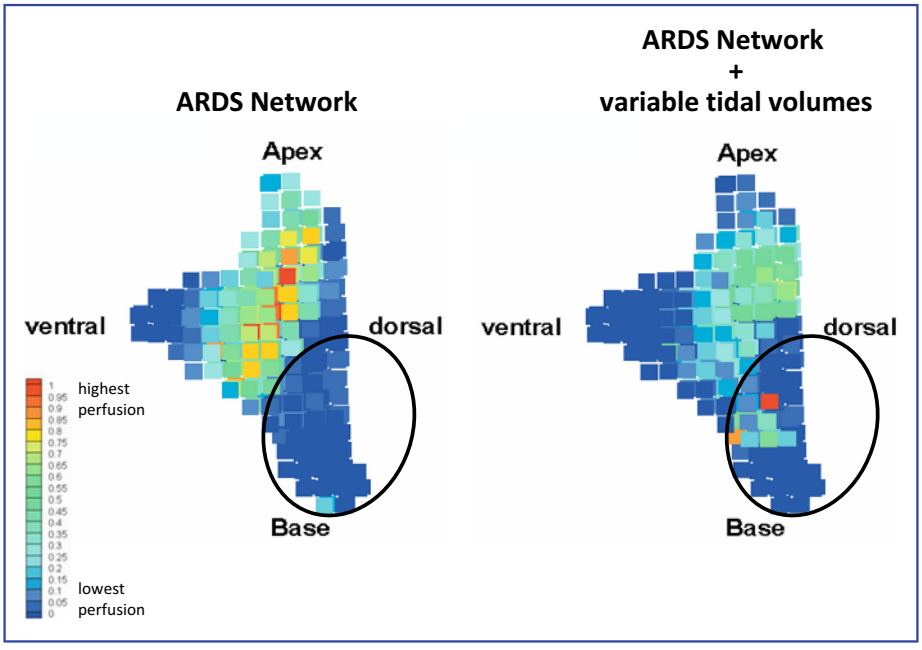

Fig. 3. Pulmonary perfusion maps of the left lung in one animal with acute lung injury induced by lavage. Left panel: Perfusion map after induction of injury and mechanical ventilation according to the ARDS Network protocol. Right panel: Perfusion map after 6 h of mechanical ventilation according to the ARDS Network protocol, but using variable tidal volumes. Note the increase in perfusion in the more dependent basal-dorsal zones (ellipses), suggesting alveolar recruitment through variable ventilation. Blue voxels represents lowest and red voxels, highest relative pulmonary blood flow. Adapted from [41].

pressures and inspiratory times may be advantageous to maximize lung recruitment and stabilization, as compared to regular patterns. Accordingly, variable controlled mechanical ventilation has been reported to improve lung function in experimental models of atelectasis [43] and during one-lung ventilation [44]. In addition, Boker et al. [45] reported improved arterial oxygenation and compliance of the respiratory system in patients ventilated with variable compared to conventional mechanical ventilation during surgery for repair of abdominal aortic aneurysms, where atelectasis is likely to occur due to increased intra-abdominal pressure.

There is increasing experimental evidence suggesting that variable mechanical ventilation represents a more effective way of recruiting the lungs than conventional recruitment maneuvers. Bellardine et al. [46] showed that recruitment following high V_T ventilation lasted longer with variable than with monotonic ventilation in excised calf lungs. In addition, Thammanomai et al. [47] showed that variable ventilation improved recruitment in normal and injured lungs in mice. In an experimental lavage model of ALI/ARDS, we recently showed that oxygenation improvement following a recruitment maneuver through sustained inflation was more pronounced when combined with variable mechanical ventilation [41]. Additionally, the redistribution of pulmonary blood flow from cranial to caudal and from ventral to dorsal lung zones was higher and diffuse alveolar damage less when variable ventilation was associated with the ventilation strategy recommended by the ARDS Network. Such a redistribution pattern of pulmonary perfusion, which is illustrated in **Figure 3**, is compatible with lung recruitment [41].

The phenomenon of stochastic resonance may explain the higher efficiency of variable ventilation as a recruitment maneuver. In non-linear systems, like the respiratory system, the amplitude of the output can be modulated by the noise in the input. Typical inputs are driving pressure, V_T, and respiratory rate, while outputs are the mechanical properties, lung volume, and gas exchange. Thus, by choosing appropriate levels of variability (noise) in V_T during variable volume controlled ventilation, or in driving pressure during variable pressure controlled ventilation [48], the recruitment effect can be optimized.

Despite the considerable amount of evidence regarding the potential of variable ventilation to promote lung recruitment, this mechanism is probably less during assisted ventilation. In experimental ALI, we showed that noisy pressure support ventilation (noisy PSV) improved oxygenation [49, 50], but this effect was mainly related to lower mean airway pressures and redistribution of pulmonary blood flow towards better ventilated lung zones.

Conclusion

In patients with ALI/ARDS, considerable uncertainty remains regarding the appropriateness of recruitment maneuvers. The success/failure of such maneuvers may be related to the nature, phase, and/or extent of the lung injury, as well as to the specific recruitment technique. At present, the most commonly used recruitment maneuver is the conventional sustained inflation, which may be associated with marked respiratory and cardiovascular adverse effects. In order to minimize such adverse effects, a number of new recruitment maneuvers have been suggested to achieve lung volume expansion by taking into account the level and duration of the recruiting pressure and the pattern/frequency with which this pressure is applied to accomplish recruitment. Among the new types of recruitment maneuver, the follow-

ing seem particularly interesting: 1) incremental increase in PEEP limiting the maximum inspiratory pressure; 2) pressure-controlled ventilation applied with escalating PEEP and constant driving pressure; 3) prolonged lower pressure recruitment maneuver with PEEP elevation up to 15 cmH_2O and end-inspiratory pauses for 7 sec twice per minute during 15 min; 4) intermittent sighs to reach a specific plateau pressure in volume or pressure control mode; and 5) long slow increase in inspiratory pressure up to 40 cmH_2O (RAMP). Moreover, the use of variable controlled ventilation, i.e., application of breath-by-breath variable V_Ts or driving pressures, as well as assisted ventilation modes such as Bi-Vent+PSV, may also prove a simple and interesting alternative for lung recruitment in the clinical scenario. Certainly, comparisons of different lung recruitment strategies and randomized studies to evaluate their impact on morbidity and mortality are warranted in patients with ALI/ARDS.

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Consequences of Pleural Effusions for Respiratory Mechanics in Ventilated Patients

J. Graf, P. Formenti, and J.J. Marini

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Introduction

Pleural effusion can be part of the primary condition that precipitates the admission of a patient to an intensive care unit (ICU), or it may develop during the course of an ICU stay [1]. In the former case, such as pneumonia or thoracic trauma, the decision to drain the fluid collection is dictated by the infectious or hemorrhagic nature of the liquid. After admission, the cause usually relates to combinations of factors leading to lung edema, such as generous fluid administration, myocardial depression, increased capillary permeability, and hypoalbuminemia. If there is no suspicion of empyema or hemothorax, the decision to intervene in this scenario is less straightforward. Increasing expertise with ultrasound among intensivists may fuel temptation to drain all pleural fluid accumulations in mechanically ventilated patients.

Knowledge about the impact of pleural effusions on the respiratory system comes from a small number of experimental studies (where fluid was instilled into the pleural cavity of healthy mechanically ventilated animals) and from clinical studies involving mostly spontaneously breathing patients whose large pleural effusions were drained. In the present chapter, we will review the complex interaction between the respiratory system and positive pressure ventilation in the presence of pleural effusion. We will attempt to explain some of the conflicting findings in the literature and to sketch a physiological approach for the management of the mechanically ventilated patient with pleural effusion. Our comments relate primarily to the setting of large, unilateral, and unloculated effusions. Beyond pleural effusion itself, we think that such analysis should supplement our understanding of the dynamic interplay of the components of respiratory system.

Origin of Pleural Effusions in the Critically Ill Patient

Pleural liquid is normally a microvascular filtrate from parietal pleural capillaries whose homeostasis is maintained mainly by a matching outflow via parietal lymphatic stomata [2]. Models of hydrostatic [3, 4] and permeability pulmonary edema [5] implicate pleural effusion accumulation from the lung interstitium. This origin is suggested by a positive correlation between extravascular lung water (EVLW) content and pleural effusion volume, effusate protein concentrations close to those of lung lymphatics [3–5], and preserved visceral pleura ultrastructure [5]. The notion that the major source of hydrostatic effusions is the lung is further supported by clinical studies showing that in patients with chronically elevated hydrostatic pres-

sures, the presence of pleural effusion correlates better with left [6] than with right heart filling pressures [7]. In hydrostatic and permeability pulmonary edema models, 21 – 29 % of the EVLW excess exits the lung via the visceral pleura into the pleural space [4, 5], implying that parietal pleural absorption is a major pathway for lung edema clearance.

Modeling the Pleural Effusion-lung Interaction

Pleural effusions can distort the lung parenchyma by at least two mechanisms: The establishment of a hydrostatic pleural pressure gradient and a space occupying effect.

A hydrostatic pleural pressure gradient should proportionally augment the vertical transpulmonary pressure and lung inflation gradients. This phenomenon can be understood even in the absence of the chest wall and has been modeled by submersion of isolated lung lobes [8 – 10]. In evaluating regional lung inflation, it is important first to differentiate the vertical gradient in regional lung volume and the vertical gradient in transpulmonary pressure. The vertical gradient in regional lung volume disappears with lung inflation because lung compliance becomes progressively smaller at higher transpulmonary pressures, even under considerable vertical gradients in transpulmonary pressure [2]. In fact, the vertical volume gradient dissipates in immersed isolated lobes inflated at 80 % lobar total lung capacity (TLC) [9]. Interestingly, these experiments have also shown smaller vertical volume gradients than predicted from pressure volume curves obtained before immersion and local transpulmonary pressure gradients computed after immersion. This unexpected behavior has been explained by mechanical interdependence between vertically distributed lung regions [9], tissue movement from more compressed to less compressed regions [8], and buoyancy-related vertical tissue stretching [10].

The space occupying effect of pleural effusion involves competition between the lung and the fluid for limited room within a single container. The lung is an elastic solid filled with gas, the pleural fluid is naturally incompressible but deformable, and the chest wall is an elastic solid container [11]. In resting equilibrium at functional residual capacity (FRC), the magnitude of the space occupying effect will be a function of the relative compliances of the lung and the chest wall at that point. With lung inflation, the space occupying effect may change in relation to the new relative compliances of both components of the respiratory system at end inspiration. In other words if the chest wall compliance at FRC is two times that of the lung, a pleural effusion would increase chest wall volume and decrease lung volume by two thirds and by one third of the fluid volume, respectively. If at TLC, chest wall compliance is four times that of the lung (as chest wall compliance has not changed and lung compliance is halved), the same effusion would now increase chest wall volume by 4/5 and reduce lung volume by only 1/5 of the fluid volume. Of course this analysis is a simplification as it neglects the effects of pleural effusion-induced lung collapse and chest wall expansion on their respective compliances. It also neglects some anatomic aspects of chest wall compliance. The chest wall is not a uniform container. Flexibility increases from the dorsal ribcage, to the ventral ribcage, and from apex to the diaphragm [12]. Chest wall expansion to accommodate pleural fluid would, therefore, be most likely on its diaphragmatic facet. Lung inflation could in turn redistribute fluid volume to these regions relieving the rest of the lung of both the spatial and hydrostatic influences of pleural effusion (**Fig. 1**).

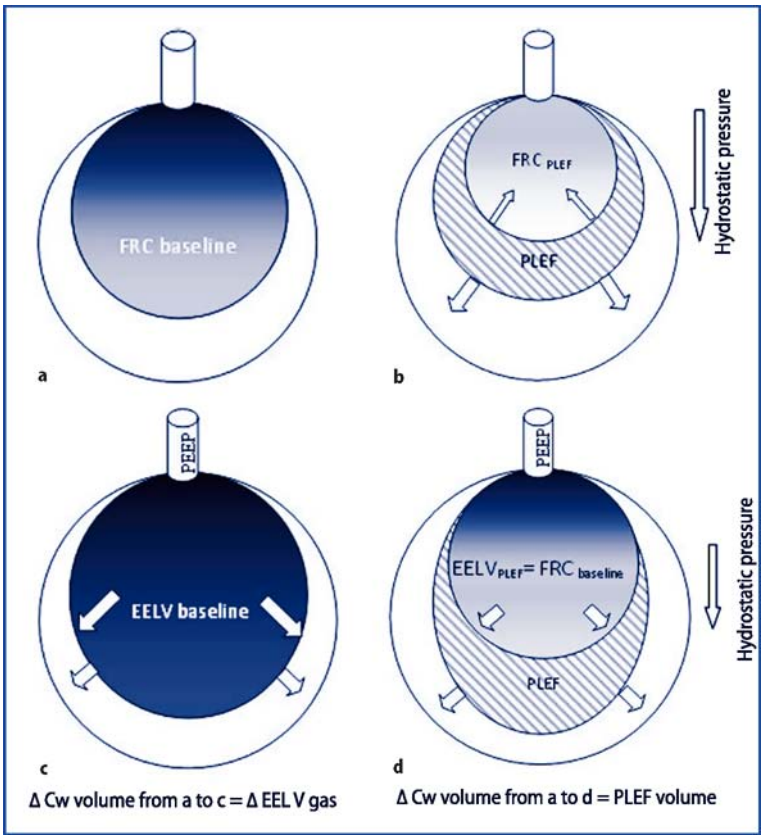

Fig. 1. The effect of pleural effusion (PLEF) and PEEP on lung and chest wall volumes at end expiration. The figure represents the respiratory system in different conditions. Baseline lung and chest wall (Cw) compliances are assumed to be normal. The inner circle represents gas volume in the lungs while the outer one represents the Cw volume. The white area between them represents intrathoracic tissues, including mediastinal organs and vessels. Colorscales are proportional to regional aeration, black representing gas. Cross-hatched area represents pleural fluid. Vertical arrows represent the hydrostatic pressure gradient. **a** Normal resting condition at zero end-expiratory pressure (ZEEP). **b** Pleural effusion at ZEEP separates pleural surfaces causing lung compression and Cw expansion represented by oblique opposing arrows. **c** PEEP expands the lung and the Cw to the same extent. **d** PEEP, acting to stiffen the lung, restores baseline functional residual capacity (FRC) and causes the whole pleural effusion volume to be accepted by the more compliant Cw. Oblique arrows in **c** and **d** represent PEEP-induced expansion of the lung and chest wall. (Note that the hydrostatic pleural pressure gradient enveloping the lung is also diminished). EELV: end-expiratory lung volume

Pleural Effusion and Respiratory Mechanics

Pleural fluid accumulations are generally expected to increase chest wall stiffness and to reduce lung volume in direct proportion to the effusion volume. This vision is prompted by a static and rather rigid view of the respiratory system. Available data on pleural effusion are scarce but suggestive of a more complex behavior.

Krell and Rodarte [13] studied unilaterally infused pleural effusion in head-up healthy dogs and found that lung volume determined by helium dilution decreased

by one third of the volume added to the pleural space at FRC and by one fifth at TLC – defined as the volume at an airway opening pressure 30 cmH_2O. Quite reasonably, they assumed that the corresponding remainders (2/3 and 4/5 of the volume added) were accepted by expanding the chest wall volume. Esophageal pressure and inspiratory capacity changed very little from baseline to the maximal fluid volume added (45 % of control TLC), suggesting that chest wall compliance was not reduced by the effusion. Regional lung volume assessment with the parenchymal marker technique showed that pleural effusion increased the normal vertical inflation gradient at FRC and created one at TLC. Consequently, the reduction in lung volumes induced by pleural effusion can be largely attributed to collapse of the dependent portions of the lung, most prominent at end expiration. It is worth noting that under these conditions, regional pleural pressure and esophageal pressure may be different. In this regard, Miserocchi et al. showed a disproportionate regional increase in pleural pressure in proximity to the effusion [14]. Modeling of the pleural space suggests that whenever there is sufficient fluid accumulation to disrupt the reciprocal lung-chest wall conformation, the vertical pleural pressure gradient becomes hydrostatic (1 cmH_2O/cm) [15]. Lung volume juxtaposed to the fluid would be expected to decrease due to the ensuing reduction in local transpulmonary pressure.

Dechman et al. [16] found opposing changes in dynamic chest wall (small increase) and lung (60 ± 20 % reduction) compliance during saline infusion of up to 60 ml/kg into the pleural cavity of supine dogs mechanically ventilated with a tidal volume of 15 ml/kg and zero end-expiratory pressure (ZEEP). Lung recruitment by expiratory port occlusion for three breaths (transpulmonary pressure ≈ 30 cmH_2O) without subsequent positive end-expiratory pressure (PEEP) application produced transient improvements in lung compliance. Interestingly, respiratory system compliance mirrored the lung compliance response to pleural infusion and recruitment maneuvers, an observation also made in smaller animal models of pleural effusion [17].

In a later study using quantitative computed tomography (CT) analysis of the thorax at end expiration, the same group confirmed the 1/3 and 2/3 proportional distribution of the effusate between lung volume loss and chest wall volume expansion in supine dogs instilled with 60 ml/kg pleural effusion [18]. An increase in the lung vertical density gradient evocative of dependent degasification of the airspaces was also noted after pleural effusion [18].

The improvement in lung compliance with recruitment maneuvers [16] and the reduced deviation from normal lung inflation at an airway opening pressure of 30 cmH_2O [13] suggests that – when the lungs and chest wall are otherwise normal – airspace collapse can be easily reversed by increasing airway pressure and that the displaced pleural fluid is readily accommodated by the compliant chest wall. Correspondingly, a number of studies in spontaneously breathing patients with unilateral pleural effusion have shown disproportionately small increases in lung volumes after near complete evacuation of large fluid collections [19–23], and no [19] or poor [20] relationship between volumes of liquid extracted and lung gas volume recovered.

In a landmark study involving spontaneously breathing patients, Estenne and collaborators [21] observed that thoracocentesis of large unilateral pleural effusions resulted in a mean increase in plethysmographic FRC equivalent to one fourth of the fluid removed (mean 1.8 l) alongside a small increase in static expiratory lung compliance and transpulmonary pressure at FRC. They documented dyspnea relief and improvement in the negative esophageal pressure generated during maximal inspiratory efforts after drainage. These results were attributed to the large reduction in

total thoracic volume (assumed to be three-fourths of the fluid removed at FRC) that restored the inspiratory muscles to a more advantageous portion of their length-tension curve [21].

As stated above, the magnitude of the opposing changes in lung and chest volume with pleural fluid accumulation or evacuation will depend on their relative compliances. The more compliant the lung, the greater the change in FRC; the more compliant the chest wall, the greater the thoracic cage adjustment with a smaller impact on lung volume [19]. This effect may help to explain the lack of impact of thoracentesis on respiratory system mechanics and gas exchange in eight mechanically ventilated ICU patients with a PaO_2/FiO_2 ratio close to 100 [24]. The removal of a mean effusion volume of ~1.5 l did not change static tidal compliance of the respiratory system, measured as close to ZEEP as possible, suggesting that all the volume change was accounted for by the chest wall with little effect on lung volume and mean pleural pressure.

Effects of Pleural Effusion on Gas Exchange

Lung collapse associated with pleural effusion should lead to hypoxemia due to ventilation-perfusion mismatch or true shunt. The extent of these abnormalities depends on the perfusion of the compressed airspaces, as determined by local factors such as hypoxic vasoconstriction and vascular compression. The single published experimental study that explored the gas exchange effects of pleural effusion was conducted in dogs without lung injury [25]. As pleural liquid volume increased, PaO_2 decreased and intrapulmonary shunt increased in a dose-dependent fashion. Cardiac output augmentation by intravascular volume expansion further increased the shunt fraction, consistent with the known association between cardiac output and shunt [26]. At the higher pleural volumes, $PaCO_2$ increased despite adjustments guided by end tidal PCO_2 in set respiratory rate, probably due to a "shunt dead space" effect [27].

In contrast with this strong experimental effect of pleural infusion on gas exchange, a number of studies in spontaneously breathing patients have shown that unilateral drainage of large pleural effusions has mild and variable effects on oxygenation [19, 23, 28, 29]. Notably, dyspnea was almost universally relieved in these patients. Agustí et al. [30] performed an in-depth study of gas exchange using the multiple inert gas elimination technique. At baseline they found little oxygenation impairment caused largely by mild intrapulmonary shunt that was unaffected by thoracocentesis.

Four studies addressing the oxygenation response to pleural effusion drainage in mechanically ventilated patients disclosed variable results. Doelken et al. using the lowest end expiratory pressure possible, both before and after the intervention, found no immediate post-procedure change in PaO_2 [24]. Ahmed et al. also found no improvement in the PaO_2/FiO_2 ratio or PA-aO_2 difference (along with a difficult to explain small reduction in shunt fraction) among 22 patients with pleural effusion drained by pigtail catheters. PEEP was not reported but tidal volume and peak inspiratory pressure did not change after drainage [31]. Conversely, Talmor et al. retrospectively identified 19 ventilated patients with pleural effusion and a PaO_2/FiO_2 ratio less than 200 after an incremental PEEP titration up to 16.6 ± 1 cmH_2O. Chest tube drainage – mean 863 ml at 8 hours – led to an immediate significant increase in the mean PaO_2/FiO_2 ratio from 151 to 253.6 that persisted after 24 hours [32].

Unfortunately, the PEEP level set after drainage was not reported, but there was no change in peak airway pressures. There was no correlation between the volume of fluid removed and oxygenation benefit [32]. Similarly, Roch and collaborators found that chest tube drainage of > 500 ml effusate in 24 patients – mean 1050 ml at 1 hour – was associated with a significant increase in mean PaO_2/FiO_2 ratio from 206 to 251 without changing PEEP (mean 6 ± 2 cmH_2O) [33]. In a second cohort of 20 patients, evacuation of smaller volumes did not affect this oxygenation index [33].

Although it is difficult to reconcile these conflicting observations, idiosyncratic differences in lung disease severity and hypoxic vasoconstriction as well as the amount of lung collapsed by pleural fluid and in the volume reexpanded by drainage should account for the variable results on gas exchange. The following section describes how lung and chest wall mechanics of pleural effusion, as already depicted, may interact with positive pressure ventilation to produce a diverse response to drainage.

Practical Implications for the Mechanically Ventilated Patient with Pleural Effusion

In mechanically ventilated patients, the effects of pleural effusion drainage on gas exchange depend on the lung volume reduction attributable to the effusion, the perfusion of these units, and the airway pressure applied. When collapse is extensive and protracted, or the external pressure exerted by the effusion and the chest wall is large, alveolar pressures generated during the ventilator-driven respiratory cycle may not be enough to reopen collapsed lung before or even after pleural effusion drainage. This inability could explain the lack of improvement in oxygenation and static compliance after pleural effusion drainage reported by Doelken et al. in patients where the least PEEP was applied [24].

In deciding whether to evacuate a pleural effusion with the intent to improve oxygenation, assessing chest wall compliance may help (**Fig. 2**). In the critically ill patient, reduced chest wall compliance frequently arises from abdominal pathology, and abdominal hypertension can be considered a clear indicator of reduced chest wall compliance [34, 35]. Direct computation of chest wall compliance requires esophageal pressure measurement. However the validity of esophageal pressure in the presence of pleural effusion has not been demonstrated.

If the chest wall compliance is normal, lung collapse and intrapulmonary shunt induced by pleural effusion are probably limited, but increasing airway pressure is likely to reverse them. We have recently observed that PEEP application maintains near baseline values for FRC, lung aeration, and tidal compliance in healthy pigs with large unilateral pleural effusion (Graf J et al., unpublished data). In these conditions, PEEP may promote recruitment not only by keeping positive transpulmonary pressures at lower vertical levels. If lung inflation by PEEP increases chest wall compliance relative to lung compliance, a greater portion of the fluid will expand the chest wall relieving some space occupying effect on the lung. PEEP induced lung inflation may also promote diaphragmatic redistribution of the fluid that could further reduce its hydrostatic effects on the lung (**Fig. 1**). When the chest wall is normal, respiratory system compliance largely reflects lung compliance [16, 17] and should help to track lung volume response to recruitment maneuver and drainage. Under these conditions a recruitment maneuver may help to define the impact of pleural effusion on lung volume and gas exchange. If the static compliance of the respiratory

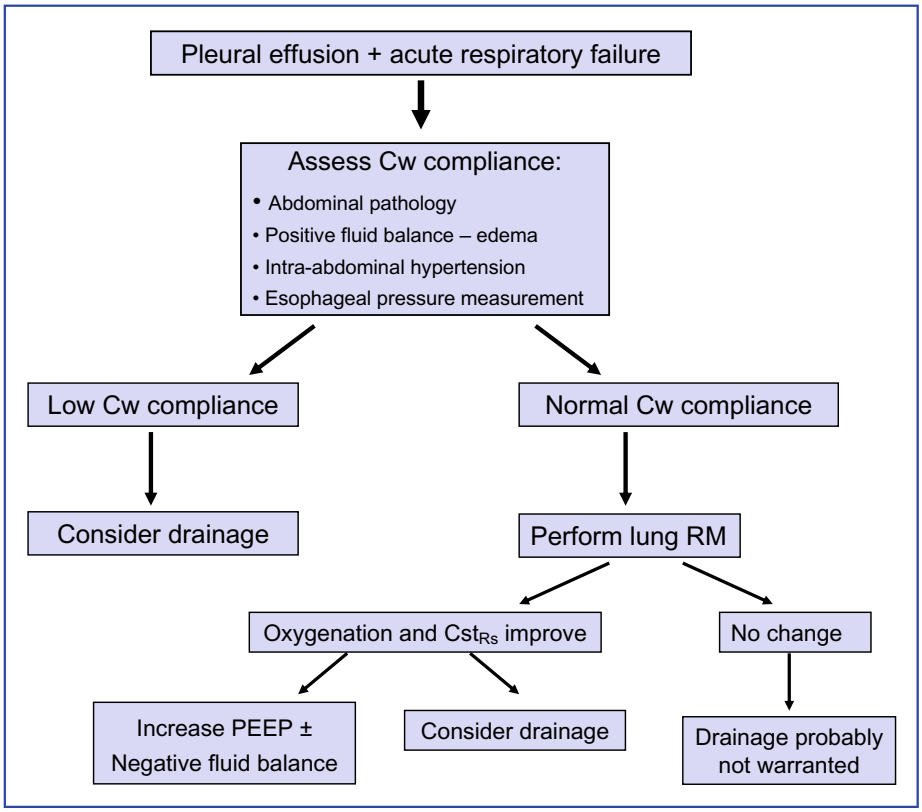

Fig. 2. Proposed algorithm for the management of pleural effusion for gas exchange considerations in mechanically ventilated patients with acute respiratory failure. Cw: chest wall; PEEP: positive end-expiratory pressure; RM: recruitment maneuver; Cst_{Rs}: static compliance of the respiratory system. From [49] with permission.

system and oxygenation improves after the recruitment maneuver, increasing PEEP may offset lung collapse attributable to pleural effusion. Alternatively drainage could reduce the PEEP level needed to sustain such recruitment. Conversely, if chest wall compliance is normal and there is no benefit from the recruitment maneuver, lung collapse due to pleural effusion is probably minor and drainage for gas exchange improvement is not warranted.

On the other hand, when chest wall compliance is low, the space occupying and hydrostatic pressure effects of pleural effusion are maximized and its impact on lung volume and gas exchange amplified. A reduced chest wall compliance also limits the improvements expected from increasing airway pressure by confining the lung. Nevertheless, a greater potential benefit of pleural effusion drainage can be expected. With a large pleural effusion and a stiff chest wall a recruitment maneuver or PEEP increase may prove ineffective, whereas the same intervention applied after pleural effusion drainage may yield impressive results. Perhaps by only including patients with pleural effusion unresponsive to high PEEP, Talmor et al. [32] selected those with low chest wall compliance, in whom the compressive effects of pleural effusion on the lung are maximal. Without an integral assessment of respiratory mechanics

– including the abdomen – the amplifying effect of pleural effusion on chest wall restriction can only be discovered by fluid drainage.

When weaning is being considered, chest wall expansion by pleural effusion becomes more relevant. Drainage increases respiratory muscle mechanical efficiency [21], relieves dyspnea [19, 21, 23, 28, 29], and reduces the work of inflation performed by the ventilator during controlled breaths [24]. Presumably the work of breathing should be reduced for the patient as well. We think this physiologic background is enough to anticipate a beneficial effect of pleural effusion drainage when a mechanically ventilated patient is being prepared to resume spontaneous breathing. In this context, pleural effusion management, either by direct intervention or by promoting negative fluid balance, may facilitate liberation from mechanical ventilation, particularly in the difficult-to-wean patient.

It should also be emphasized that, although ultrasonographic guidance and use of small bore catheters may facilitate pleural effusion drainage and reduce its complications, mainly bleeding and pneumothorax [36–39], these risks should always be weighed against the potential benefits of the intervention.

Pleural Effusions and Ventilator-induced Lung Injury?

If the chest wall and underlying lung are normal, the dependent lung collapse associated with pleural effusions should be readily reversible not only when approaching TLC, but also during tidal ventilation. If tidal volume is large enough, low pressure tidal recruitment could take place as the fluid is cyclically displaced and accepted by a compliant chest wall that intermittently relieves the space occupying and hydrostatic lung compression.

Cyclic airspace collapse has been invoked as one of the mechanisms of ventilator-induced lung injury (VILI) [40]. This concept stems mainly from small animal models of surfactant deficiency/depletion where ventilation with low PEEP [41, 42] or low mean airway pressures on high frequency oscillation [43] was followed by bronchiolar epithelial lesions, hyaline membrane formation, and molecular evidence of lung inflammation [44]. This low lung volume injury or atelectrauma [40] was averted in these studies by the use of high PEEP/high mean airway pressure, particularly if preceded by brief sustained lung inflation. Large tidal volume ventilation from ZEEP in small intact animals [45] or below FRC in open chest large animals [46] leads to acute permeability lung edema. Neither experimental setup resembles the kind of tidal recruitment that could take place with moderate tidal volumes in lungs under pleural effusion. More recently, however, D'Angelo et al. observed bronchiolar injury and increased airway resistance in open chest rabbits ventilated with moderate tidal volumes from ZEEP for 3–4 hours [47]. There was no evidence of alveolar damage in this model. A subsequent study in endotoxemic rats, with and without thoracotomy, ventilated with moderate tidal volumes for 2 hours showed marked interstitial inflammatory cell infiltration only in those subjected to thoracotomy [48]. In both reports, a low PEEP level was enough to prevent the documented damage. It remains to be determined whether pleural effusions have the potential to induce or augment VILI through lung volume reduction.

Conclusion

Pleural effusion arises when lung edema flow to the pleural space exceeds the high absorptive capacity of parietal pleural lymphatics. Pleural effusion induces lung distortion by creating a hydrostatic pleural pressure gradient and by a space occupying effect. Increases in local pleural pressure reduce regional transpulmonary pressure and lung volume. The space occupying effect of pleural effusion is shared between chest wall expansion and lung collapse in proportion to their relative compliances. Normally the chest wall accepts most of the effusion volume, buffering its pleural effusion effects on the lung. Therefore, if chest wall compliance is reduced, pleural effusion may dramatically amplify chest wall restriction and compress the lung. The oxygenation effects of pleural effusion drainage are usually small in non-ventilated patients but variable in ventilated ones. Here, chest wall compliance is probably a major determinant of the response to pleural effusion drainage, and its assessment may predict whether evacuation will improve oxygenation. If there is evidence for reduced chest wall compliance, pleural effusion drainage should have a positive impact on gas exchange and respiratory mechanics. If chest wall compliance is normal, a recruitment maneuver may help to predict the impact of pleural effusion drainage – the effect of a recruitment maneuver should parallel the effect of either PEEP increase or drainage on lung volume and gas exchange. As chest wall expansion by pleural effusion reduces respiratory muscle efficiency and contributes to dyspnea during spontaneous breathing, drainage may help in weaning from ventilatory support. In addition, hemodynamic status, timing and procedural complication risks should be considered when choosing the best approach to pleural effusion management.

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Weaning Failure of Cardiac Origin: Recent Advances

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Introduction

Mechanical ventilation generally exerts negative hemodynamic effects in patients with normal cardiac function mainly because of the reduction in venous return induced by positive intrathoracic pressure at each insufflation [1]. By contrast, positive pressure ventilation exerts beneficial effects in patients with cardiogenic pulmonary edema such that it is routinely used as a therapy in this category of patients [2, 3]. Conversely, cardiac consequences of spontaneous breathing may be responsible for weaning failure in patients with left heart disease, even though the mechanical ventilation was required for respiratory failure of non-cardiac origin. Since its first description more than twenty years ago [4], cardiogenic pulmonary edema has been recognized as a frequent cause of weaning failure in patients with underlying left cardiac dysfunction.

In this chapter, we first briefly summarize the mechanisms by which pulmonary edema can develop during weaning. We then emphasize how weaning failure of cardiac origin can be detected at the bedside since significant progress has recently been made in this field. Finally, we describe the therapeutic options currently available.

Mechanisms Contributing to the Development of Weaning-induced Pulmonary Edema

The mechanisms that contribute to development of cardiogenic pulmonary edema during weaning have been extensively detailed in a previous review [5]. These mechanisms are complex and mainly include the inspiratory fall in intrathoracic pressure, the increase in work of breathing, and the catecholamine discharge that occur during abrupt transfer from mechanical ventilation to spontaneous breathing [5]. Inspiratory fall in intrathoracic pressure tends to increase the systemic venous return pressure gradient and the central blood volume [5], and to decrease the left ventricular (LV) ejection pressure gradient with a resulting increase in LV afterload [5]. A marked increase in work of breathing may increase cardiac work and myocardial oxygen demand [5]. The increased adrenergic tone may also increase venous return, LV afterload, cardiac work, and myocardial oxygen demand and may thus potentially result in myocardial ischemia in predisposed patients [4, 6]. In patients with pre-existing right ventricular (RV) disease, an increase in weaning-induced RV afterload may occur because of hypoxemia or worsening of intrinsic positive end-expiratory pressure (PEEPi) [5]. In addition to the simultaneous increase in systemic

venous return, the increased RV afterload may lead to a marked RV enlargement during weaning, thus impeding the diastolic filling of the left ventricle through a biventricular interdependence mechanism [5]. In summary, elevation of the LV filling pressure can occur during weaning because of an increase in LV preload and/or decrease in LV compliance (myocardial ischemia, biventricular interdependence) and/or increase in LV afterload. However, in the absence of left heart disease, the rise in pulmonary artery occlusion pressure (PAOP) is limited [7, 8]. In contrast, marked increases in PAOP have been reported to occur during unsuccessful weaning in patients with left heart disease [4, 9–12], who can thus be suspected to have failed to wean because of the onset of cardiogenic pulmonary edema.

V

Diagnosis of Weaning-induced Pulmonary Edema

Clinical Context

The diagnosis of weaning-induced pulmonary edema should be suspected when intolerance to a spontaneous breathing trial (SBT) occurs and other causes of weaning failure have been discarded. The suspicion is reinforced by the fact that the patient has a previous history of left heart disease. Patients with a combination of left heart disease and chronic obstructive pulmonary disease (COPD) are at higher risk of weaning-induced pulmonary edema. In this situation, the increase in airway resistance amplifies two mechanisms responsible for LV filling pressure elevation: 1) the fall in intrathoracic pressure is exaggerated at inspiration leading to a marked increase in LV afterload during spontaneous breathing; and 2) the work of breathing further augments leading to increased myocardial oxygen demand with inherent risks of myocardial ischemia in predisposed patients. In addition, the biventricular interdependence phenomenon can be marked in COPD patients with pre-existing RV dilation and thus can significantly contribute to LV filling pressure elevation.

The early onset of respiratory distress after starting a weaning trial is assumed to be suggestive of weaning-induced pulmonary edema, although there is no clear evidence in the literature to support this assumption. In our experience, the combined increase in arterial pressure and heart rate during unsuccessful weaning is quite suggestive of weaning failure of cardiac origin [11, 12], although false positive and false negatives can be encountered [11].

Right Heart Catheterization

Right heart catheterization can be helpful in the evaluation of acute dyspnea in patients with concomitant pulmonary and cardiac disease, since it allows measurement of PAOP, pulmonary artery pressure, right atrial pressure, and oxygen-derived variables [13]. In this regard, right heart catheterization was first proposed to establish the diagnosis of weaning-induced pulmonary edema. A higher than normal value of PAOP measured during an unsuccessful SBT is highly suggestive of weaning-induced pulmonary edema [14]. There is no definite value of PAOP above which cardiogenic pulmonary edema develops, although 18 mmHg is recognized as a classical cut-off value [15]. Numerous studies have shown increases in PAOP during weaning in patients who failed to wean [4, 9–12]. Lemaire and colleagues [4] reported an average increase in transmural PAOP from 8 to 25 mmHg in unsuccessful weaning trials in 15 patients with both COPD and left heart disease. Interestingly, after diuretic therapy, 60 % of these difficult-to-wean patients could be suc-

cessfully weaned with no further increase in PAOP during weaning [4]. This strongly suggests that the weaning-induced elevation of PAOP played a major role in the difficulty to wean of these patients.

In all these studies, the increase in PAOP during unsuccessful weaning was not associated with a decrease in cardiac output [4, 10–12]. In fact, the weaning process is quite similar to an exercise test such that an increase in cardiac output is expected to occur in response to the increased work of breathing and to the stress created by the abrupt transfer of the patient from mechanical ventilation to spontaneous breathing [16]. Patients with impaired cardiac function may fail to sufficiently increase cardiac output and oxygen transport in response to increased oxygen requirements. These patients may thus experience not only an increase in PAOP but also a decrease in mixed venous blood saturation (SvO_2) during weaning as reported in clinical studies [10–12]. Although the decrease in SvO_2 is obviously not an indicator of cardiogenic pulmonary edema, it can identify weaning failure from cardiac origin as well as the elevation in PAOP can. As long as the central venous oxygen saturation ($ScvO_2$) reflects SvO_2, simple central venous catheterization could thus be a tool to detect weaning failure from cardiac origin. Further studies are, however, needed to confirm this hypothesis.

To summarize, right heart catheterization can be helpful for diagnosing weaning failure from cardiac origin since it may not only identify patients with elevated PAOP during weaning but also provide important information about the mechanisms responsible for weaning-induced acute cardiac dysfunction. Nevertheless, pulmonary artery catheterization remains an invasive procedure [13]. Recent research studies have been undertaken to find less invasive tools for identifying weaning failure from cardiac origin.

Transthoracic Echocardiography

Echocardiography has become a routine tool for evaluating the cardiovascular status in critically ill patients. It is now possible to estimate LV filling pressures using Doppler transmitral flow and Doppler tissue imaging variables [17]. Doppler transmitral flow allows the early (E) and late (A) peak diastolic velocities to be measured, and tissue Doppler imaging of the mitral annulus allows the early (Ea) peak mitral annulus diastolic velocity to be measured. In a series of 39 difficult-to-wean patients, Lamia and colleagues [12] tested the hypothesis that E/A and E/Ea could be used to detect weaning-induced elevation defined by a PAOP $\geq$ 18 mmHg during a SBT. The major finding of this study was that the combination of $E/A > 0.95$ and of $E/Ea > 8.5$ at the end of the SBT predicted a PAOP $\geqq$ 18 mmHg with good sensitivity (82 %) and specificity (91 %) while the cut-off values of E/A alone and of E/Ea alone had weak specificity (68 % and 73 %, respectively). The study by Lamia and colleagues [12] thus provides evidence that a totally non-invasive method can identify patients with weaning-induced pulmonary edema. Moreover, as echocardiography is a valuable method to evaluate cardiac function at the bedside, it can also provide clinicians with important information about the main mechanisms responsible for cardiac dysfunction during weaning. However, echocardiography is an operator-dependent method that requires a long training period to ensure critical care physicians are skilled enough to use it properly. Other tools that can more simply detect weaning-induced pulmonary edema are, therefore, necessary.

Cardiac Biomarkers

B-type natriuretic peptide (BNP) and N-terminal proBNP (NT-proBNP) are peptides synthesized by the ventricular myocytes in response to an increased myocardial stretch. Both systolic and diastolic dysfunction of the left ventricle can result in high circulating BNP and NT-proBNP levels. In critically ill patients, such cardiac biomarkers are increasingly used as screening tools to rule out cardiac dysfunction [18, 19]. Two recent studies addressed the question of whether BNP or NT-proBNP could be used to identify patients who fail to wean for cardiac reasons [20, 21]. However, the results of these two studies are not straightforward. Mekontso-Dessap and colleagues showed that, before the first weaning attempt, the plasma BNP level was higher in patients with subsequent weaning failure [20]. The area under the receiver operating characteristic (ROC) curve for plasma BNP to predict weaning failure was 0.89 ± 0.04 and a cut-off value of 275 pg/ml was associated with the highest diagnostic accuracy (86 %). However, one may wonder whether it is really pertinent to predict results of a simple and safe test such as a SBT, rather than performing it. Indeed, simply observing how a patient breathes during an unsuccessful SBT can provide a large amount of information about the mechanisms responsible for the weaning failure. Therefore, in our opinion, there is no real need to measure the BNP level simply in order to avoid performance of a SBT. Moreover, the fact that plasma BNP concentration was higher before the SBT in patients who subsequently failed the SBT does not mean that cardiac dysfunction and cardiogenic pulmonary edema occurred during the SBT. High baseline plasma BNP concentration before the SBT may rather reflect a more severe global condition in patients who did not tolerate the SBT. It should be stressed that the plasma BNP level can be elevated in cases of advanced age, sepsis, renal dysfunction, and pulmonary hypertension, even in the absence of left heart dysfunction [18]. In this context, systolic cardiac dysfunction assessed by echocardiography did not differ between patients who succeeded and patients who failed the weaning trial in the study by Mekontso-Dessap and colleagues [20]. Moreover, there was no difference in the BNP level before and at the end of the weaning trial in the two groups of patients. Overall the results reported by Mekontso-Dessap and colleagues [20] underline the uncertainty of using plasma BNP levels to reliably identify patients who experience weaning failure of cardiac origin. The study by Grasso and colleagues [21] evaluated the significance of NT-proBNP in detecting weaning failure of cardiac origin in COPD patients. The cardiac origin of weaning failure was determined by one cardiologist and one critical care physician blinded to the results of the NT-proBNP measurements [21]. Their diagnosis was based on the review of echocardiograms, electrocardiograms (EKGs), and clinical, hemodynamic, gas exchange and respiratory variables obtained at baseline and at the end of the SBT. Interestingly, the elevation of NT-proBNP during a SBT but not the baseline NT-proBNP predicted weaning-induced cardiac dysfunction with an acceptable accuracy [21]. Because of the limited number of patients included in this study, confirmation in a larger cohort of patients is needed.

Clearly, suspicion of acute cardiac dysfunction during weaning using a change in NT-proBNP levels should prompt further cardiac evaluation (e.g., echocardiography) aimed at confirming the cardiac origin of weaning failure. In our opinion, the divergent results reported by Mekontso-Dessap and colleagues [20] and Grasso and colleagues [21] should urge caution in the use of natriuretic peptide values for diagnosing weaning-induced pulmonary edema. It must be stressed that in neither of these two studies was pulmonary artery catheterization performed to evidence elevation of PAOP during weaning. Further studies are thus mandatory.

Detection of Weaning-induced Hemoconcentration

Weaning-induced pulmonary edema is assumed to be a hydrostatic pulmonary edema resulting from an increased LV filling pressure. Hydrostatic pulmonary edema is accompanied by transfer of a hypo-oncotic fluid from the lumen of the pulmonary capillaries toward the interstitium [22]. When the amount of transferred fluid is large enough, hydrostatic pulmonary edema may result in hemoconcentration that could be detected on the basis of changes in plasma protein or hemoglobin concentrations or hematocrit [22] (**Fig. 1**). In a recent study, we hypothesized that an acute occurrence of hemoconcentration during weaning could help to diagnose weaning-induced pulmonary edema [11]. We defined weaning-induced pulmonary edema as intolerance to spontaneous breathing and elevation of PAOP above 18 mmHg at the end of a SBT. We inserted a pulmonary artery catheter in 46 patients who failed two consecutive SBTs although there was no obvious cause of weaning failure [11]. Twenty-four of these patients experienced weaning-induced pulmonary edema with an increase in the median value of PAOP from 13 mmHg (range: 7 – 16 mmHg) to 26 mmHg (range: 18 – 50 mmHg) during the third SBT [11]. In these patients, the plasma protein concentration increased significantly during the SBT. An increase in plasma protein concentration greater than 6 % during the weaning trial enabled weaning-induced pulmonary edema to be detected with a sensitivity of 87 % and a specificity of 95 % [11]. This 6 % cut-off provided a very high positive likelihood ratio value (19.25) and a negative likelihood ratio value of 0.13 [11]. The area under the ROC curve generated for changes in plasma protein concentration (0.93 ± 0.04) was significantly higher than that generated for changes in SvO_2 during the SBT (0.70 ± 0.08) [11]. Interestingly, in 13 patients who experienced weaning-induced pulmonary edema at the third SBT, the fourth weaning trial was again monitored with a pulmonary artery catheter after they had received diuretics and/or vasodilators [11]. None of these patients experienced recurrent weaning-induced pulmonary edema and the plasma protein concentration did not change during their

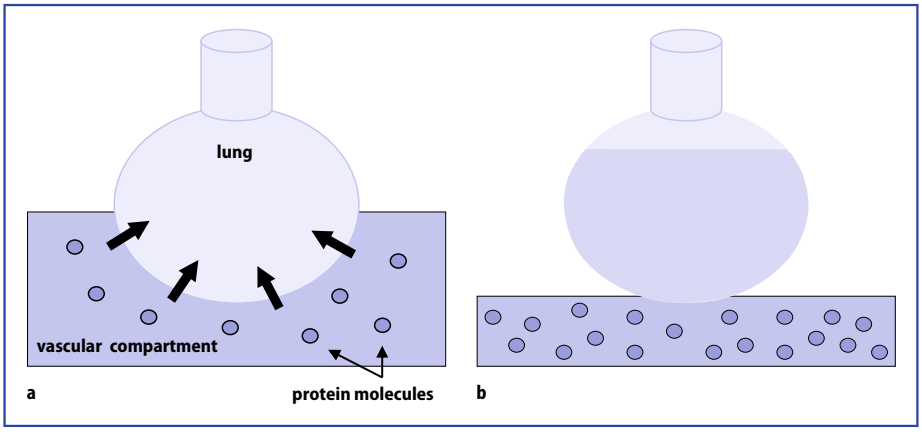

Fig. 1. a As weaning-induced pulmonary edema is of a hydrostatic nature, its development is characterized by transfer of a hypo-oncotic fluid from the pulmonary capillary lumen toward the interstitial compartment and then the alveoli. Molecules like proteins cannot flow across the lung barrier owing to their high molecular weight. **b** After equilibrium is reached, weaning-induced pulmonary edema is thus characterized by a contraction of the vascular compartment and an augmentation in the plasma protein concentration.

fourth SBT [11]. This study strongly suggests that measuring acute changes in plasma protein concentration during a weaning trial represents a minimally invasive alternative to right heart catheterization for identifying patients that experience weaning-induced pulmonary edema.

No study has compared the different tools aimed at diagnosing the cardiac origin of weaning failure. In our opinion, measuring the change in plasma protein concentration during a SBT is the simplest tool for reliably screening patients for weaning-induced pulmonary edema. Echocardiography can provide further confirmation, and can also offer useful information about the mechanisms responsible for the weaning failure.

V Therapeutic Options

The treatment of weaning-induced pulmonary edema should obviously take into account the mechanism suspected to be mainly responsible for the weaning failure. It is thus important to first carefully analyze the cardiovascular response to a SBT and then to monitor the chosen therapy using an invasive or non-invasive hemodynamic tool.

Diuretic therapy must be considered when excessive increased preload during weaning is suggested as the main mechanism responsible for weaning failure. In this context, in the study by Lemaire and colleagues [4], 9 of the 15 patients who initially failed to wean because of development of pulmonary edema successfully weaned after one week of treatment with furosemide, which resulted in fluid losses equivalent to 5 litres. After treatment, PAOP was lower at the end of a SBT than it was before treatment was administered (9 ± 3 vs 25 ± 15 mmHg). The attitude of empirically giving diuretics in every difficult-to-wean patient has become more and more frequent. Nevertheless, it seems to us difficult to recommend such an approach since extra-cardiac causes are responsible for weaning failure in at least 50 % of this group of patients [11, 12] and since uncontrolled diuretic therapy can have potentially harmful effects.

In cases where excessive increased afterload is suspected as the main mechanism, administration of vasodilators may be chosen instead of (or in addition to) diuretics. In our experience, the onset of a marked increase in systolic arterial pressure during a SBT represents a reasonable indication for vasodilator administration. Nitrates may be a good therapeutic choice since this treatment can decrease both LV afterload and central blood volume (cardiac preload effect). In addition, because of its coronary vasodilating effects, it can be even more helpful when myocardial ischemia is one of the mechanisms responsible for the weaning failure.

Use of β_1-agonist agents, such as dobutamine, is not logical in this context since weaning-induced pulmonary edema can hardly be caused by a reduction in cardiac contractility (see above). Moreover, unsuccessful weaning is associated with a huge increase in endogenous catecholamine discharge and administration of β_1-agonist agents can further increase myocardial oxygen demand with its inherent risks of myocardial ischemia in predisposed patients. However, phosphodiesterase inhibitors, such as enoximone, have been reported to be efficacious for treating the weaning-induced pulmonary edema that can develop after cardiac surgery [9]. It is likely that the vasodilating effect of these drugs could have significantly contributed to their beneficial impact. Finally, calcium channel blockers have been reported to facilitate successful weaning in the particular context of hypertrophic cardiomyopathy [23].

In terms of ventilatory modalities, there is no definite recommendation. After unsuccessful weaning of cardiac origin, reinstitution of mechanical ventilation is mandatory. The practice of progressive decrements of pressure support levels while keeping 5 to 8 cmH_2O of PEEP could be an interesting option since pressure support is assumed to increase LV afterload less than spontaneous breathing [24]. After extubation, non-invasive positive pressure ventilation using a face mask could be used. However, there is no definite recommendation about this practice [25].

Conclusion

Acute cardiac dysfunction and cardiogenic pulmonary edema may occur during weaning from mechanical ventilation, especially in patients with a history of left heart disease and COPD. Among the complex and intricate mechanisms, myocardial ischemia, excessive increased LV afterload, and increased cardiac preload play predominant contributing roles. Measuring the elevation in PAOP using right heart catheterization was first proposed as a means of diagnosing weaning failure of cardiac origin. Less invasive tools, such as transthoracic echocardiography or measurements of plasma protein concentration, have recently been proposed as valuable alternative diagnostic methods for weaning-induced pulmonary edema. There is no codified treatment for weaning-induced pulmonary edema. Use of diuretics and/or nitrates should be considered after careful analysis of the main contributing mechanisms.

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VI Respiratory Failure

The Effects of Pleural Effusion

D. Chiumello, V. Berto, and E. Gallazzi

Introduction

In healthy subjects, the pleural space, which is delimited by the visceral and parietal pleura, contains only a small amount of fluid, ranging from 10 to 20 ml [1]. This liquid usually originates from the capillaries of the parietal pleura and is drained by the lymphatics of the parietal pleura. However, in ill patients the fluid can originate from the visceral pleura or directly from the peritoneal cavity through the diaphragm. Basically, liquid accumulates every time there is an excess in liquid formation or a reduction in drainage. Medical or surgical patients are rarely admitted to the intensive care unit (ICU) for primary pleural disease; however, the pleura can be affected by various pulmonary or extrapulmonary conditions that promote the development of pleural effusions, which can affect the respiratory system [2].

The incidence of pleural effusion is estimated at 1 million cases in the United States per year [3]. The incidence of parapneumonic effusions among individuals with pneumonia ranges from 20 to 97 % [4–7], while in decompensated congestive heart failure the incidence may be as high as 87 % [8]. In a series of medical ICU patients, the incidence of pleural effusion was 8.4 % per year [9]. In a group of one hundred consecutive patients admitted to medical intensive care, 41 had pleural effusion at admission and an additional 21 patients developed an effusion during their ICU stay [2]. The mean age of patients with pleural effusion was 54 ± 2 years and of those without effusion was 47 ± 2 years. The albumin concentration in the group with pleural effusions was less (2.4 ± 0.1 g/dl) than that in patients without effusion (3.0 ± 0.1 g/dl) and those with effusions had longer ICU stays (9.8 ± 1.0 vs 4.6 ± 0.7 days) and duration of mechanical ventilation (7.0 ± 1.3 vs 1.9 ± 0.7 days).

Pathogenesis

Pleural effusions can originate from pulmonary or extrapulmonary conditions, including lung infections, tumors, congestive heart failure, hypoalbuminemia, atelectasis, sepsis, and acute kidney injury [10]. The altered pleural liquid turnover leads to a pleural effusion when filtration exceeds absorption or when one of the important absorbing systems is primarily altered and the compensatory mechanisms cannot maintain the homeostasis. The formation of pleural effusions may be due to several causes that act by modifying the pressure mounted by the pleura, by damaging the lymphatic drainage system, or by increasing the permeability of membranes in the capillary endothelium and mesothelium. The result is an increase in fluid in

the pleural cavity with or without an increase in protein concentration, a condition which allows the effusion to be classified as a transudate or an exudate. Transudates are defined as the liquid that accumulates because of increased permeability of capillaries and the mesothelium, which alters the filtration rate of the pleura; it may also accumulate in absence of altered pleural liquid turnover by entering the pleural space through a non-physiological means, such as pleuro-peritoneal communication during peritoneal dialysis or presence of ascitic fluid driven by the pressure gradient between the abdomen and the pleural space., Exudates, according to Light's criteria, are primarily generated by an impairment in lymphatic drainage and caused, for example, by tumors, infections and gastrointestinal diseases. An exudative effusion is defined by a ratio between pleural fluid proteins and plasma proteins of greater than 0.5, a ratio of lactate dehydrogenase in the pleural fluid and plasma greater than 0.6, or by a lactate dehydrogenase content of the pleural fluid equal to 2/3 of the value contained in normal serum [11]. Transudative effusions are usually related to congestive heart failure, hepatic hydrothorax, or nephrotic syndrome. Exudative effusions may be due to infection, e.g., empyema or parapneumonic effusion, or non-infectious conditions, e.g., surgery or intra-abdominal malignancy [12].

In a report from a population of critically ill patients, non-infectious causes of pleural effusion were present in 82 % of patients; heart failure was the leading cause of all effusions (35 %) and atelectasis was the second cause (23 %) [2]. The most common cause of bilateral effusions was again heart failure (38 %), while atelectasis was the most frequent cause of unilateral effusion (36 %) [2]. Effusions due to hypoalbuminemia were reported in only 8 % of the patients and were caused by severe malnutrition. Roch et al. reported that pleural effusion was predominantly parapneumonic (41 %) and/or consecutive to heart failure in 20 % of cases, to hypoalbuminemia in 18 %, and to peritonitis in 11 % [13].

Effects of Acute Pleural Effusion on Lung Volume, Respiratory System Mechanics, and Gas Exchange

Animal studies, in which fluid was introduced into the pleural space, demonstrated a gravitationally oriented gradient of pleural pressure of about 1 cmH_2O per cm of height [14]. This increase in pleural pressure gradient should promote lung atelectasis and airway closure.

Krell and Rodarte studied the effect of acute pleural effusion on the lung and chest wall in six head-up anesthetized dogs [15]. The functional residual capacity (FRC) was measured by a helium dilution technique, while total lung capacity was defined as the volume at an airway pressure of 30 cmH_2O. Mean effusion volumes were 9, 25 and 45 % of the total lung capacity and were introduced into the thorax via a polyethylene catheter in the right pleural space. An esophageal balloon positioned in the lower half of the esophagus, approximately at the level of the heart, was used to estimate the pleural pressure. More than 90 % of the added saline was recovered from the dogs' thoracic cavities, indicating that no significant absorption of saline occurred during the study. Both FRC and total lung capacity decreased with increasing amounts of saline added to the pleural space. The decrease in FRC was about one third the amount of saline added; the other two thirds of the saline volume must, therefore, have increased the chest wall volume. A similar volume change was observed at total lung capacity although the decrease in gas lung volume was slightly less than one third the added saline volume. The pleural effusion did not

change the volume of the rib cage; thus, the added saline volume caused a downward displacement of the diaphragm.

Dechman et al. investigated the changes in the dynamic mechanical properties of the respiratory system and its components (lung and chest wall) induced by progressive development of a pleural effusion [16]. Saline was infused into the pleural space in 60 ml increments until 60 ml/kg body weight had been administered. The effusate loading of the pleural space caused progressive changes in the elastance of the lung and the chest wall. The extent of the changes was closely related to the volume of the effusion. Lung elastance increased steadily throughout effusate loading. This was due to parenchymal distortion which occurs as the lung rotates around its long and transverse axes, and to a decrease in FRC as dependent lung regions are displaced by the fluid. The decrease in FRC may occur as a result of airspace closure or a uniform decrease in volume throughout the lungs. Conversely, the chest wall elastance decreased supporting the hypothesis of increased chest wall volume.

In a controlled study of pleural effusion and pneumothorax (stepwise injection), the respiratory system and lung elastance increased significantly, while the FRC decreased in a similar amount [17]. The main mechanism associated with hypoxemia in the presence of a pleural effusion is lung collapse and reduction in the FRC. However, some studies have suggested that effusion could impair right ventricular relaxation, causing a 'thoracic tamponade' state [18–20]. To better elucidate this point, Nishida et al. evaluated the effects of graded bilateral pleural effusions in anesthetized pigs randomized to conditions of low, normal, or elevated intravascular volume [21]. The volumes of pleural fluid were 20, 40 and 80 ml/kg while the intravascular volume was altered by phlebotomy or transfusion to reach low, normal, or high conditions. Oxygenation was reduced and intrapulmonary shunt increased in a dose dependent manner as pleural volume increased findings present at all intravascular volumes. The pleural volume did not affect the cardiac output or the systemic mean arterial pressure (MAP). Conversely, the central venous pressure (CVP) and pulmonary artery occlusion pressure (PAOP) were directly proportional to pleural volume. These data suggest that hypoxemia occurs as an early phenomenon and appears not to be a result of hemodynamic alterations. However, it is possible that extreme increases in pleural volume may decrease cardiac output and MAP but this was not investigated in this study [21].

From the above data, it is clear that, at least in experimental models, a controlled infusion of pleural effusion negatively affects lung gas volume, respiratory mechanics, and gas exchange.

Effects of Thoracentesis on Lung Volume, Respiratory System Mechanics, and Gas Exchange

As pleural effusion is frequently associated with restricted pulmonary volumes, hypoxemia, and longer ICU stay, thoracentesis is frequently performed in these patients to reduce dyspnea and improve gas exchange [22–24]. However, the short term effects of this technique on pulmonary function have not been clearly established.

In a group of nine spontaneously breathing patients with large unilateral pleural effusions from differing causes (tuberculosis, congestive heart failure, tumor), pulmonary mechanics were measured immediately prior to and three hours after thoracentesis [22]. The pulmonary volumes before thoracentesis were in line with a restrictive pulmonary defect; in particular, thoracentesis caused a significant improvement in FRC (2.63 ± 0.61 vs 2.95 ± 0.61 l) and in total lung capacity (4.10 ±

1.60 vs 4.57 ± 1.17 l) without any change in residual volume or vital capacity. The authors did not find any relationship between the volume of fluid aspirated and the increase in pulmonary volumes.

Doelken et al. evaluated the effects of thoracentesis on respiratory function in sedated, paralyzed mechanically ventilated patients [23]. Immediately following thoracentesis, respiratory mechanics were measured with the patient in the same position and under the same ventilator settings as during the initial measurements. There were no significant changes in peak or plateau airway pressure or compliance of the respiratory system. Thoracentesis significantly decreased the pleural liquid pressure from 11.1 to –6.6 cmH_2O. The authors hypothesized that the absence of change in compliance was likely due to the limited size of the pleural effusions removed, an average of 1495 ± 153 ml, suggesting that the human respiratory system can accommodate relatively large amounts of pleural fluid without affecting the compliance of the respiratory system. In contrast, there was a trend to decreasing compliance after thoracentesis, suggesting that thoracentesis had a stiffening effect on the chest wall due to restoration of the dome shape of the diaphragm by the abdominal pressure or that the newly aerated lung alveoli are less compliant.

After fluid removal from the pleural space, one of the following changes in pulmonary gas volume and size of the thoracic cavity can be present: First, an increase in pulmonary gas volume without any decrease in the size of the thoracic cavity, i.e., the increase in gas volume is equal to the aspirated volume; second, a decrease in the size of the thoracic cavity with no change in pulmonary gas volume; third, a combination of a decrease in the size of the thoracic cavity and an increase in the pulmonary gas volume. The results will depend on the compliance of the lung compared to the compliance of the chest wall, i.e., the more compliant the lung is, the greater will be the increase in gas volume.

Thoracentesis can be performed at the bedside in patients with severe respiratory failure unresponsive to positive end-expiratory pressure (PEEP). In a retrospective study of 199 mechanically ventilated patients with acute respiratory failure, 19 patients had a poor response to PEEP and presented pulmonary effusions on plain chest radiographs [25]. On average, 863 ± 164 ml were drained by thoracentesis during the first 8 hours. Drainage of pleural effusion improved oxygenation immediately in 17 of 19 patients. Although oxygenation increased significantly after thoracentesis, the differences were not significant after 24 hours (124 ± 12 vs 199 ± 27 vs 132 ± 14 mmHg, respectively). There was no correlation between the volume of fluid removed and oxygenation either immediately or after 24 hours.

In 44 patients admitted for coma, trauma, acute heart failure, pneumonia, or peritonitis, oxygenation increased significantly 12 hours after pleural fluid drainage in patients with a drained effusion of greater than 500 ml, but not in patients with a drained effusion less than 500 ml [13]. There was a positive correlation between the drained volume and improvement in oxygenation in patients with drained effusions of greater than 500 ml. Ahmed et al. prospectively studied patients admitted to surgical intensive care with pleural effusions large enough to require drainage [26]. In 22 mechanically ventilated patients with acute respiratory failure, thoracentesis was performed with a mean amount of 1262 ± 760 ml of serous liquid drained. Oxygenation did not change but oxygen delivery increased due to a combination of nonsignificant increase in both cardiac output and oxygen content in arterial blood.

Perpina et al. studied 33 patients with unilateral pleural effusions of various causes during spontaneous breathing [24]. Gas exchange, physiological and anatomical shunt were measured before thoracentesis and 20 minutes, 2 hours, and 24 hours

after the procedure. The mean volume of fluid removed was 1297 ± 495 ml; oxygenation was slightly higher compared to baseline after 20 minutes, 2 and 24 hours (65.8 ± 8.6 vs 72.7 ± 12.5 vs 72.8 ± 8.3 mmHg, respectively). No significant changes were found in carbon dioxide or pH. The physiological and anatomical shunt decreased significantly after the thoracentesis. These results suggest that after thoracentesis some previously collapsed non-ventilated but perfused alveoli may open, thus reducing the anatomical shunt. Matching of ventilation to perfusion may also be improved by the decompression of previously constricted capillaries supplying ventilated alveoli. In contrast, in a similar group of patients the drainage of an average pleural volume of 693 ± 424 ml did not affect oxygenation or the degree of intrapulmonary shunt [27]. Possible explanations for these differing results include differences in the duration of the effusion at the time of drainage, in the amount of pleural effusion, in the lung-chest wall compliance, in the presence of intra abdominal hypertension, and in the presence or absence of concomitant underlying lung parenchymal disease.

Pleural Effusion in Patients with ALI/ARDS

Patients with ALI/ARDS are characterized by non-cardiogenic pulmonary edema which increases lung weight and promotes lung collapse/atelectasis. In addition, the presence of pleural effusion could further decrease lung gas volume, increase shunt, and impair gas exchange. The computed tomography (CT) scan is the gold standard to quantify the amount of pleural effusion [10] and the amount of lung collapse [28]. In selected patients with ALI/ARDS, i.e., patients with a higher potential of lung recruitment, the application of adequate PEEP levels reduced the lung collapse and improved gas exchange [29].

We investigated the relationship between pleural effusion and response to PEEP in a group of ALI/ARDS patients. Two levels of PEEP (5 and 15 cmH_2O) were randomly applied. CT scan was performed at end-expiration (5 cmH_2O of airway pressure) and at 45 cmH_2O. Lung gas volume and the amount of pleural effusion were computed using a custom designed software package. Seventeen patients were enrolled and their baseline characteristics are reported in **Table 1**. The mean volume

Table 1. Baseline clinical characteristics.

	Characteristics at enrollment (n = 17)
Sex (M)	14
Age (years)	063.0 ± 15.1
BMI (kg/m^2)	24.8 ± 2.5
Cause of respiratory failure n (%)	
ARDS	10 (58.8 %)
ALI	7 (41.2 %)
Minute ventilation (l/min)	08.7 ± 1.6
PEEP (cmH_2O)	09.4 ± 2.0
PaO_2/FiO_2	196.7 ± 62.3
$PaCO_2$ (mmHg)	42.0 ± 6.5
EELV (ml)	0909.1 ± 355.1
Respiratory system compliance (ml/cmH_2O)	054.6 ± 12.3
Lung compliance (ml/cmH_2O)	022.7 ± 10.4
Chest wall compliance (ml/cmH_2O)	022.9 ± 10.5

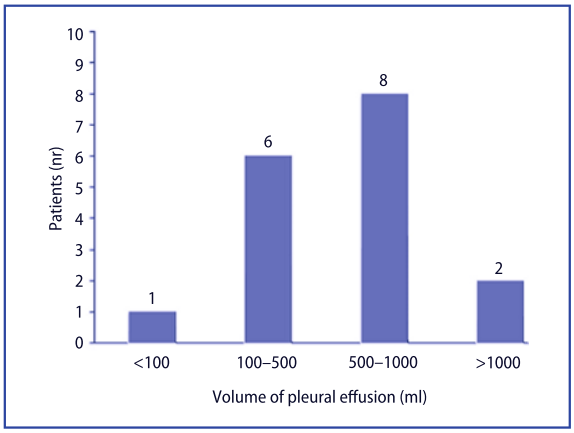

Fig. 1. Distribution of pleural effusion volumes

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Table 2. Characteristics of patients with high and low volume pleural effusion

	High Volume Pleural Effusion (n = 8)	Low Volume Pleural Effusion (n = 9)
Sex (M)	6	8
Age (yrs)	066.6 ± 16.5*	0057.8 ± 11.90
BMI (kg/m^2)	26.3 ± 2.0*	24.0 ± 2.0
Cause of respiratory failure n (%)		
ARDS	3 (37.5)	7 (77.7 %)
ALI	5 (62.5 %)	2 (22.3 %)
PEEP (cmH_2O)	8.9 ± 1.8	09.7 ± 2.4
PaO_2/FiO_2	000237 ± 56.7**	167.3 ± 50.1
$PaCO_2$ (mmHg)	0 37.0 ± 3.5**	46.5 ± 5.5
EELV (ml)	852.1 ± 342.40	973.2 ± 381.3
Respiratory system compliance (ml/cmH_2O)	54.8 ± 12.70	54.4 ± 12.1
Lung compliance (ml/cmH_2O)	20.8 ± 10.40	24.9 ± 10.6
Chest wall compliance (ml/cmH_2O)	20.9 ± 10.50	25.0 ± 10.7

* $p < 0.05$, **$p < 0.0001$ (vs low volume pleural effusion)

of the pleural effusion was 598.9 ± 328.4 ml. **Figure 1** shows the distribution of volumes of pleural effusion in the entire population. We divided the patients into two groups according to the volume of pleural effusion: More or less than the median value of 551.27 ml. Patients with a larger pleural effusion were older, had a greater body mass index, lower oxygenation and similar lung gas volume to patients with smaller pleural effusions (**Table 2**). The changes in oxygenation and in carbon dioxide with PEEP were similar in the two groups: PaO_2/FiO_2 157 ± 36 vs 234 ± 62 and 154 ± 36 vs 201 ± 36, respectively, and $PaCO_2$ 47.4 ± 5.4 vs 45.7 ± 4.6 and 47.1 ± 4.9 vs 47.5 ± 5.6 mmHg, respectively. The volume of pleural effusion was not related to the lung gas volume ($p = 0.37$, $r^2 = 0.01$) (**Fig. 2**).

Conclusion

Although the pathogenesis of pleural effusion is similar in patients with or without acute respiratory failure, pleural effusions do not seem to further impair the respiratory system in patients with ALI/ARDS.

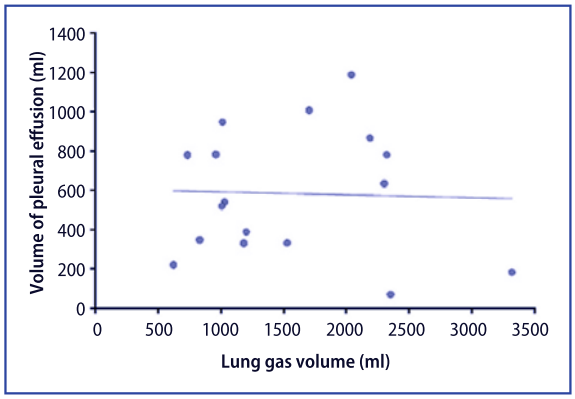

Fig. 2. Relationship between lung gas volume at 5 cmH_2O PEEP and volume of pleural effusion.

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Fluid Management in Acute Lung Injury and ARDS

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Introduction

The ventilatory treatment of acute respiratory distress syndrome (ARDS) has greatly improved in recent years. During the same period, numerous non-ventilatory therapies have been evaluated – some promising, others disappointing in their physiological effects and outcome. Among them, modulation of fluid state and of plasma oncotic pressure has been the object of studies in patients. ARDS is particularly characterized by pulmonary edema owing to an increase in pulmonary capillary permeability. In the early phase of ARDS, an associated septic state is usually responsible for hypovolemia. At this stage, hemodynamic optimization by early and adapted filling has proved to have prognostic value [1] and a fluid restriction strategy can result in hemodynamic aggravation and dysfunction of associated organs, determining the mortality of patients presenting with ARDS [2]. Subsequently, hemodynamic stabilization is generally associated with a resumption of diuresis and a decrease in body weight. Passage from one phase to another is often complex and difficult to distinguish but it is probably by identifying the transition between these two phases that one can detect the moment when a strategy of optimization of fluid balance on the restrictive side is possible. After a review of the physiopathologic bases, this chapter will present the principal clinical studies that have made it possible to advance in the optimization of the fluid state during ARDS.

The Consequences of Pulmonary Edema during ARDS

Although pulmonary edema is only, in certain aspects, the reflection of the extent of alveolocapillary barrier lesions, it nevertheless has an impact on respiratory function at several levels [3]. An increase in pulmonary water triggers an early reduction in pulmonary compliance which is responsible for an increase in respiratory work. At the alveolar edema stage, the shunt is responsible for hypoxemia. The edema interacts with mechanical ventilation to facilitate pulmonary inflammation by rendering the lung heterogeneous at a ventilatory level, altering the surfactant and worsening alveolocapillary barrier lesions. Finally, edema is one of the principal determinants of pulmonary arterial hypertension, not only because of hypoxemia but also because of the pulmonary vascular compression that it triggers.

Any attempt to reduce edema can, therefore, potentially have beneficial effects on respiratory function and even on outcome. However, data that point to a prognostic role of the quantity of edema fluid in patients with ARDS or at risk of ARDS are very limited. In 1987, Simmons et al. [4] observed that the evolution of body weight

and fluid balance in ARDS patients was correlated with outcome but these authors did not establish a cause and effect relationship between these two parameters. Recently, Sakka et al. [5] retrospectively analyzed 373 ICU patients and noted that the maximum quantity of pulmonary water measured was a predictive factor for outcome. However, there was no prognostic effect of the quantity of edema fluid, as measured by thermodilution, in patients with ARDS. By definition, ARDS patients have severe pulmonary edema in the region of 15 to 20 ml/kg of body weight [6, 7] and it is probable that other (extrapulmonary) factors will have a more marked prognostic impact. It should, therefore, be remembered that the degree of hypoxemia is a controversial prognostic factor during ARDS [8, 9].

In summary, it makes sense to consider that limiting the development of pulmonary edema or accelerating its resorption could be beneficial. However, the prognostic role of the quantity of pulmonary edema fluid remains uncertain.

VI ARDS: Lesional or Hemodynamic Edema?

Under physiologic conditions, there is a passage of fluid from the capillary lumina toward the interstitium. In fact, the endothelium has some permeability but the consequences of the forces acting on one part or another of the endothelium favor an extravasation of fluid [10]. Fluid flux through the endothelium, and particularly the pulmonary endothelium, is quite correctly estimated by Starling's equation which expresses the fact that net filtration flux is the product of the hydraulic conductance of the exchange surface barrier by effective filtration pressure. The equation is expressed as follows:

$$Jv = K\,[(Pc - Pi) - S\,(\pi c - \pi i)]$$

where Jv is the flow of fluid through the capillary wall, K is the capillary hydraulic filtration coefficient reflecting endothelial water permeability, Pc is capillary hydrostatic pressure, Pi is interstitial hydrostatic pressure, S is the oncotic reflection coefficient, πc is the capillary oncotic pressure, and πi is the interstitial oncotic pressure. The first part of the equation represents the hydrostatic pressure gradient which tends to produce a flow of fluid out of the vessels. The second part represents the oncotic pressure gradient which opposes this transudation of fluid. The influence of oncotic pressure on fluid flux through the endothelium is modulated by the oncotic reflection coefficient (S) which represents the permeability of the endothelium to oncotically active substances.

Schematically, two principal mechanisms can work towards an increase in pulmonary water and possibly alveolar flooding: On one hand, an increase in pulmonary microvascular pressure, and on the other hand, an increase in alveolocapillary barrier permeability. During ARDS, an increase in endothelial permeability is a fundamental element in the formation of pulmonary edema [11]. At a hydrodynamic level, the capillary hydraulic filtration coefficient increases and the reflection coefficient of oncotically active substances diminishes or even reaches near zero in certain zones. Thus, the oncotic pressure gradient, which normally opposes the formation of edema, is less or no longer effective. Consequently, a given increase in hydrostatic pressure will trigger a greater increase in fluid efflux if alveolocapillary barrier permeability is increased. This has been well illustrated in experimental studies, already old, by Guyton [12], showing that edema forms faster and at a lower hydrostatic pressure threshold when one has first damaged the alveolocapillary barrier before

Table 1. Mean values for mean pulmonary arterial pressure (MPAP), pulmonary capillary pressure (PCP), and pulmonary artery occlusion pressure (PAOP) in several clinical studies that have studied these parameters in patients with ARDS.

Number of patients	MPAP	PCP	PAOP	Reference number
15	40 ± 2	27 ± 2	22 ± 1	[42]
10	28 ± 1	17 ± 1	13 ± 1	[18]
18	34 ± 2	25 ± 1	17 ± 1	[19]
7	27 ± 3	15 ± 1	10 ± 1	[20]
8	39 ± 2	28 ± 2	15 ± 1	[43]

progressively increasing left atrium pressure. Moreover, other experimental studies have shown that even a modest decrease in pulmonary capillary pressure by vasodilatation or early reduction of volemia in a lesional edema model can limit the formation of pulmonary edema [13–15].

Clinically, even though the presence of a pulmonary artery occlusion pressure (PAOP) < 18 mmHg has been defined for a diagnosis of lesional edema, it does not exclude a hydrostatic role in this edema, and all the more since PAOP underestimates capillary filtration pressure. If the capillary hydraulic filtration coefficient is doubled, the critical hydrostatic pressure will only be 10 mmHg. The notion that there is no normal capillary pressure in case of permeability edema constitutes a theoretical justification for limiting pulmonary filtration pressure in cases of lesional edema or in patients at risk and, therefore, for measuring or estimating capillary pressure, which is a fairly true reflection of this parameter. Most clinical studies have shown that the majority of patients with ARDS have a PAOP that is superior to critical filtration pressure values when the barrier is damaged (**Table 1**). Knowing that the PAOP is inferior to capillary hydrostatic pressure, one can suppose that these patients will more often have a capillary pressure that is beyond critical pressure. However, these hypotheses should be moderated owing to the limited reliability of PAOP measurement in mechanically ventilated patients who generally have an elevated positive expiratory pressure and a modified distribution of West zones.

Nevertheless, one can understand the potential interest in limiting pulmonary microvascular pressure during the period for which endothelial permeability is increased. However, in practice this is difficult for several reasons. The first is that in the early phase of inflammatory pulmonary aggression when the edema is forming, the therapeutic strategy is usually oriented toward systemic hemodynamic recovery, associating vascular filling, and vasopressors with the quite contradictory aim to reduce pulmonary capillary pressure. The second reason is the difficulty in measuring or evaluating pulmonary capillary filtration pressure. Some factors, such as vasoplegia and hypovolemia, combine to diminish pulmonary capillary pressure whereas the local production of vasoconstrictor mediators or myocardial depression can increase. In addition, effective filtration pressure is the resulting complex of venous, capillary, and arteriolar pressures, all three of which can be affected by vasomotor mediators with contradictory effects.

On balance, maintaining a low pulmonary capillary pressure is understandable, especially early, during the phase where permeability is increased. However, making it a therapeutic objective is more difficult, in particular because capillary pressure is difficult to measure.

Resorption and Drainage of Pulmonary Edema

As we have seen, ARDS is particularly characterized by pulmonary edema. The excess pulmonary water is both alveolar and interstitial. The part of the interstitial water that is in excess and that will not flood the alveoli is to a minor extent drained by the lymphatic network. Fluid that is not drained by the lymphatic network – because it is saturated – accumulates in the loose peri-bronchovascular conjunctive tissue of the hila, which is the first accumulation site in pulmonary edema. These zones have very low resistance to fluid flux and major compliance at the same time. Thus, since interstitial pressure remains low, there is little or no resorption of interstitial edema as a result of pulmonary vascular resorption with the pressure remaining in favor of transudation of the vascular sector towards the interstitium. On the other hand, interstitial drainage will depend on the capacity of lymphatic flow to increase as well as the capacity of the perihilar tubes to drain into the mediastinum and the interstitial edema to evacuate towards the pleura and then the lymphatic system. Edema drainage will, therefore, be increased if right auricular pressure decreases and if pleural pressure is low.

Once in the alveoli, the water is absorbed from the alveoli towards the interstitium by active transepithelial ionic migration, which in turn creates an osmotic gradient leading to water reabsorption towards the interstitium [16]. This water then goes into the interstitial edema drainage circuit. Thus, alveolar edema resorption is not performed by vessels communicating with the pulmonary circulation. During ARDS, active transport of ions and fluid by the epithelium is altered owing to rupture of the alveolocapillary barrier and epithelial cell dysfunction. Water reabsorption requires that the fluid leak first be reduced not only by reduction of endothelial permeability but also possibly by modifications in epithelial cell form, making the epithelium more solidly impermeable. Alveolar fluid clearance is altered in most patients with ARDS, so maintenance of normal clearance or an increase in clearance is reported as being associated with better outcome [17].

In summary, one can theoretically improve interstitial pulmonary edema clearance and facilitate edema prevention mechanisms by diminishing both central venous pressure (CVP) and pleural pressure. Parallel stimulation of alveolar edema resorption toward the interstitium could be complementary.

Fluid Restriction and Diuretics: Clinical Studies and Practical Consequences

Even if limitation of pulmonary capillary pressure and facilitation of edema drainage by fluid restriction can limit edema formation or aid its elimination, it is not known whether diminishing pulmonary edema is of benefit. There are insufficient data to firmly establish that edema restriction has a beneficial effect on pulmonary function.

In addition to ventilatory or inotropic therapies, one can theoretically reduce capillary pressure in two manners: By diminishing volemia or by vasodilitating the pulmonary vessels. Selective pulmonary vasodilatation, in particular by inhaled nitric oxide (NO) or prostaglandins, has been the object of experimental studies in lesional edema models. Some authors have reported that a reduction in pulmonary water or endothelial permeability could be connected to a decrease in capillar filtration pressure [15]. However, most of the clinical studies in ARDS patients have only shown

modest effects of these drugs on pulmonary capillary pressure [18–20] and the most recent large studies have not reported prognostic benefit with the systematic use of inhaled NO in cases of acute lung injury (ALI) or ARDS [21].

Fluid restriction, which is more or less associated with diuretic treatment, makes it possible to reduce both pulmonary capillary pressure and CVP. The problem with fluid restriction is that it is frequently difficult because of the often precarious hemodynamic state of such patients. Until recently, only a few prospective studies had been undertaken and had suggested a reduction in respiratory morbidity with fluid restriction. In 1990, Humphrey et al. [22] suggested that interventional reduction of PAOP in ARDS patients improved mortality; however, the study presented numerous limitations. In a very limited population studied retrospectively, the authors showed that in patients whose PAOP could be reduced by 25 %, mortality was lower than in those whose PAOP could not be lowered. A link between PAOP reduction and outcome could not be established. In 1992, Mitchell et al. [7] performed a randomized study of 101 ICU patients. In 52 patients, hydration was based on the measurement of extravascular lung water (EVLW) by double dilution and 49 patients were monitored by pulmonary arterial catheter and PAOP. In the group monitored by EVLW measurement, the hydration strategy was based on restriction of fluid intake associated with the use of vasopressors if EVLW was > 7 ml/kg or on preferential filling in cases of low EVLW, whereas in the other group, the PAOP objective was 10 mmHg if the hemodynamic state was normal and 18 mmHg in cases of hypotension. In patients with a higher PAOP, vasopressors or vasodilators were used depending on the blood pressure. Filling was used in patients with lower PAOP. The strategy based on the search for low EVLW resulted in a shorter duration of both ventilator-days and ICU stay than the PAOP strategy. The cumulated fluid result for the first 3 days was + 2 liters in the PAOP group compared to zero in the EVLW group in which PAOP was also significantly diminished. EVLW decreased by 25 % in the EVLW group but did not change in the other group, suggesting that it was really fluid restriction that acted on the reduction in pulmonary water and that it influenced outcome. There was no increase in vasopressor requirements. In addition to demonstrating the interest of zero fluid balance by fluid restriction in cases of ARDS, the above study suggested that measurement of pulmonary water could be useful in clinical practice and not only for research. It should be noted, that this is the only study that strongly suggests that a strategy of zero fluid balance improves morbidity of patients through a pulmonary effect, in this case, on the edema [7]. One of the notable limits of the study was the significantly higher age in the PAOP group.

It is only recently that a randomized multicenter study of fluid restriction has been performed [23]. This study, the Fluid and Catheter Treatment Trial (FACTT), evaluated a strategy of fluid restriction, which was more or less associated with diuretic treatment, prescribed in the absence of hypotension and renal failure in patients with ALI and ARDS. Patients were included in the study approximately 48 hours after admission to the ICU. The decision to submit patients to filling or to diuretic treatment depended on the presence of oliguria and the level of CVP or PAOP. Schematically, the aim was to obtain a CVP of 8 mmHg or less in the "conservative-strategy" group or 14 mmHg in the "liberal-strategy" group. In the patients monitored with a pulmonary arterial catheter, the targets for PAOP were 12 mmHg in the conservative-strategy group and 18 mmHg in the liberal-strategy group. The protocol was applied for 7 days after inclusion of the patient but was not applied in case of hypotension. The conservative strategy resulted in zero fluid in 7 days

whereas the fluid result in the liberal-strategy was + 6 liters over 7 days. The conservative strategy discreetly improved oxygenation in patients and increased the number of days without ventilation (14.6 ± 0.5 vs 12 ± 0.5, $p < 0.001$) but did not influence mortality at 60 days which was the principal aim of the study. This study confirmed the impression that limiting fluid intake in patients with isolated respiratory failure can limit respiratory morbidity without aggravating other organ dysfunctions. However, the exclusion of hemodynamically unstable patients or patients with renal failure makes it impossible to generalize these results or to create a 'gold standard' for management of the fluid state of all ARDS patients. In addition, the absence of an effect on mortality reminds us that the management of fluid intake in ICU patients cannot simply be broken down into liberal or conservative. In most patients, ARDS is described within the framework of an early and generalized systemic inflammation that is responsible for hemodynamic dysfunction. At this stage, hemodynamic restoration based on early filling constitutes one of the cornerstones for improving outcome [1]. It is only once the initial phase of instability has passed that a reasonable policy of fluid intake aimed at zero fluid can contribute to reducing the duration of ventilation and ICU stay [24]. The importance of a 'biphase' fluid strategy was recently illustrated by a retrospective study that included 212 patients with ALI complicating septic shock [25]. In this study, non-performance of early adapted filling and the absence of a negative fluid balance during a minimum of the first 2 consecutive days within the 7 days following the occurrence of septic shock were independent risk factors for mortality by multivariate analysis. Along these lines, the Surviving Sepsis Campaign [26] recommends a conservative fluid strategy in patients with ARDS or ALI who are not in shock. Other recent studies have stressed the influence of fluid balance on outcome [27, 28]. However, their design does not make it possible to confirm whether an interventional strategy, such as that of the FACTT study, can influence the outcome of ARDS patients. According to the literature, the beneficial effect of conservative therapy may also be because of extrarespiratory mechanisms. Thus, the patients treated with a conservative strategy in the FACTT study [23] had a better neurological status – perhaps because their sedation level was reduced earlier owing to a better respiratory status, perhaps because they had less severe cerebral edema. Moreover, the patients with conservative treatment received fewer transfusions, the potentially deleterious effects of which are well known in intensive care [29]. A simplified version of the algorithm used in the FACTT study was published by the ARDS Network and discussed in a recent review on the subject [30].

Modulation of Oncotic or Osmotic Pressure: The Effects of Administering Albumin or Hypertonic Saline

From a hemodynamic point of view, when there is a decrease in plasma oncotic pressure, which is clinically illustrated by hypoprotinemia/hypoalbuminemia, pulmonary edema forms at a lower hydrostatic pressure because the oncotic pressure gradient between the plasma and the interstitium decreases. Therefore, experimentally, whereas edema starts to develop at a pressure of 24 mmHg when oncotic pressure is normal, it begins at 11 mmHg when it is reduced [12]. Hypoprotinemia therefore facilitates hydrostatic pulmonary edema. This is potentially important in ICU patients in whom hemodilution and catabolism associate to reduce protinemia. However, the importance of oncotic pressure in the limitation of flux is only con-

ceivable if the barrier is intact. In the presence of endothelial lesions, interstitial edema will be richer in proteins than the plasma, theoretically limiting the value of increasing the plasmatic oncotic pressure. Thus, in animal models, an increase in oncotic pressure in the early phase of a lesional edema will not limit the formation of edema [13].

By analyzing a cohort of 455 septic patients at risk of ARDS, Mangialardi et al. [31] found that hypoprotinemia was an independent predictor of the occurrence of ARDS. Subsequently, the same team [32] evaluated the value of a strategy of diuretic treatment associated with albumin filling in ARDS patients with protinemia < 50 g/l. Of the 37 patients included in the study, 19 received a combination of albumin (75 g/d) and furosemide for 5 days and 18 received placebo. When protinemia was > 60 g/d in the treated group, the treatment was replaced by placebo. Continuous infusion of furosemide was adjusted to obtain a weight loss of at least 1 kg/d without exceeding 8 mg/h of furosemide. The patients in the treated group had a PaO_2/FiO_2 ratio that was slightly and transitionally better than that of the placebo group, without other beneficial or deleterious effects, particularly on renal function. In a second study [33], in order to distinguish the effects of albumin and diuretics, the same authors randomized 40 patients into a group of 20 who received furosemide alone and 20 who received furosemide and albumin (75 g/d) for 3 days. When protinemia was > 80 g/l in the treated group, albumin was replaced by a placebo. Albuminemia increased by 13 g/l in the albumin + furosemide group, reaching 30 g/l at the end of treatment and increased by 3 g/l in the furosemide alone group, reaching 20 g/l at the end of treatment. Once again, the effects can be summarized by a discrete improvement in oxygenation when albumin was associated with diuretic treatment compared to diuretic treatment alone. A large randomized study [34] demonstrated that albumin filling was equivalent to filling with saline in ICU patients. At this time, the very limited clinical data do not make it possible to recommend administration of albumin to improve pulmonary function and respiratory morbidity in ARDS patients.

The use of hyperosmolar filling solutions such as hypertonic saline could be an advantage because of the limited amount of fluid administered, thus limiting the development of pulmonary edema in case of an increase in the alveolocapillary barrier. Moreover, the use of hypertonic solutions, compared with isotonic solutions, has been associated with reduced pulmonary injury following hemorrhagic shock in experimental models as a result of improved splanchnic output and reduced adhesion and cytotoxicity of neutrophils [35, 36]. In clinical practice, evolution towards ALI was less frequent when patients had received filling with hypertonic saline and dextran in a retrospective study of 422 polytrauma patients [37].

We used a porcine model of hemorrhagic shock to compare the effects of filling with isotonic and hypertonic solutions on the occurrence of pulmonary lesions and on inflammation according to precise hemodynamic criteria [38]. The use of hypertonic saline did not prevent the appearance of ALI or pulmonary edema after hemorrhage in this study. There was even a deleterious effect when hypertonic saline was administered before the experimental ischemia-reperfusion was performed by clamping the pulmonary arteries [39]. This effect appeared to be independent of the hemodynamic effects of saline but was more probably linked to a direct effect on alveolocapillary barrier permeability.

Increasing Resorption of Alveolar Edema – A Complementary Objective

This therapeutic goal does not strictly imply manipulation of fluid balance in patients. However, it deserves a mention because it clearly shows that resorption of alveolar edema does not occur by manipulation of vascular pressures, but rather by stimulation of active water transport from the alveoli toward the interstitium, which would be complementary to strategies favoring the draining of interstitial edema.

Despite severe epithelial lesions, alveolar clearance is usually pharmacologically achievable. Several experimental studies have shown that the exogenous administration of cyclic AMP agonists, in particular beta-2 agonists, accelerates the resolution of edema, be it hemodynamic or lesional [40]. Beta-2 agonists principally act via an increase in the quantity and activity of Na/K pumps in the basal membrane and sodium canals in the pneumocyte apical membrane, the effect of which is to increase the sodium gradient between the alveoli and the interstitium and, therefore, the absorption of water. A recent clinical study [41] showed that the administration of intravenous salbutamol at a dose of 15 μg/kg/h for 7 days in patients with ARDS was associated with a reduction in pulmonary water as measured by transpulmonary thermodilution, without affecting oxygenation, the duration of ventilation, or outcome. However, this was a preliminary study with only 40 patients.

Conclusion

Fluid management aimed at obtaining zero fluid balance in ARDS patients without shock or renal failure significantly increases the number of days without mechanical ventilation [23]. However, patients with hemodynamic failure must undergo early and adapted vascular filling [1]. Liberal and conservative filling strategies are, therefore, complementary and should ideally follow each other in time in the same patient as the hemodynamic state progressively stabilizes. At present, albumin administration does not appear to be justified for the limitation of pulmonary edema and respiratory morbidity.

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Life-threatening Respiratory Failure from H1N1 Influenza: Lessons from the Southern Cone Outbreak

C.M. Luna, R. Valentini, and O. Rizzo

Introduction

A sharp increase in the hospitalization rate for pneumonia, particularly among adults between 20 and 40 years old, and an unusual series of deaths, coincident with an increase in laboratory-confirmed influenza cases, were reported in the spring of 2009 in Mexico. This outbreak appeared after the end of influenza season, and was associated with mortality in a younger age-group than the pattern observed in temperate areas in the northern hemisphere [1]. The concurrent finding of a novel, swine-origin influenza A virus (so called pandemic influenza [H1N1] 2009) from infected children in the United States [2] completed the picture.

This outbreak evolved rapidly and in a few weeks the number of cases with the same epidemiological and clinical characteristics increased globally; in 30 to 40 days the virus began to be clearly more virulent in the Southern Cone (a geographic region composed of the southernmost areas of South America, south of the tropic of Capricorn) and, consequently, by the first half of August, Argentina became the country with the highest rate of fatalities from pandemic influenza H1N1 2009 in relation to its population. During some weeks in June, the intensive care units (ICUs) in Buenos Aires experienced a sharp increase in cases of severe acute respiratory distress syndrome (ARDS) and these subjects typically became the predominant population of mechanically ventilated patients in these ICUs.

The aim of this chapter is to overview the characteristics of life-threatening respiratory failure from pandemic influenza H1N1 2009, trying to reflect on some practical issues that arose during this outbreak, and summarizing some of the rich experiences from Buenos Aires (**Table 1**) together with data retrieved from other recent international publications.

Why was Pandemic (H1N1) 2009 Flu So Prevalent in the Southern Cone?

Attack rates from influenza have been highly variable from outbreak to outbreak but are most commonly in the range of 5 to 10 % of the general population. During the pandemic of 1957, it was estimated that the attack rate of clinical influenza exceeded 50 %, but an additional 25 % or more of individuals were probably subclinically infected with influenza A virus [3].

Perhaps the coincidence between the beginning of the winter season in the southern hemisphere and the high air-traffic between United States and Mexico and the countries from the Southern Cone, especially Argentina [4], produced an unusual

Table 1. Demographic and clinical data from 34 mechanically ventilated patients with severe influenza H1N1 2009 infection admitted during June, 2009 in the ICUs of two institutions in Buenos Aires [11, 36].

Characteristics	N = 34
Age	47.9 ± 16.9
Male sex, n (%)	15 (44.1 %)
APACHE II score*	20.6 ± 7.0
SOFA score*	7.3 ± 1.6
Associated Conditions	
Pregnancy	3
COPD or asthma	3
Organ transplant	2
AIDS	2
Colonic or lung Cancer	6
Chronic myeloid leukemia	1
Inmunosuppressive therapy	3
Body mass index > 30	6
Invasive mechanical ventilation, n (%)	34 (100 %)
ARDS, n (%)	31 (91.2 %)
PaO_2/FiO_2	114 (52 – 250)
Days on mechanical ventilation	13 (7 – 40)
Days on mechanical ventilation, survivors	27 (7 – 40)
Days on mechanical ventilation, non–survivors	13 (10 – 14)
Mortality	13 (38.2 %)

sharp increase in the number of cases and rapidly Argentina and Brazil became the countries with the highest numbers of deaths due to microbiologically confirmed pandemic influenza (H1N1) 2009. Consistent with this particular situation, the health system in the metropolitan area of Buenos Aires began to show evidences of collapse, use of ventilators increased critically, achieving an extremely unusual level; about a quarter of the available ICU beds were occupied by young and previously healthy patients with ARDS associated with severe bilateral pneumonia due to 'swine flu' who needed mechanical ventilation.

How Big was the Outbreak?

By the time of writing this chapter, during the end of the winter in the southern hemisphere, it is evident that pandemic H1N1 influenza is highly prevalent in South America. In September 2009, the World Health Organization (WHO) Director General, Margaret Chan, estimated that up to 30 % of people in densely populated countries risk being infected with H1N1 pandemic 2009 influenza, while Dr. Thomas Frieden, head of the US Centers for Disease Control and Prevention, predicted that about 800,000 people may potentially have been infected in New York City by the spring. These figures are difficult to extrapolate globally and to confirm, as epidemiological studies looking at the population at risk in different world areas are lacking, but the huge number of severely ill patients with ARDS due to primary influenza pneumonia (an extremely unusual complication) observed in the Southern Cone, suggest that these estimations could be realistic. Calculating the population-corrected mortality rate from estimations made in New Zealand [5], it can be inferred that by the end of winter in the southern hemisphere, up to about 40 % of the population in Argentina could be infected by this novel agent.

Common Complications of Influenza

Influenza complications during seasonal influenza occur most frequently in patients older than 64 years old, in those with chronic disorders, including cardiac or pulmonary diseases, diabetes mellitus, hemoglobinopathies, renal dysfunction, and immunosuppression. Pregnant women in the second or third trimester, particularly in the 1918 and 1957 pandemics, had a higher risk of complications, especially of primary influenza pneumonia, and higher hospitalization rates.

Pneumonia is the most significant complication of influenza. The presentation of pneumonia includes: 'Primary' influenza viral pneumonia secondary bacterial pneumonia and mixed viral and bacterial pneumonia. Primary influenza viral pneumonia may be the least common of the pneumonic complications but it is also the most severe. It presents as acute influenza that does not resolve but instead progresses relentlessly, with persistent fever, dyspnea, and eventual cyanosis. Sputum production is generally scanty, but the sputum can contain blood. Few physical signs may be evident early in the illness. In more advanced cases, diffuse rales may be noted, and chest X-ray findings consistent with diffuse interstitial infiltrates and/or ARDS may be present (**Fig. 1**). Viral cultures of respiratory specimens, especially if

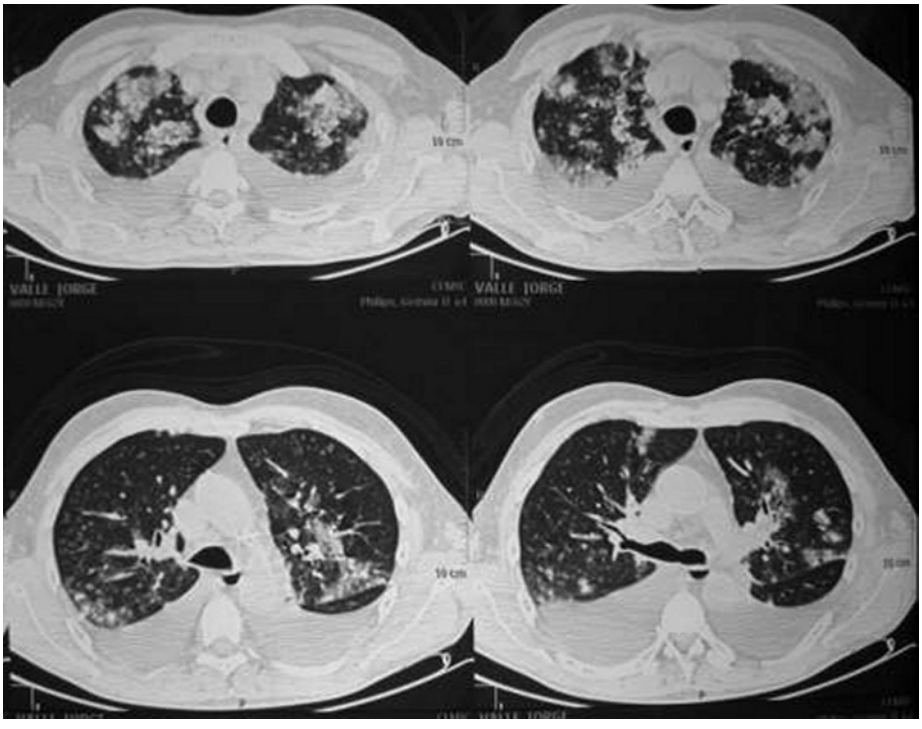

Fig. 1. Four slices of the lung computed tomography (CT) scan of a 62 year-old renal transplant patient with an influenza-like illness showing severe bilateral multilobar infiltrates and acute respiratory distress syndrome. Real time reverse-transcriptase polymerase chain reaction (RT-PCR) of a pharyngeal swab was positive for influenza A H1N1 2009. The CT scan shows patchy distributed air-spaced consolidation, more evident in the upper lobes and predominant in the periphery of the lungs. Moderate bilateral pleural effusion is also present.

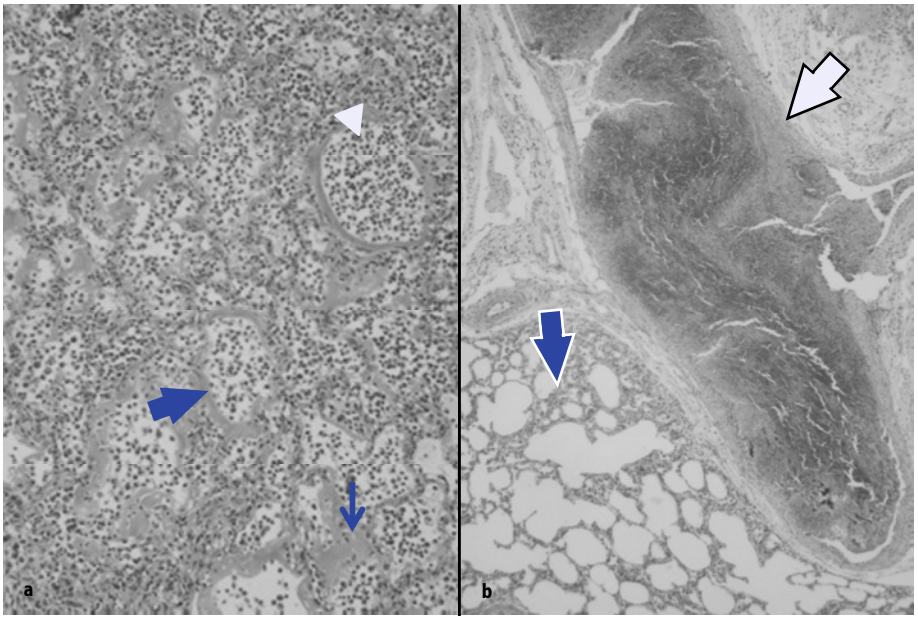

Fig. 2. A 29 year-old obese male with arterial hypertension secondary to Cushing's disease (hypophyseal adenoma) developed bilateral pneumonia and died from respiratory failure secondary to acute respiratory distress syndrome (ARDS) after 13 days on mechanical ventilation, with multiple organ failure, including renal and hemodynamic compromise requiring high doses of vasopressors. His disease began as an influenza-like illness 5 days before admission; influenza A H1N1 was confirmed with RT-PCR performed on pharyngeal swab. Post-mortem microscopic histopathologic findings in the lung included extensive alveolar edema (small arrow) replacing up to 90 % of the effective alveolar space, with hyaline membrane development (big arrow); alveolar cellular infiltrate and bacterial superinfection (arrowhead) were also observed (diffuse alveolar damage pattern) (panel a). There was also mild evidence of a fibroproliferative stage, microthrombi (gray arrow), small areas with well preserved pulmonary parenchyma (blue arrow), and hemorrhagic infarcts (panel b). Suprarrenal hyperplasia and acute tubular necrosis were found.

samples are taken early in illness, yield high titers of virus. In fatal cases of primary viral pneumonia, histopathologic examination reveals a marked inflammatory reaction in the alveolar septa, with edema and infiltration by lymphocytes, macrophages, occasional plasma cells, and variable numbers of neutrophils (**Fig. 2**). Fibrin thrombi in alveolar capillaries, along with necrosis and hemorrhage, have also been noted. Hyaline membranes can be found lining alveoli and alveolar ducts. Primary influenza viral pneumonia has a predilection for individuals with cardiac disease, particularly those with mitral stenosis, but has also been reported in otherwise-healthy young adults as well as in older individuals with chronic pulmonary disorders.

Secondary bacterial pneumonia follows acute influenza; in these cases typically improvement in the patient's condition over 2 to 3 days is followed by a reappearance of fever along with clinical signs and symptoms of pneumonia, including cough, purulent sputum, and physical and X-ray signs of consolidation. The most common bacterial pathogens in this setting are *Streptococcus pneumoniae*, *Staphylococcus aureus*, and *Haemophilus influenzae* – usual nasopharynx colonizers. Secondary bacterial pneumonia occurs most frequently in high-risk individuals with

chronic pulmonary and cardiac disease and in elderly individuals. Patients with secondary bacterial pneumonia often respond to antibiotic therapy when it is instituted promptly.

Risk Factors for the Acquisition of Severe H1N1 2009 Primary Influenza Pneumonia

The risk factors for acquiring severe H1N1 2009 primary influenza pneumonia include age (particularly young children) and comorbidities; some series have observed a particular prevalence of overweight individuals in this group of patients [1, 6, 7]. Obesity has not previously been mentioned among the risk factors for complications in patients with influenza. Being overweight is associated with a chronic increase in pro-inflammatory cytokines, such as interleukin (IL)-6 and tumor necrosis factor (TNF)-α. In an experimental model of influenza A, Smith et al. described higher mortality rates in overweight patients than in lean controls related to minimally expressed interferon (IFN)-α and -β and a delay in expression of the pro-inflammatory cytokines, IL-6 and TNF-α, which may lead to increased morbidity and mortality from viral infections [8].

Differences Comparing this Pandemic with the usual Seasonal Flu

In contrast to what happens with the usual annual seasonal influenza outbreak, in this outbreak of pandemic influenza H1N1 2009, young adults are dying and between one quarter and one half of the deaths around the world have happened in patients who were previously in good health and without any specific risk factors. In one of the earlier case report publications during the beginning of the pandemic in Mexico, the authors observed that 87 % of deaths and 71 % of cases of severe pneumonia involved patients between the ages of 5 and 59 years, compared with average rates of 17 % and 32 %, respectively, in that age group during the reference periods [1]. Features of this epidemic were similar to those of past influenza pandemics in that circulation of the new influenza virus was associated with an off-season wave of disease affecting a younger population [1].

Management

In the setting of a disease with very high mortality, with no available controlled human clinical data to guide clinicians, in which most patients present with severe disease, a number of combined strategies should be considered for therapy. These include pharmacological strategies (antiviral treatment) and non-pharmacological strategies (standardization of optimal ventilator and fluid management, especially for ARDS, and management of other complications) necessarily given empirically, as diagnostic confirmation using real time reverse-transcriptase polymerase chain reaction (RT-PCR), can take from several hours to days.

Non-pharmacologic Therapy

Ventilatory settings

Most of these patients have ARDS, and in these patients, ventilatory support should follow the concepts of protective ventilation, with a tidal volume (V_T) of 6 ml/kg of predicted body weight [9]. ARDS is usually severe, with PaO_2/FiO_2 < than 150 and positive end-expiratory pressure (PEEP) should be high and optimized according to a mechanical basis. In our experience, we initially select PEEP according to the methods used in the ExPress trial where PEEP was adjusted based on airway pressure and was kept as high as possible without increasing the maximal inspiratory plateau pressure above 28 to 30 cmH_2O [10]. In more severe respiratory failure, we also set PEEP according to the transpulmonary pressure, by using esophageal-pressure measurements. In secondary, but also in primary ARDS the lungs can suffer substantial effects of chest wall elastance and may be effectively compressed by high pleural pressures with their alveoli collapsed at the end of expiration, even though moderate or high PEEP levels are applied. Therefore, PEEP is set at a level necessary to obtain a positive end-expiratory transpulmonary-pressure to improve the oxygenation, an end-inspiratory transpulmonary-presure less than 20 cmH_2O to minimize stress-inducing ventilator lung injury, and a pulmonary driving pressure (end-inspiratory transpulmonary pressure less end-expiratory transpulmonary pressure) ≤ 10 cmH_2O to avoid strain-inducing ventilator lung injury (**Fig. 3**). Using these premises, the mean PEEP applied in patients with severe influenza H1N1 2009 and ARDS was 20 cmH_2O.

Interestingly, in contrast to other etiologies of ARDS, in primary influenza pneumonia, high PEEP levels were necessary for many days. In a group of 23 patients

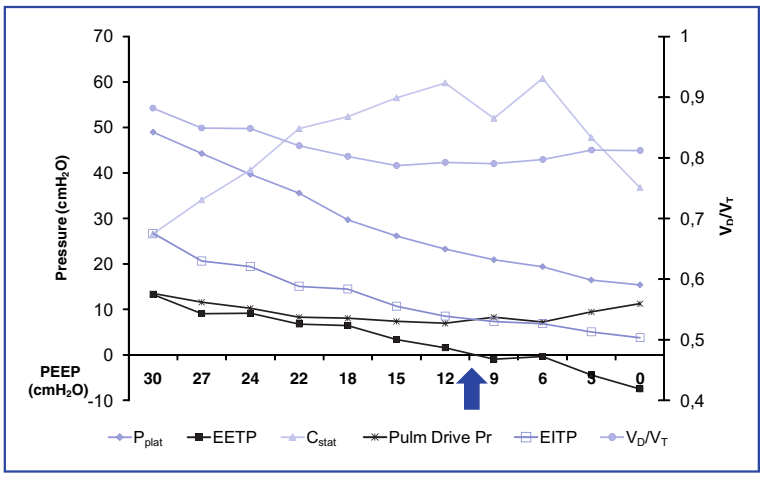

Fig. 3. Transpulmonary pressure and dead space ventilation during a decremental positive end-expiratory pressure (PEEP) maneuver in five patients with influenza H1N1 2009 pneumonia and severe ARDS. From these observations, we selected to use PEEP levels between 18 and 22 cmH_2O. At these PEEP levels, the end-inspiratory transpulmonary pressure (EITP) was less than 20 cmH_2O, the end-expiratory transpulmonary pressure (EETP) was positive, and the transpulmonary driving pressure (Pulm Driv Pr = EITP – EETP) was less than 10 cmH_2O. EETP became negative at PEEP less than 11 cmH_2O (arrow). Dead space ventilation (V_D/V_T) was high (range 0.79 – 0.88). V_D/V_T was lowest at a PEEP of about 15 cmH_2O. Pplat: plateau pressure; Cstat: static lung compliance.

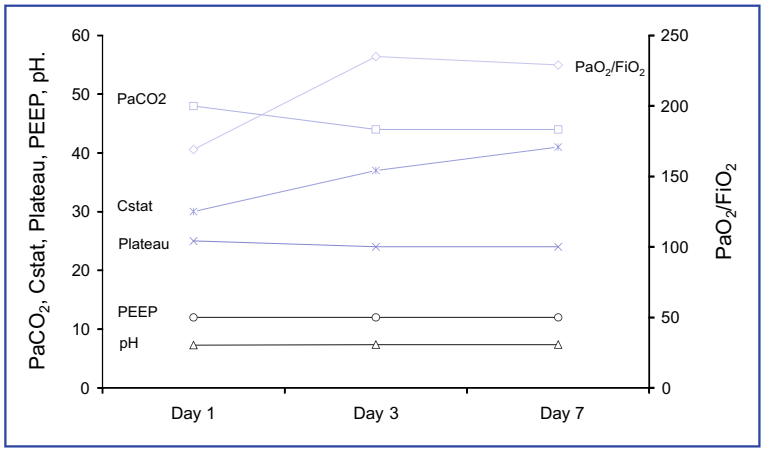

Fig. 4. Variation in gas exchange and respiratory system mechanics from the onset of mechanical ventilation in a group of mechanically ventilated ARDS patients with H1N1 pneumonia observed in one of our ICUs [11]. All variables improved from day 0 to day 3 of mechanical ventilation; however, in the majority of the patients the PaO_2/FiO_2 ratio remained low for many days, inducing us to maintain high levels of PEEP. Cstat: static lung compliance; PEEP: positive end-expiratory pressure

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managed by one of us (RV) in CEMIC Medical Center, the mean PEEP after 10 days on mechanical ventilation was 18 cmH_2O [11]. At the beginning of this outbreak, we decreased the PEEP level after a few days of mechanical ventilation, based on improvement in oxygenation levels; however, this produced a dramatic worsening of the PaO_2/FiO_2 ratio. Because of this observation, it was decided that, in patients with severe ARDS, high PEEP levels should be maintained for at least two weeks regardless of the oxygenation levels (**Fig. 4**).

Recruitment maneuvers

Most of the patients with severe influenza pneumonia responded to recruitment maneuvers. A recruitment maneuver in pressure controlled ventilation (PCV) with a PEEP of 25–30 cmH_2O and an inspiratory pressure of 25 cmH_2O (peak pressure 50–55 cmH_2O) was performed in patients with a $PaO_2/FiO_2 < 200$ mmHg. Many of these patients were young, healthy and had good cardiac performance and tolerance of high ventilatory pressures during the recruitment maneuver with adequate intravascular volume repletion.

Prone position ventilation

Several trials have demonstrated no survival benefit in ARDS patients managed in the prone position. However, these trials did not select the most severe patients. Many of our patients had severe ARDS with $PaO_2/FiO_2 < 100$ mmHg despite PEEP optimization and recruitment maneuvers. In this setting, prone ventilation was used and, if PaO_2/FiO_2 did not reach > 200 mmHg, a recruitment maneuver was applied in the prone position. Prone ventilation was used in 22 % of the patients with ARDS and in 50 % of patients with severe ARDS, and was associated with improved oxygenation and reduced distending pressures.

Adjunctive therapies to mechanical ventilation

We suggest the use of adjunctive therapies when plateau pressure is higher than 35 cmH_2O, despite a V_T of 6–8 ml/kg predicted weight, severe hypercapnic acidosis, and refractory hypoxemia (defined as a PaO_2/FiO_2 ratio < 100 mmHg after optimization of PEEP, recruitment maneuvers, prone position, and recruitment maneuvers in the prone ventilatory position). The adjunctive therapies developed to reduce the stress of mechanical ventilation on the already damaged lungs include: Nitric oxide (NO), extracorporeal membrane oxygenation (ECMO), arterial venous carbon dioxide removal, high-frequency oscillatory ventilation, and liquid ventilation. We prefer to use NO because of its availability and easy implementation and we have observed better improvement in oxygenation combining this therapy with prone ventilation, as previously described [12].

Non-invasive positive pressure ventilation (NPPV): NPPV has been used in respiratory failure due to viral pneumonia, even in cases of high transmission risk like in the epidemic of severe acute respiratory syndrome (SARS) in Hong Kong [13]. In one study, the efficacy in SARS pneumonia with mild acute lung injury (ALI) was high and no cases of healthworker infection were observed. However, application of NPPV to patients with H1N1 influenza has not been well evaluated and it is not indicated for impending respiratory failure. In mild cases or in patients with chronic obstructive pulmonary disease (COPD) or chronic respiratory restriction, NPPV could be useful to support the respiratory system, but it should be applied in healthcare facilities where staff have been adequately trained and with strict enforcement of personal protection measures; use of expiratory viral and bacterial filters are necessary to provide safer ventilation.

Pharmacologic Therapy

Antivirals

Most of the patients with influenza H1N1 2009 will recover without any antiviral therapy. Antivirals are indicated to prevent the rapid spread of the disease in a specific population, to prevent the pneumonia syndrome in susceptible patients, or to treat patients with influenza pneumonia. For critically ill influenza patients, antiviral treatment options are limited because no parenteral drug is available and no drug has been proved to be effective once life-threatening disease occurs. Currently, four antiviral drugs are available for the treatment of influenza: Amantadine, rimantadine (both cannot be used for the treatment of H1N1 influenza due to resistance), oseltamivir, available only for oral administration, and zanamivir, available as an inhalation agent; the two latter drugs are both sialic acid analogs that inhibit viral neuraminidases by competitively binding with the active enzyme site of influenza A and B viruses. The neuraminidase is critical for viral release from infected cells after replication. The earlier the administration of these agents, and the shorter the duration of fever, the greater the benefit of drug intervention [14, 15]. Oseltamivir has also been shown to reduce lower respiratory tract complications such as bronchitis and pneumonia [16]. In a prospective case control study, multivariate analysis suggested that treatment with oseltamivir decreased the likelihood of death (odds ratio 0.21 [confidence interval 0.06–0.80, p = 0.02]) [17]. Immunosuppressed patients (leukemia, organ transplantation, and hematopoietic stem cell transplantation) have a higher rate of viral pneumonia and higher attributable mortality [18]; viral shedding is also prolonged in these patients to an average of 11 days [19], which is associated with the development of resistance [20]. A standard dose and duration of

antivirals may not be adequate in this population; for these reasons, some authors have advocated a higher dose of oseltamivir (300 mg daily) in these patients [18].

During the pandemic, the therapeutic strategy proposed by the Argentinean Health Authority for mechanically ventilated patients with presumptive primary influenza pneumonia was to use oseltamivir at a dose of 300 mg daily during an extended period of time, typically until the patient was weaned from mechanical ventilation. The most frequent reported adverse effect seen with oseltamivir is nausea and vomiting, but this leads to medication interruption in only a small number of cases. Neuropsychiatric disorders (seizure, confusion or hyper-excitation of the nervous system) and severe skin reactions (e.g., toxic epidermal necrolysis) are more severe adverse events that have been observed in some cases during the pandemic. These unusual events have been related to a single nucleotide polymorphism in a gene located near the enzymatic active site of human cytosolic sialidase, a homolog of the virus neuraminidase that is the target of oseltamivir. This polymorphism has been found to occur in 9.3 % of the Asian population [21].

Antibacterial antimicrobials

Because of the high frequency of bacterial co-infection, antibiotic administration is recommended for all patients with pandemic H1N1 2009 influenza infection who require admission to a critical care unit. In immunocompetent patients, without recent antibiotic exposure, combination therapy with a beta-lactam plus a macrolide or a respiratory fluorquinolone, is recommended [22].

Corticosteroid therapy

Corticosteroids may be used to treat airflow obstruction due to asthma or COPD, to maintain immunosuppression in transplant patients, and when adrenal dysfunction is suspected because of refractory vasodilatory shock. Corticosteroids are not indicated for ALI; prolonged or high-dose corticosteroid therapy can result in serious adverse events, including opportunistic infections. In patients with H5N1 pulmonary infection, corticosteroids were not effective and in one series mortality was 59 % in 29 recipients of corticosteroids, compared with 24 % in 38 patients who did not receive corticosteroids [23]. One exception to this is cryptogenic organizing pneumonia (COP) described below under ‘complications’.

Complications

Bacterial Infection

In addition to primary viral pneumonia, viral and bacterial co-infection and secondary bacterial pneumonia are frequent. Co-infection with *S. pneumoniae, S. aureus*, and *Mycoplasma pnemoniae* has been detected in some of the reported series from Argentina; this co-infection occurs after several days of influenza infection and occurs more frequently in the elderly and in patients with chronic pulmonary diseases [24]. It has been observed in one series that 9 % of hospitalized patients with community-acquired pneumonia had dual infection with a respiratory virus and a bacterial pathogen, influenza being the most common viral agent [25]. Proposed theories for the high incidence of superimposed bacterial infections in influenza pneumonia emphasize the synergistic effects of viral and bacterial pathogens in producing lung injury. Studies suggested that influenza virus can directly damage the respiratory epithelium, allowing free access to invading bacteria. It has also been demonstrated that some

Staphylococcus and *Streptococcus* strains may increase viral replication and pathogenicity, contributing to influenza viral pneumonia [26].

Pulmonary Embolism

Pulmonary embolism has not been recognized as a common complication of severe influenza with ARDS. However, in a series of 10 patients with pandemic influenza H1N1 2009 infection and ARDS at a tertiary-care ICU in Michigan, five had pulmonary emboli [6]. Influenza infections have been associated with procoagulant changes [27]. Pathologic fibrin deposition also occurs in the vasculature in ARDS and pulmonary artery thrombi are found, implying an anatomic mechanism for the occurrence of increased pulmonary vascular resistance in ARDS [28]. It remains unknown whether these cases were secondary to some of the several risk factors that these bed-ridden severely ill patients had, or whether it was a direct consequence of a particular risk in influenza patients. Meanwhile, clinicians should periodically search for thrombosis and if necessary use chest multislice spiral computed tomography (CT) to confirm pulmonary embolism.

Extrapulmonary Manifestations

Influenza virus does not replicate in the alveoli or tissues beyond the respiratory tract. Histopathological analyses revealed that no virus was detected in the liver, spleen, kidney, or brain of animals inoculated with influenza H1N1 2009 virus at 3 or 7 days after inoculation [29]. However, myocarditis and pericarditis have been described in association with influenza infection and it has been suggested that influenza-associated myocarditis can take two forms: Immediate, associated with fulminating disease, and delayed, occurring during late convalescence [30].

Renal Failure

Renal failure has been described in a number of influenza patients [7, 31]. It is usually the consequence of shock and multiorgan dysfunction. We recommend adequate fluid replacement and, in patients with severe ARDS, fluid infusion should not be restrictive and diuretic use should be avoided to prevent the progression of renal dysfunction [11]. Using this strategy in our patients, the positive fluid balance at the 7^{th} day was 10,000 ml and hemodialysis was necessary in only 18 % of patients [11]. Occasionally, rhabdomyolysis may facilitate the development of renal failure; in fact, high levels of serum creatine phosphokinase have been described in reports of H1N1 infection [31].

Cryptogenic Organizing Pneumonia

This condition, occasionally associated with influenza, is characterized by progressive respiratory failure after 1 week of influenza symptoms with chest computerized axial tomography demonstrating multiple, bilateral, patchy alveolar opacities [11]. If identified, this complication must be treated with high doses of corticosteroids [32].

Prognostic Factors for Fatal Influenza Pneumonia

Ho et al. performed a study to define the prognostic factors for fatal adult influenza pneumonia [33]. Univariate analysis demonstrated that, compared with survivors of septic shock, a respiratory rate ≥ 25 breaths per min, an arterial pH < 7.35, a PaO_2/FiO_2 ratio < 150 mmHg, a creatinine value ≥ 2 mg/dl, a pneumonia severity index (PSI) of IV or V, and an APACHE II score ≥ 20 were all associated with decreased survival. Adjustments were made for septic shock, respiratory rate, arterial pH, creatinine and PSI in the Cox proportional hazard model. The multivariate analysis demonstrate that only the PaO_2/FiO_2 ratio < 150 mmHg ($p = 0.024$) and an APACHE II score ≥ 20 ($p = 0.017$) remained associated with death. In another study, the development of ARDS and a history of immunosuppression were independent risk factors for hospital mortality in critically ill patients with confirmed influenza virus infection [34].

Preventive Measures

The emergence of an antigenically novel influenza virus to which little or no antibody was present in a community, resulted in an extensive outbreak; the absence of antibody is worldwide, and for that reason there has been a pandemic. Independent of this antigenically new virus, questions regarding the potential effectiveness of vaccination for seasonal influenza arises. In one interim analysis of the pandemic in Australia, the authors found that there was no evidence of significant protection from seasonal vaccine against pandemic influenza virus infection in any age group [35]. A new vaccine has been developed, but there have been concerns based on the experience during the 1976–77 flu season, during which a swine flu outbreak at Fort Dix, New Jersey led the federal government to expedite vaccine production. Some 40 million people had been vaccinated by the time Guillain-Barré syndrome was identified as a side effect. However, with the pandemic as a reality, it is considered that the benefit of the vaccine far outweighs the risks.

Conclusion

Pandemics provide the most dramatic evidence of the impact of influenza. The morbidity and mortality caused by this first influenza pandemic in the 21st century, characterized by an unusual increase in the number of cases of primary viral severe community-acquired pneumonia requiring mechanical ventilation, has been substantial. Interestingly this higher incidence of severe cases appeared in a younger age group than that usually involved in the annual seasonal flu outbreak. The percentage of the population that acquired influenza during this pandemic has not yet been estimated but certainly it was much higher than during seasonal influenza; this higher incidence may explain the high number of cases of severe primary pneumonia observed in the Southern Cone. The apparently less aggressive nature of the infection and the younger population affected may explain an estimated mortality rate of 0.05–0.1 %, lower than that observed in seasonal influenza, as complications and mortality in seasonal flu are more frequent among patients ≥ 65 years old and in those with chronic disorders, including cardiac or pulmonary diseases, diabetes mellitus, hemoglobinopathies, renal dysfunction, and immunosuppression, also usually associated with older age.

Improved and standardized optimal ICU care for patients with influenza H1N1 2009, including young and immunocompetent patients, with or without comorbidities, should lead to lower mortality than that previously observed for influenza pneumonia when mechanical support is required.

The pandemic H1N1 2009 influenza has resulted in tremendous pressures on the critical care system. The unexpected and rapid influx of such a large number of patients to emergency room and critical care services has highlighted not only a shortage of critical care capacity but also an inadequate supply of critical care resources. The extreme severity of ARDS in these patients has necessitated a change in the usual approach to the management of these patients to improve success rates.

The health system must be prepared to reallocate resources in response to demand. Therefore, early recognition of probable viral pneumonia is crucial in order to implement early infection-control strategies and to reduce transmission to health-care workers who are at high risk for exposure to these pathogens.

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VII Infections

Cytomegalovirus Infections in Non-immunocompromised Critically Ill Patients

D.F. Florescu and A.C. Kalil

Introduction

Patients with a prolonged intensive care unit (ICU) stay represent 5.6 % of ICU admissions and 39.7 % of ICU bed-days [1]. Based on these incidence rates, it would be useful to identify risk factors associated with prolonged ICU and hospital stays to help guide the delivery of ICU care. Cytomegalovirus (CMV) infection could be one of the markers for this subgroup of more critically ill patients. CMV is well recognized as an important pathogen in patients with acquired immunodeficiency syndrome (AIDS) [2], and in solid organ [3] and hematopoetic stem-cell [4] transplant recipients. The direct (end-organ disease) and the indirect (allograft rejection, atherosclerosis, CMV-induced immunosuppression with increased risk of post-transplant lymphoprolipherative disorders and secondary bacterial and fungal infections) effects of CMV infection are well described in immunocompromised hosts [3, 5, 6].

Approximately 300 cases of CMV infection (meningitis, encephalitis, transverse myelitis, retinitis, uveitis, pneumonia, vascular thrombosis, myocarditis, gastritis, colitis, hepatitis, hemolytic anemia, hemophagocytic syndrome, and thrombocytopenia) in non-immunocompromised hosts have been published in the literature [7]. CMV infection should be of greater concern in non-immunocompromised critically ill patients because a significant proportion of these patients become immunocompromised during their ICU admission [6]. However, the risk factors for CMV reactivation, its incidence and its impact on morbidity and mortality are still not completely elucidated. CMV serology, polymerase chain reaction (PCR), and culture are not part of routine diagnostic testing in critically ill non-immunocompromised patients. On the other hand, it is difficult to establish a diagnosis of active CMV infection in critically ill patients because most of the time clinical signs and symptoms are very non-specific. In addition, detection of the virus is not, in the majority of the cases, followed by tissue biopsy to assess for CMV disease. Hence, the question of a causal relation (cause-effect or effect-cause) between CMV infection and morbidity/mortality in this ICU population needs to be elucidated in future studies. During the last year, several studies, two prospective [8, 9], one retrospective [10], and one systematic review and meta-analysis [11], have been performed in the ICU setting with the goal of better understanding the role of CMV detection in critically ill patients (**Table 1**).

Clinical Studies

Using quantitative CMV assessments, Limaye et al. [8] evaluated, in a prospective study, the impact of CMV reactivation on mortality and ICU and hospital lengths of

Table 1. Active cytomegalovirus infection in non-immunocompromised intensive care unit patients

	Limaye 2008 [8]	Ziemann 2008 [10]	Chiche 2009 [9]	Kalil 2009 [11]
Incidence	33 %	35 %	16 %	17 %
Proportion of CMV sero-positive patients	100 %	73 %	80 %	NA
Incidence in CMV sero-positive patients	33 %	56 %	19 %	31 %
ICU type	burn, trauma, medical, cardiac	surgical	medical	medico-surgical, medical
Risk factors for CMV disease	Male sex	NA	Prior admission to other wards, corticosteroid use before ICU admission, blood transfusion during ICU stay, enteral feeding	Surgical ICU, high disease severity, severe sepsis and septic shock
Potential consequences of CMV infection				
Bacterial infections	NA	NA	Yes	NA
Prolonged mechanical ventilation	NA	Yes	Yes	NA
Longer ICU stay	Yes	Yes	Yes	NA
Increased mortality	No	Yes	Yes	Yes

NA: Not available

stay in a broad range of critically ill non-immunocompromised patients. All patients enrolled in this study were CMV sero-positive. The cumulative incidence estimate of viremia at any level in the study group was 33 %. The heterogeneity of the patients included in this study was reflected in the significant variability between the incidences of infection in patients in different ICUs (55 % burn ICU, 38 % trauma ICU, 25 % medical ICU, and 15 % cardiac ICU), the number of days to first detectable CMV viremia in different units (median 19 days for burn ICUs, 8 days for medical ICUs) and the duration of viremia for patients in different units (median 20 days for burn ICUs vs 4 days for cardiac ICUs). CMV was detected early, within the first 12 days, in 50 % of the patients who were ever positive and in the first 30 days in 95 % of these patients. By logistic regression analysis, only male sex (OR 3.6, $p = 0.005$), but not APACHE score or ICU type, was found to be a risk factor for CMV reactivation. In multivariable models, Limaye et al. found that CMV viremia was independently associated with death or continued hospitalization at 30 days (OR 4.6, $p< 0.001$).

The study by Ziemann et al. [10] was a retrospective study of patients admitted for at least 14 days to a surgical ICU. The aim of the study was to assess the prevalence and impact on outcome of CMV infections. CMV reactivation was detected by CMV DNA analysis in the stored plasma samples from these patients. Seventy-three percent of the patients in this study were CMV sero-positive. The overall prevalence of CMV infection in the study population was 35 %, and 56 % in the CMV sero-positive subgroup. Active CMV infection was associated with a longer stay in the ICU

(32.6 vs 22.1 days) for the surviving patients, prolonged mechanical ventilation (506 vs 389 hours), and increased mortality (28.6 % vs 10.9 %). In this study, sepsis on admission to the ICU ($p = 0.09$), infection on admission ($p = 0.64$), and different comorbidities, like chronic obstructive lung disease ($p = 1.00$), diabetes mellitus ($p = 0.38$), malignant disease ($p = 1.00$) were not associated with a higher prevalence of CMV infection.

The study by Chiche et al. [9] was a prospective epidemiologic study in a medical ICU conducted to determine the incidence of, risk factors for, and outcome from active CMV infection in non-immunosuppressed mechanically ventilated (for at least 2 days) patients. Eighty percent of the enrolled patients were CMV sero-positive. The diagnosis of CMV infection in this study relied on antigenemia. The incidence of active CMV infection was 16 %. CMV infection had a delayed onset, being diagnosed at a median of 16 days after ICU admission. Patients with CMV infection had a longer duration of mechanical ventilation (27 vs 10 days, $p < 0.001$) and longer ICU stay (32 vs 12 days, $p < 0.001$). Interestingly, this study showed that patients with active CMV infections were more prone to develop complications like bacterial nosocomial infections (69 % vs 33 %, $p < 0.001$), including bacteremia (26 % vs 11 %, $p < 0.001$), bacterial ventilator-acquired pneumonia (56 % vs 23 %, $p < 0.001$), and also acute renal failure requiring renal replacement therapy (38 % vs 22 %, $p = 0.042$). These data are consistent with what is already known, that CMV favors bacterial infections in immunocompromised patients. Using logistic regression analysis, Chiche et al. identified several risk factors associated with active CMV infection: Prior admission to other wards (OR 2.49, $p = 0.043$), corticosteroid use before ICU admission (OR 2.26, $p = 0.08$), blood transfusion during ICU stay (OR 3.31, $p = 0.04$), and enteral feeding (OR 3.00, $p = 0.005$). Active CMV infection was associated with a non-statistically significant increase in ICU (54 % vs 37 %, $p = 0.082$) and in-hospital mortality (59 % vs 41 %, $p = 0.58$).

To better define the incidence of CMV infection in non-immunocompromised patients in ICUs and its impact on morbidity and mortality, we performed a systematic review and a meta-analysis on the published evidence regarding active CMV infection in this population [11]. Thirteen articles were included in our study. We found an overall rate of CMV infection in non-immunosuppressed critically ill patients of 17 %, with differences in rates of infections based on the diagnostic methods used (12 % with CMV culture and 20 % with more sensitive diagnostic methods like CMV PCR and/or antigen). The rate of infection varied by type of ICU setting (8 % medico-surgical ICU, 23 % surgical-only ICU). CMV infections tended to be diagnosed late during ICU admission, shown by the low rate (1 %) of CMV infections in studies with early screening (before 5 days) compared with the higher rate (21 %) in studies with late screening (after 5 days). Another interesting aspect, was that disease severity had an impact on the CMV infection rate – 32 % for high disease severity vs 13 % for low disease severity. The rate of active infections was much higher (32 %) for trials that included only patients with severe sepsis and septic shock than for those that included patients admitted to the ICU with or without severe sepsis (15 %). CMV infection significantly increased the mortality (OR 1.93, $p = 0.001$) with very low heterogeneity among different study populations and study designs. We also analyzed all studies for the rate of infection and mortality by two eras, before and after year 2001 (when drotrecogin alfa [activated] and low-dose steroids became more frequently used in the ICU) and found no significant difference.

Conclusion

The high incidence of active CMV infection reported in studies published in the last year (17–35 %) [8–11] highlights once more that CMV infection may be a frequently unrecognized problem in most ICUs. The risk factors for CMV infection varied among these studies and included male sex [8], previous ward admission [9], steroid use before ICU admission [9], blood transfusions during ICU stay [9], and enteral feeding [9]. So what is the clinical significance of CMV infection in non-immunocompromised critically ill patients? Although it remains uncertain whether CMV is a determinant or a marker of disease severity, these four new studies lend further support to the former hypothesis, i.e., CMV does not appear to be only an innocent bystander, since it has been associated with prolonged ICU stay [8–11], prolonged mechanical ventilation [9, 10], and higher mortality [8–11]. We conjecture that CMV infection is more prevalent in the ICU than previously thought and that it constitutes a potentially modifiable risk factor for death and prolonged hospitalization. So, should we start treating these patients? The data currently available do not support (or refute) antiviral therapy in this group of patients, and even if antiviral therapy may be warranted, a viral load threshold for the initiation of anti-CMV therapy should be established to avoid unnecessary treatment and adverse effects, such as significant neutropenia.

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Prevention of Central Venous Catheter-related Infection in the Intensive Care Unit

D. Frasca, C. Dahyot-Fizelier, and O. Mimoz

Introduction

In the USA, more than five million patients require central venous access each year. Unfortunately, central venous access can be associated with adverse events that are hazardous to patients and expensive to treat. Infection remains the main complication of intravascular catheters in critically ill patients. Catheter-related bloodstream infections have been reported to occur in 3 to 8 % of inserted catheters and are the first cause of nosocomial bloodstream infection in intensive care units (ICUs), with 80,000 cases annually at a cost of $300 million to $2.3 billon [1]. Additional financial costs may be as high as $30,000 per survivor, including one extra week in the ICU and two to three additional weeks in the hospital. Attributable mortality rates range from 0 to 35 %, depending on the degree of control for severity of illness.

The physiopathology of catheter infection is now more clearly understood. Colonization of the endovascular tip of the catheter precedes infection and arises by two main pathways: The extraluminal and the intraluminal routes (**Fig. 1**) [2]. Migration

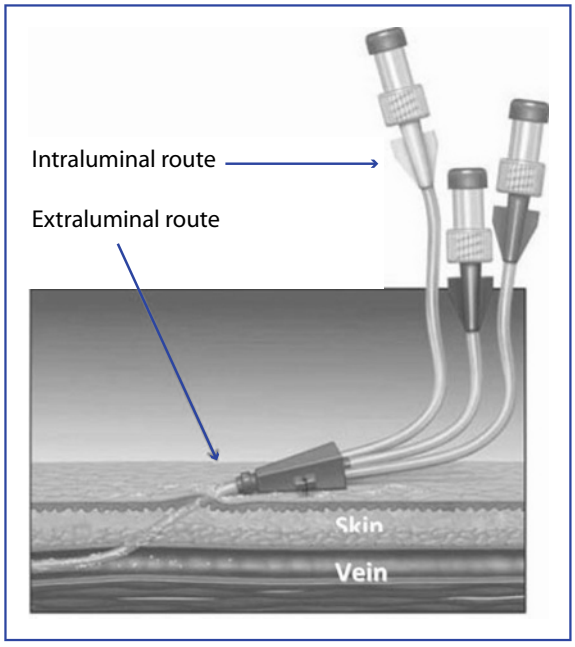

Fig. 1. Pathophysiology of central line infection

of skin organisms from the insertion site into the cutaneous catheter tract with colonization of the catheter tip is the most common route of infection for short-term central venous catheters (CVCs). For long-term catheters (i.e., catheters staying in place more than 15 days), the main cause of colonization is manipulation of the venous line with migration of organisms along the internal lumen of the catheter. The adherence properties of microorganisms to host proteins, such as fibronectin, commonly present on catheter tips make this colonization easier. Coagulase-negative staphylococci are the most common microorganisms associated with catheter-related bloodstream infections. Other microorganisms commonly involved include *Staphylococcus aureus*, *Candida* species, *Enterococci* and Gram-negative bacilli [3].

The Centers for Disease Control and Prevention identifies catheter-associated adverse events, including bloodstream infections, as one of its seven health care safety challenges, with a goal to reduce such complications by 50 % in five years [4]. Several preventive measures have been studied to reduce the incidence of these infections. The most effective are those that reduce colonization at the catheter skin insertion site or the infusion line, and include: Adequate knowledge and use of care protocols; qualified personnel involved in catheter changing and care; use of biomaterials that inhibit microorganism growth and adhesion; good hand hygiene; use of an alcoholic formulation of chlorhexidine for skin disinfection and manipulation of the vascular line; preference for the subclavian vein route for insertion of CVCs using full-barrier precautions; and removal of unnecessary catheters.

Catheter Care Protocols

Programs that help health-care providers to monitor and evaluate care are crucial for the success of preventive measures. Educational programs with hygiene training and written protocols concerning catheter insertion (e.g., preparation of the equipment, skin antisepsis, detailed insertion techniques), catheter manipulation (e.g., hand hygiene, manipulations of taps) and catheter care (e.g., catheter replacement modalities, type and frequency of dressings, and line repair) are effective when staff members are involved in designing the measures included in the program [5, 6]. Regular evaluation of the incidence of catheter-related infections and of clinical practice is a useful measure when information and feedback is provided to all actors [7, 8]. Catheter insertion in emergency conditions increases the risk of non-compliance to the insertion protocol and, consequently, to infectious complications; these catheters must be replaced as soon as the patient's condition is stabilized [9].

Staff Educational/Quality Improvement Program

Educating and training of health-care providers who insert and maintain CVCs is essential for preventing catheter-related infection, improving patient outcomes, and reducing healthcare costs [10]. The experience of the operator is an important issue as the risk of infectious complications is inversely proportional to the operator skills. An educational intervention in catheter insertion significantly improved patient outcomes and simulation-based training programs are valuable in residency education [11]. Programs for training nurses in long-term catheter care ("IV teams") were associated with a reduction in catheter-related infections in the USA [12]. Nevertheless, without such teams the use of care protocols and nursing staff education

allowed comparable results to be obtained [13]. Nursing staff reductions below a critical level may contribute to increase catheter-related infection by making adequate catheter care difficult. One study reported a four times greater risk of catheter infection when the patient-to-nurse ratio was doubled [14]. Moreover, replacement of regular nurses by float nurses further increases the risk of device-related infections [15]. These studies clearly indicate that trained nurses, in sufficient numbers, must be available for optimal patient care in the ICU.

Type of Catheter

Catheter material is an important determinant in the prevention of catheter-related infection. The material should be biocompatible, hemocompatible, biostable, chemically neutral, not altered by administered drugs, and deformable according to surrounding strengths. Furthermore, the catheter must be flexible, resistant, as radioopaque as possible, thin walled with a high internal to external diameter ratio, resistant to sterilization, and with locked connections such as 'luer-lock' type. Teflon® or polyurethane catheters have been associated with fewer infectious complications than catheters made of polyvinyl chloride or polyethylene [16, 17]. The majority of catheters sold in the USA and in many European countries are, therefore, no longer made of polyvinyl chloride or polyethylene.

Catheters coated with antimicrobial or antiseptic agents decrease microorganism adhesion and biofilm production, and, hence, the risk of catheter-related infection. The use of such catheters may potentially decrease hospital costs, despite the additional acquisition cost of the antimicrobial/antiseptic coated catheter [18]. Commercialized catheters are mainly coated with chlorhexidine/silver sulfadiazine or minocycline/rifampin [19]. Fifteen randomized studies evaluating the performance of a catheter coated on its extraluminal side with chlorhexidine/silver sulfadiazine (first generation) were included in a meta-analysis. Compared to a standard catheter, the use of the coated catheter decreased the risk of catheter colonization (relative risk, RR: 0.59 [95 % CI: 0.50 – 0.71]) and bloodstream infection (RR: 0.66 [95 % CI: 0.47 – 0.93]) [20]. Two studies evaluated catheters coated on both their external and internal surfaces (second generation) and provided comparable results concerning colonization (RR: 0.44 [95 % CI: 0.23 – 0.85]) and a non-significant reduction in bloodstream infection (RR: 0.70 [95 % CI: 0.30 – 1.62]), probably due to a lack of power. Five studies evaluated catheters covered with minocycline/rifampin and reported a decrease in colonization (RR: 0.40 [95 % CI: 0.23 – 0.67]) and bloodstream infection (RR: 0.39 [95 % CI: 0.17 – 0.92]) compared to standard catheters. Two studies concluded that silver-coated catheters (even with platinum or carbon coating) had no beneficial effects on colonization (RR: 0.76 [95 % CI: 0.57 – 1.01]) or on bloodstream infection (RR: 0.54 [95 % CI: 0.16 – 1.85]), but the studies were underpowered. A multicenter randomized study evaluated catheters impregnated with ionic silver in 577 ICU patients and 617 CVCs [21]. Compared to standard catheters, impregnated catheters had no effect on colonization (RR: 1.24 [95 % CI: 0.83 – 1.85]) or bloodstream infection prevention (RR: 0.93 [95 % CI: 0.35 – 2.44]). Two studies compared first generation antiseptic catheters with antibiotic-coated catheters and concluded that the latter were superior for preventing catheter colonization (RR: 0.36 [95 % CI: 0.25 – 0.53]) and bloodstream infection (RR: 0.12 [95 % CI: 0.02 – 0.67]). No study has compared antibiotic-coated catheters with second generation antiseptic impregnated catheters. At this time, there is no evidence for multi-

resistant bacteria selection with antibiotic-coated catheters, but the number of studies is limited. Rare but serious cases of anaphylactic reactions to chlorhexidine/silver sulfadiazine have been reported, mainly in Japan. However, despite a Food and Drug Administration (FDA) alert in 1998 encouraging the declaration of these events, the number of cases reported in the USA remains low. Considering their costs and their theoretical ecological impact, the use of CVCs coated with antimicrobial agents should be reserved for ICUs where the incidence of catheter-related infection remains high despite adherence to guidelines and recommended measures [22].

CVCs with multiple lumens allow simultaneous administration of incompatible drugs and may separate the administration of vasopressors and parenteral nutrition. Five randomized studies have evaluated the risk of the use of multilumen catheters on catheter colonization and bloodstream infection [23]. Most of these studies are old, were conducted outside the ICU, and included few patients. Compared to mono-lumen catheters, the use of multiple lumen catheters was associated with comparable risks of catheter colonization (RR: 0.80 [95 % CI: 0.43 – 1.50]), but higher risks of bloodstream infection (RR: 2.26 [95 % CI: 1.06 – 4.83]). The increased risk of bloodstream infection is explained by one study which included long-term catheters (mean duration of catheterization longer than 20 days) for parenteral nutrition and reported a surprisingly high level of infection with multiple lumen catheters (13.1 % versus 2.6 % with mono-lumen catheters). Excluding this study from the meta-analysis gave a comparable risk of bloodstream infection between the groups (RR: 1.29 [95 % CI: 0.49 – 3.39]). The choice of the number of lumens should, therefore, be made based on the patient's requirements rather than on the risk of infectious complications. Any solution containing lipids (parenteral nutrition, propofol) must be delivered through a dedicated lumen.

Catheter Insertion Site

The site at which a catheter is inserted may influence the subsequent risk of catheter-related infection because of differences in the density of local skin flora and risks of thrombophlebitis. A randomized study of 270 catheters inserted in the femoral or subclavian veins of ICU patients [24] reported a higher colonization rate with femoral catheters (RR: 6.4 [95 % CI: 1.9 – 21.2]) without any increase in bloodstream infections (RR: 2.0 [95 % CI: 0.2 – 22.1]). A meta-analysis of three prospective non-randomized studies compared catheters inserted in the internal jugular (n = 278) and subclavian (n = 429) veins. The use of the internal jugular vein was associated with a non-significant increase in the risk of bloodstream infection (RR: 2.24 [95 % CI: 0.2 – 22.1]) compared to the subclavian route. Moreover, multivariate analysis of several prospective studies has shown more frequent infectious complications when using femoral or internal jugular access [25].

A randomized multicenter study evaluated the risk of complications with dialysis catheters in the ICU according to femoral or internal jugular insertion site. A total of 750 catheters with an average duration of insertion of 6 days were included. The risk for colonization was comparable for both sites (incidence of 40.8 vs 35.7 per 1000 catheter-days for the femoral and jugular sites, respectively, RR: 0.85 [95 % CI: 0.62 – 1.16]). Nevertheless, the risk of colonization with internal jugular access was increased in patients with a body mass index less than 24.2 (RR: 2.10 [95 % CI: 0.23 – 0.69]) and decreased in patients with a body mass index greater than 28.4 (RR: 0.40 [95 % CI: 1.13 – 3.91]) [26].

The subclavian site is preferred for infection control purposes, although other factors (e.g., the potential for mechanical complications, risk of subclavian vein stenosis, and catheter-operator skill) should be considered when deciding where to place the catheter. When the subclavian route is contraindicated, the choice between the femoral and internal jugular vein should be made according to the body mass index of the patient. The risk of thrombophlebitis should also be taken into consideration, as it is higher with the femoral route than when using the subclavian or internal jugular veins.

Ultrasound-guided Placement

The use of ultrasound guidance has been promoted as a method to reduce the risk of complications during central venous catheterization. In this technique, an ultrasound probe is used to localize the vein and to measure its depth beneath the skin. Under ultrasound visualization, the introducer needle is then guided through the skin and into the vessel. The location of the vein with ultrasound decreases the number of puncture failures and complications (e.g., arterial puncture), and reduces the time for catheter insertion. This technique may provide advantages for the jugular internal vein location. In a meta-analysis of eight studies, the use of bedside ultrasound for the placement of catheters substantially reduced mechanical complications compared with the standard landmark placement technique (RR: 0.22; [95 % CI: 0.10 – 0.45]) [27]. Data available for subclavian or femoral veins are encouraging but limited. In a randomized study with 900 ICU patients, ultrasound-guided placement resulted in a reduction in bloodstream infection (10.4 % vs 16.0 %, $p < 0.01$) [28]. In hospitals where ultrasound equipment is available and physicians have adequate training, the use of ultrasound guidance should be routinely considered before CVC placement is attempted.

Insertion Technique

When inserting a catheter, one should use maximal sterile-barrier precautions, including a mask, a cap, a sterile gown, sterile gloves, and a large sterile drape. This approach has been shown to reduce the rate of catheter-related bloodstream infections and to save an estimated $167 per catheter inserted [29]. The insertion site should be widely disinfected with a chlorhexidine-based solution. Catheters should then be inserted using the Seldinger technique and adequately secured.

Skin Antisepsis

The density of microorganisms at the catheter insertion site is a major risk factor for catheter-related infection and skin antisepsis is one of the most important preventive measures. Povidone iodine and chlorhexidine are the most commonly used antiseptic agents, both available as aqueous and alcoholic solutions. Their respective efficacy in preventing catheter colonization and bloodstream infections has been compared in numerous studies.

One meta-analysis included eight randomized trials that compared chlorhexidine to aqueous povidone iodine for the care of 4143 short-term catheters (1568 CVC,

1361 peripheral venous catheters, 704 arterial catheters, and 395 pulmonary artery catheters) in hospitalized patients [30]. Chlorhexidine solutions were either an aqueous solution of 2 % chlorhexidine (2 trials), a 70 % alcoholic solution of 0.5 % chlorhexidine (4 trials), an alcoholic solution of 1 % chlorhexidine (1 trial), or a combination of 0.25 % chlorhexidine, 0.025 % benzalkonium chloride and 4 % benzylic alcohol (1 trial). Catheter insertion sites and duration of catheterization were comparable between the two groups. The use of chlorhexidine rather than povidone iodine aqueous solution significantly reduced catheter-related bloodstream infections by approximately 50 % (RR: 0.51 [95 % CI, 0.27 – 0.97]). For every 1000 catheter sites disinfected with chlorhexidine solutions rather than povidone iodine solutions, 71 episodes of CVC colonization and 11 episodes of infections would be prevented. Similar findings with an alcoholic formulation of 2 % chlorhexidine were reported after publication of the meta-analysis [31], confirming that aqueous povidone iodine should not be used for this indication.

In most of these studies, chlorhexidine's superiority was explained, at least in part, by a synergistic effect with alcohol, even for low chlorhexidine concentrations. This synergistic effect was also demonstrated with povidone iodine. A randomized multicenter crossover trial compared the effectiveness of two pre-insertion cutaneous antisepsis protocols using aqueous 10 % povidone-iodine or a solution of 5 % povidone iodine in 70 % ethanol [32]. The incidences of catheter colonization (RR: 0.38 [95 % CI: 0.22 – 0.65]) and catheter-related infection (RR: 0.34 [95 % CI: 0.13 – 0.91]) were significantly lower in patients managed using the alcoholic povidone iodine solution protocol compared to the aqueous povidone iodine solution protocol. No significant effect was observed on bloodstream infections, but the study was underpowered to explore this issue.

Only one trial has compared a chlorhexidine-based solution to 5 % alcoholic povidone iodine. A total of 538 catheters were randomized and 481 (89.4 %) produced evaluable culture results [33]. Compared to alcoholic povidone iodine, the used of a chlorhexidine-based solution significantly reduced the incidence of catheter colonization by 50 % (11.6 % vs 22.2 % p = 0.002; incidence density, 9.7 vs 18.3 per 1000 catheter-days). The use of the chlorhexidine-based solution was also associated with a trend toward lower rates of catheter-related bloodstream infection (1.7 % vs 4.2 % p = 0.09; incidence density, 1.4 vs 3.4 per 1000 catheter-days). In this study, independent risk factors for catheter colonization were catheter insertion in the jugular vein (RR: 2.01 [95 % CI: 1.24 – 3.24) and use of alcoholic povidone iodine as skin disinfectant (RR: 1.87 [95 CI: 1.18 – 2.96]). Although more studies are needed to confirm these results, chlorhexidine-based solutions do seem to be more effective than povidone iodine, even in an alcoholic formulation, and should be used as first-line antiseptics for CVC care.

Tolerance to chlorhexidine-based solutions is generally excellent. Contact dermatitis is occasionally observed whatever the formulation used and severe anaphylactic reactions have been exceptionally reported (less than 100 cases in the world).

Antibiotic Prophylaxis

No studies have demonstrated any reduction in CVC infection rates with oral or parenteral antibacterial or antifungal drugs given during catheter insertion. In contrast, numerous studies have reported that antibiotic administration in patients with a CVC *in situ* significantly reduced the risk of catheter colonization and of blood-

stream infections [24]. In pediatric patients, two studies have assessed vancomycin prophylaxis for CVC flushing (antibiotic lock); both demonstrated a significant reduction in catheter-related bloodstream infection without any effect on mortality [34, 35]. Because prophylactic use of vancomycin is an independent risk factor for vancomycin-resistant *Enterococcus* (VRE) acquisition, the risk of VRE emergence likely outweighs the benefit of using prophylactic vancomycin. Systemic antibiotic prophylaxis should not be used during catheter insertion or maintenance just for the purpose of preventing catheter infection.

Tunneling

Subcutaneous tunneling of short-term CVCs is thought to reduce the incidence of catheter infection, presumably by increasing the distance between the venous entry site and skin emergence. Catheter emergence in a skin area that is less colonized by skin pathogens is another possible mechanism. Another advantage of tunneling is better fixation of the catheter. Evidence from studies on tunneling efficacy have suggested that this technique reduces CVC infections in patients with short-term devices, where most colonized pathogens arise from the catheter insertion site. A meta-analysis of randomized controlled trials demonstrated that tunneling decreased catheter colonization by 39 % and bloodstream infection by 44 % compared to non-tunneling [36]. These results were partly due to one trial with CVCs inserted via the internal jugular vein, and no significant risk reduction was observed when only the data from five subclavian catheter trials were pooled. Mechanical complications or difficulties during placement were not increased by tunneling but these outcomes were not evaluated in depth. Although, this meta-analysis concluded that tunneling decreased catheter-related infections, the data do not support routine subcutaneous tunneling of short-term venous catheters unless subclavian access is not possible (or contraindicated) and the duration of catheterization is anticipated to be more than 7 days.

Dressing

Because occlusive dressings trap moisture on the skin and provide an ideal environment for quick local microflora growth, dressings for insertion sites must be permeable to water vapor. The two most common types of dressing used are sterile, transparent, semi-permeable polyurethane dressings coated with a layer of an acrylic adhesive, and gauze and tape dressings. Transparent, semipermeable polyurethane dressings have become a popular way of dressing catheter insertion sites because they allow continuous visual inspection of the site, allow patients to have baths and to shower without saturating the dressing, and require less frequent changes than do standard gauze and tape dressings; finally these dressings are time-saving for the staff. However, as there is no evidence regarding which type of dressing provides the greatest protection against infection the choice of dressing can be a matter of preference. If blood is oozing from the catheter insertion site, a gauze dressing may be preferred.

In a meta-analysis, the use of a chlorhexidine-impregnated sponge placed over the site of short-term vascular and epidural catheters significantly reduced the risk of catheter colonization but not catheter-related bloodstream infection compared to

standard dressing [37]. More recently, a study performed in seven ICUs in France included 1636 patients randomized to receive catheter dressings with or without a chlorhexidine gluconate-impregnated sponge [38]. A total of 3778 catheters (28,931 catheter-days) were evaluated. The median duration of catheter insertion was 6 (interquartile range, 4–10) days. Use of chlorhexidine gluconate-impregnated sponge dressings decreased the rates of major catheter-related infections (10/1953 [0.5 %], 0.6 per 1000 catheter-days vs 19/1825 [1.1 %], 1.4 per 1000 catheter-days; hazard ratio [HR], 0.39 [95 % CI, 0.17–0.93]; p = 0.03) and catheter-related bloodstream infections (6/1953 catheters, 0.40 per 1000 catheter-days vs 17/1825 catheters, 1.3 per 1000 catheter-days; HR, 0.24 [95 % CI, 0.09–0.65]). Use of chlorhexidine gluconate-impregnated sponge dressings was not associated with greater resistance of bacteria in skin samples at catheter removal and was well tolerated. The authors concluded that the use of chlorhexidine gluconate-impregnated sponge dressings with intravascular catheters in the ICU reduced the risk of infection even when background infection rates were low, and should be recommended [38]. However, the antiseptic solution used for catheter care was povidone iodine. As previously discussed, chlorhexidine is more effective than povidone iodine to disinfect the skin. Therefore, whether there is any benefit from using chlorhexidine-impregnated sponge for catheters in patients in whom chlorhexidine is used for catheter care remains unknown.

The optimal frequency for routine changing of catheter dressings is unknown. It is probably of little use to change dressing before 7 days, except when the insertion site is soiled with blood or moisture or the dressing is unstuck [38]. The dressing site should be disinfected with the same antiseptic solution used for catheter placement.

Venous Line Maintenance

The optimal time interval for routine replacement of intravenous administration sets has been studied in three well-controlled trials [39–41]. Replacing administration sets no more frequently than 72 hours after initiation of use is safe and cost-effective [42]. Because blood, blood products, and lipid emulsions (including parenteral nutrition and propofol) have been identified as independent risk factors for catheter-related infection [43], tubing used to administer these products should be replaced within 24 hours or immediately after the end of administration.

An aseptic technique is very important when accessing the system. Catheter, tubing, or syringe manipulations must be done only after cleaning hands with an alcohol-based handrub solution. Hubs and sampling ports should be disinfected with chlorhexidine-based antiseptic solutions before accessing [44]. During prolonged catheterization, infection risk is strongly connected to the duration of catheter stay and frequent catheter hub access increases catheter-related infection risk from colonized catheter hubs rather than from the insertion site. The number of manipulations of the central venous line, especially when an aseptic technique is not respected, increases the risk of catheter-related bloodstream infection. The use of the enteral or oral route to deliver drugs and diet should, thus, be encouraged whenever possible.

The continued need for the catheter should be assessed every day and removal considered when the catheter is no longer essential for medical management. Catheter replacement at scheduled time intervals as a method to reduce catheter-related

infection has not been shown to be beneficial [45, 46]. Scheduled guidewire exchanges of catheters have also been proposed, but a meta-analysis of 12 randomized controlled trials failed to demonstrate any reduction in infection rates with routine guidewire exchange compared to catheter replacement on an as-needed basis [47]. On the contrary, exchanging catheters with the use of a guidewire increases the risk of bloodstream infection, while replacement involving insertion of catheters at new sites increases the risk of mechanical complications [46]. Thus, routine replacement of CVCs is not necessary for functional catheters with no evidence of local or systemic complications. Catheter guidewire exchange is acceptable for replacement of a non-functional catheter.

Application of antibiotic or antiseptic ointments (e.g., bacitracin, mupirocin, neomycin, and polymyxin) to catheter-insertion sites increases the rate of catheter colonization by fungi, promotes the emergence of antibiotic-resistant bacteria, and has not been shown to lower the rate of catheter-related bloodstream infections [48]. These ointments should not be used. No data are available to support the efficacy of in-line filters in preventing infections associated with intravascular catheters and infusion systems, although the use of these devices increases the cost of the venous line. Administration of prophylactic heparin reduces the risk of thrombosis around the catheter. Because thrombi and fibrin deposits on catheters may be a nidus for microbial colonization of intravascular catheters, anticoagulant therapy may have a role in prevention [49]. Moreover, these agents are also indicated in the management of in-bed patients with multiple risk factors for venous thrombosis.

Conclusion

Catheter-related bloodstream infection remains the most serious complication of central venous access and a leading cause of nosocomial infection in the ICU. Prevention of catheter-related infection involves several measures which should be used in combination (**Table 1**) [50 – 52]. The most important include the use of a checklist to guide catheter insertion and maintenance; adequate training of the nursing staff involved in the management of vascular access and an adequate patient-to-nurse

Table 1. Interventions to prevent central venous catheter (CVC) infection

- Use protocols for catheter insertion and maintenance
- Check for adequate training, experience, and numbers of nurses caring for patients with CVC
- Use antimicrobial-coated CVCs if the incidence of catheter-related infection remains high despite adherence to guidelines and recommended measures.
- Use maximal sterile-barrier precautions during catheter insertion
- Insert catheters using the subclavian venous site
- Use ultrasound guidance during catheterization (?)
- Consider tunneling if subclavian access is not possible and the CVC is anticipated to be in situ for more than 7 days
- Clean hands with an alcohol-based handrub solution before any manipulation of the infusion line
- Change dressings not more frequently than 7 days if not soiled, wet, or unstuck.
- Avoid the use of antibiotic prophylaxis at catheter insertion, and antibiotic ointments or inline filters during catheter maintenance
- Use the enteral route or peripheral venous access instead of the CVC as soon as possible
- Do not schedule routine catheter changes
- Remove catheters when they are no longer needed

ratio; the use of maximal sterile barrier precautions during catheter insertion; preference for a chlorhexidine-based solution for skin antisepsis and use of the subclavian vein whenever possible; cleaning hands with an alcohol-based handrub solution before any manipulation of the infusion line; and removing any useless catheters. The use of antimicrobial-coated CVCs should be reserved for ICUs where the incidence of catheter-related infection remains high despite adherence to guidelines and recommended measures. As with any device used in the ICU, healthcare workers caring for a patient with a central venous access device need to be adequately trained, and assessed as being competent in using CVCs and adhering to infection prevention practices.

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Standardization of Care to Improve Outcomes of Patients with Ventilator-associated Pneumonia and Severe Sepsis

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Introduction

Translating the results of research into clinical practice in critically ill patients is a challenging endeavor and often a slow, complex process. The medical literature is replete with evidence-based guidelines and protocols aimed at standardizing processes of medical care in an attempt to improve patient outcomes [1]. Despite the widespread availability of such documents, non-adherence to guidelines is readily apparent and directly impacts patient care [2]. Explanations for the lack of guideline adherence include excessive workloads for bedside healthcare providers (nurses, therapists, physicians), disagreement in interpretation of clinical trials, limited evidence in support of specific pharmacologic or non-pharmacologic treatment strategies, and simply the hesitancy to change practices at the beside (1,2).

Examples of successful quality improvement initiatives focused on the development and implementation of treatment pathways or protocols in critically ill patients include weaning from mechanical ventilation [3–7], sedation utilization [8, 9], intensive insulin therapy to achieve tight glucose control [10–12], and the prevention of nosocomial infections [13–20]. This chapter will focus on the impact of protocols directed at the management of patients with ventilator-associated pneumonia (VAP), severe sepsis, and septic shock. We will demonstrate how protocols can lead to improvements in patient outcomes, both in terms of preventing infections that can cause sepsis and in optimizing the antimicrobial treatment of these life-threatening infections (**Fig. 1**).

Prevention and Treatment of VAP

The antimicrobial management of VAP is a balancing act of providing appropriate initial treatment in a timely manner with broad-spectrum antibiotic therapy based on knowledge of local pathogens and their antimicrobial susceptibility versus avoidance of developing further antimicrobial resistance. The latter aim is somewhat more difficult to achieve and usually requires antimicrobial avoidance. Protocols aimed at changing from broad- to narrow-spectrum antibiotic therapy after 48 to 72 hours of empiric treatment, based on antimicrobial susceptibility testing, and using the shortest course of treatment that is clinically acceptable are the principle strategies of antibiotic avoidance to be employed. The ‘de-escalation’ strategy attempts to unify these principles into a single approach that will optimize patient outcomes with early appropriate therapy while minimizing the emergence of antibiotic resistant pathogens.

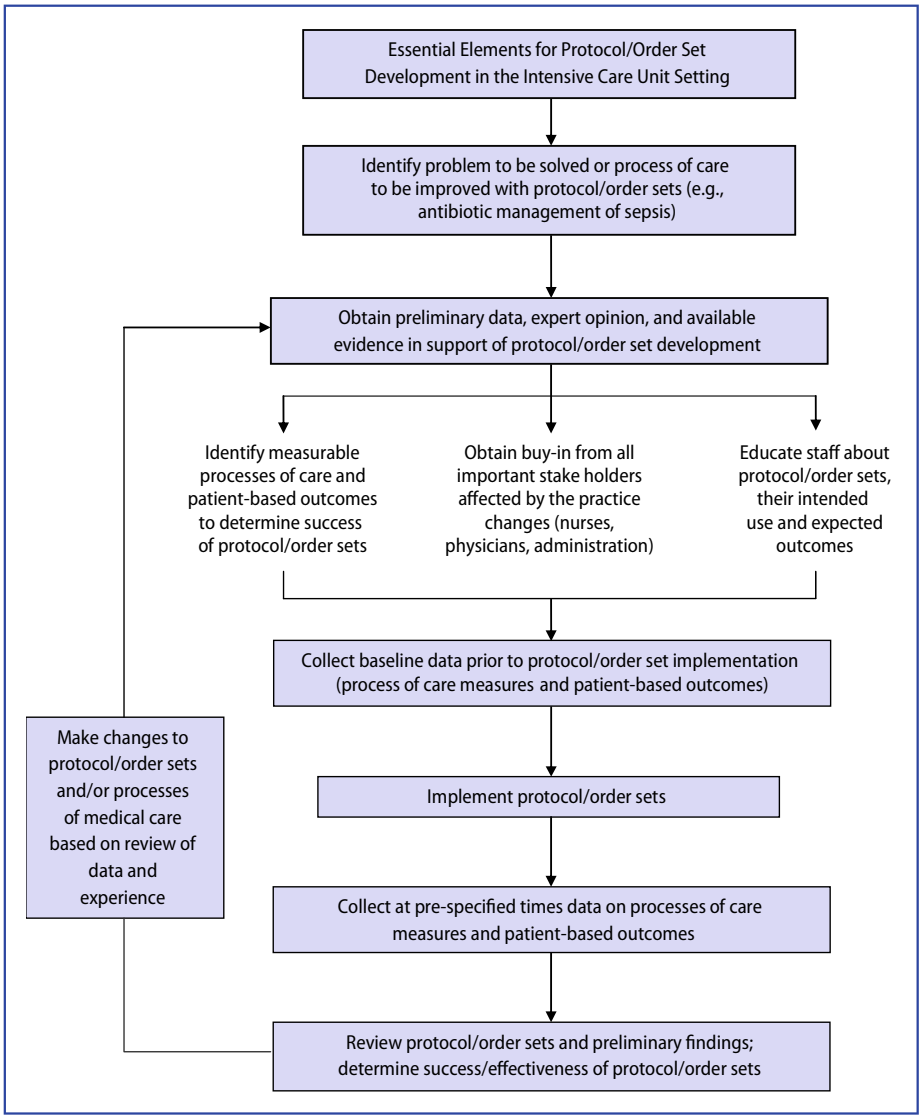

Fig. 1. General approach for the development, implementation, and review of a protocol/order set aimed at improving the care of patients in the intensive care unit setting.

Failure to provide treatment with an appropriate initial antimicrobial regimen for VAP has resulted in significantly higher rates of septic shock and hospital mortality [21–23]. Additionally, treatment delays of greater than 24 hours after meeting diagnostic criteria for VAP have been associated with statistically higher rates of bacteremia and in-hospital mortality [24]. Importantly, escalation of an initially inappropriate VAP treatment regimen according to subsequent culture and sensitivity results does not result in outcomes equal to those achieved in patients treated with antimicrobial therapy that is active against the offending pathogen from the outset

of administration [21, 23]. In an effort to optimize the likelihood of prescribing an initially appropriate regimen for clinically suspected VAP, the American Thoracic Society/Infectious Disease Society of America (ATS/IDSA) evidence-based guideline for nosocomial pneumonia recommends a combination of antimicrobials targeting the most common bacterial pathogens associated with early- and late-onset infection [25]. It is important to recognize that the predominant pathogens associated with hospital-acquired infections, including VAP, may vary among hospitals as well as among specialized units within individual hospitals [26, 27]. Therefore, clinicians should be aware of the prevailing bacterial pathogens in their hospitals and of associated antimicrobial susceptibilities when developing a local treatment protocol for VAP or other healthcare-associated infections.

The benefits of a protocol for VAP management were tested in a clinical setting by Ibrahim et al. who conducted a before-and-after study evaluating the impact of a VAP treatment guideline on initial administration of appropriate antimicrobial therapy [28]. In the particular medical intensive care unit (ICU) where this protocol was implemented, *Pseudomonas aeruginosa* and methicillin-resistant *Staphylococcus aureus* (MRSA) were the most common causes of VAP based on historical data. Consequently, the protocol dictated the combination of imipenem-cilastatin, ciprofloxacin, and vancomycin be prescribed initially as this regimen provided, at that time, *in vitro* coverage for greater than 90 % of *P. aeruginosa* and 100 % of MRSA isolates. In cases that had a bacterial pathogen identified, patients managed via the protocol were statistically more likely to receive initial appropriate treatment compared to those treated prior to protocol implementation (94.2 % versus 48 %; $p < 0.001$). Similarly, Wood and colleagues reported that a high percentage (76 %) of critically ill trauma patients with VAP were prescribed appropriate initial antibiotic coverage after altering their clinical pathway based on historical pathogen incidence [29]. Patients received ampicillin/sulbactam if they were diagnosed with early-onset VAP (through day 7 of hospitalization) and cefepime plus vancomycin for late-onset VAP (after day 7). These regimens were chosen due to the low incidence of *P. aeruginosa, Acinetobacter baumannii*, and MRSA as a cause of early-onset VAP in their population.

Lancaster et al. [30] also developed a protocol for the antimicrobial treatment of hospital-associated pneumonia based on the ATS/IDSA guidelines. Implementation of the protocol led to an increase in the proportion of patients who received appropriate empiric antibiotic coverage and in appropriate antibiotic de-escalation according to protocol recommendations. Compared with the pre-protocol group, use of the protocol also decreased the duration of intravenous antibiotic therapy, was associated with a trend for a shorter duration of stay in the ICU, and did not significantly affect mortality. Soo Hoo and colleagues [31] evaluated the role of a protocol for the management of severe hospital-associated pneumonia. Patients managed with the protocol had a higher percentage of appropriate initial treatment with a lower mortality rate at 14 days. Appropriate carbapenem use (as defined by the guidelines) occurred in 74 % of the cases, and there was no increase in the number of carbapenem-resistant organisms isolated during the course of the study. These studies support the use of guidelines as a tool to increase the appropriateness of empiric antibiotic therapy for patients with severe infections, such as VAP, as will also be illustrated below for severe sepsis and septic shock.

In addition to the prescription of appropriate initial antibiotic therapy, antimicrobial de-escalation should occur when possible based on the patient's clinical response to the empiric antimicrobial treatment and microbiologic testing results.

This approach includes decreasing the number and spectrum of antibiotics, based on the susceptibility patterns of the identified pathogens, and shortening the duration of therapy when appropriate. Rello and colleagues [32] examined the impact of a VAP treatment protocol incorporating de-escalation principles in 115 patients. Per treatment protocol, patients demonstrating clinical improvement 48 hours after initiation of broad-spectrum antimicrobials were subject to streamlining therapy. The approach included narrowing to a single agent if *P. aeruginosa* was not identified; focusing the antimicrobial spectrum of activity based on susceptibility data, i.e., changing from combination therapy to monotherapy for *P. aeruginosa*; and limiting the course of therapy to 5 days in patients remaining afebrile for 48 hours. Under this protocol, de-escalation occurred in 31.4 % of the patients.

In a study by Micek and colleagues [33] at Barnes-Jewish Hospital, patients with clinically-diagnosed VAP were randomly assigned to have the duration of antibiotic therapy determined by the clinical judgment of the treating physician (standard therapy) or by a formalized discontinuation protocol. Patients assigned to the discontinuation protocol group were monitored during the weekday by a clinical pharmacist who made recommendations to stop one or more antibiotics if a non-infectious etiology for pulmonary infiltrates was identified or if all of the following criteria were met: 1) temperature < 38.3 °C; 2) white blood cell count < 10×10^3 or decreased 25 % from peak value; 3) improvement or lack of progression of the chest radiograph; 4) absence of purulent sputum; and 5) PaO_2/FiO_2 ratio > 250 mmHg. Eighty-nine percent of patients in the discontinuation protocol group had at least one antibiotic discontinued within 48 hours of recommendation. The overall duration of treatment was significantly shorter in the discontinuation group compared to standard therapy (6.0 ± 4.9 days vs 8.0 ± 5.6 days, p = 0.001). No differences were observed with respect to in-hospital mortality, ICU and hospital length of stay, the duration of mechanical ventilation, or the acquisition of a second episode of VAP.

Protocols have also been successfully employed for the prevention of VAP. A hospital based education program directed toward respiratory care practitioners and ICU nurses was developed by a multidisciplinary task force to highlight correct practices for the prevention of VAP [34]. The program consisted of a ten-page self-study module on risk factors and practice modifications involved in VAP, educational in-services at staff meetings, and formal didactic lectures. Each participant was required to take a pre-intervention test before the study module and identical post-intervention tests following completion of the study module. Following implementation of the education module, the rate of VAP decreased to 5.7 per 1,000 ventilator days from 12.6 per 1,000 ventilator days, a decrease of 57.6 % (p < 0.001). This educational protocol was then implemented across the four largest hospitals in the local healthcare system [35]. Completion rates for the module were calculated by job title at each hospital. VAP rates for all four hospitals combined decreased by 46 %, from 8.75/1,000 ventilator days in the year prior to the intervention to 4.74/1,000 ventilator days in the 18 months following the intervention (p < 0.001). Statistically significant decreased rates were observed at the pediatric hospital and at two of the three adult hospitals. No change in rates was seen at the community hospital with the lowest rate of study module completion among respiratory therapists (56 %). In addition to showing the effectiveness of a protocol for VAP prevention, these studies highlight the importance of compliance with the elements of the protocol to insure its success.

Severe Sepsis and Septic Shock

Unscrambling of the complex pathophysiology associated with severe sepsis has substantially improved our current understanding of this process [36, 37]. The challenge for clinicians is to integrate the various available supportive and pharmacologic therapies to confer a measurable survival benefit for their patients [38]. The Surviving Sepsis Campaign has teamed with the Institute for Healthcare Improvement to create the Severe Sepsis Bundles which were designed in an effort to optimize the timing, sequence, and goals of the individual elements of care as delineated in the Surviving Sepsis Guidelines [39]. The creation and use of comprehensive treatment protocols integrating goal-directed hemodynamic stabilization, early appropriate antimicrobial therapy, and associated adjunctive severe sepsis therapies initiated in the emergency department and continued in the ICU have been reported in several trials [39].

The significance of early, aggressive volume resuscitation and hemodynamic stabilization was demonstrated in a randomized, controlled, single-center trial in patients who presented to the emergency department with signs of the systemic inflammatory response syndrome (SIRS) and hypotension [38]. Administration of crystalloids, red blood cell transfusions, vasopressors and inotropes based on aggressive monitoring of intravascular volume and a tissue oxygen marker within 6 hours of presentation to the emergency department resulted in a 16 % decrease in absolute 28-day mortality. The major differences in treatment between the intervention and control groups were in the volume of intravenous fluids received, the number of patients transfused packed red blood cells, the use of dobutamine, and the presence of a dedicated study team for the first six hours of care. As important as rapid hemodynamic stabilization is the administration of appropriate initial antimicrobial treatment for patients with severe sepsis. Several investigations have found appropriate therapy to be a key determinant of patient outcome [40 – 42] with early administration possibly playing a pivotal pathogenic role [43].

Treatment pathways mimicking the interventions of the well-scripted, carefully performed procedures employed by Rivers et al. have been put into practice in the clinical setting. Trzeciak et al. [44] described the results of incorporating clinical research into a real-life setting whereby the emergency department and the ICUs at an academic medical center collaborated in a therapeutic quality initiative focused on implementing early goal-directed therapy. Upon institution of a hospital-specific, early goal-directed therapy protocol, 91 % of patients managed met central venous pressure, mean arterial pressure, and central venous oxygen saturation ($ScvO_2$) goals within a median of 6 hours of presentation.

Shapiro et al. [45] described the creation of the Multiple Urgent Sepsis Therapies (MUST) protocol, a multidisciplinary collaborative effort that combines all sepsis bundle elements, including EGDT and early, appropriate antimicrobial therapy. During the first 6 hours (resuscitation phase) of therapy, patients managed via the MUST protocol received significantly more intravenous fluids, were more likely to receive vasopressor, and had a significant improvement in appropriate antibiotic coverage compared to historical controls. The intensified approach to early resuscitation dictated by the MUST protocol in combination with other therapies resulted in a 9.1 % absolute risk reduction in 28-day mortality (20.3 % versus 29.4 %; $p = 0.3$). Key to the successful implementation of a complex process of care protocol, such as the MUST protocol, is the significant education initiative associated with each endeavors. Such labors include training classes for emergency department and

ICU physicians and nurses, bedside reference guides, educational websites, protocol summary posters, and ultimately a sepsis order set specific to individual hospital capabilities, such as computerized physician order entry systems.

Several studies have detailed the impact of adopting severe sepsis protocols on treatment processes and patient outcomes. Micek and colleagues [46] compared 60 patients presenting to the emergency department who were managed prior to the implementation of the standardized order set (before-group) that focused on intravenous fluid administration and the appropriateness of initial antimicrobial therapy and 60 patients treated after the roll out of the protocol (after-group). Patients in the after-group received statistically more intravenous fluids while in the emergency department, were more likely to receive intravenous fluids greater than 20 ml/kg of body weight prior to vasopressor administration, and consequently were less likely to require vasopressor administration at the time of transfer to the ICU. Patients in the after-group were also more likely to be treated with an appropriate initial antimicrobial regimen compared to patients in the before-group. As a result of the aggressive medical management initiated in the emergency department and continued in the ICU, patients cared for via the severe sepsis order sets had shorter hospital lengths of stay and a lower risk for 28-day mortality.

In a study by Kortgen and colleagues [47], patients managed according to a standard operating procedure for the treatment of severe sepsis and septic shock were compared to control patients managed prior to the introduction of the pathway. Cohorts of 30 patients each were compared. Patients receiving therapy under the auspices of the standard operating procedure were statistically more likely to be treated with dobutamine, hydrocortisone, drotrecogin alfa (activated), and insulin infusions within 24 hours of initial organ failure. These differences, in combination with other fundamental therapies including goal-directed volume resuscitation, lung-protective ventilation strategies, and appropriate antimicrobial therapy resulted in a statistically lower 28-day mortality rate amongst patients managed with the standard operating procedure.

Gao et al. [48] evaluated the outcomes of patients with a severe sepsis syndrome after hospital admission in terms of whether compliance with sepsis care bundles occurred during their management. These patients were managed on medical or surgical wards or in accident and emergency areas at two acute National Health Service Trust Teaching hospitals in England. The sepsis care bundles provided recommendations for the administration of intravenous fluids, blood transfusions, antibiotics, and vasopressors. There was an overall compliance of 52 % with the sepsis bundles for this population. Despite being comparable in terms of baseline demographics and severity of illness, the compliant patients had a statistically lower risk of hospital mortality compared to the non-compliant patients. Thiel et al. [49] also demonstrated differences in outcome relative to presumed compliance with a sepsis protocol at Barnes-Jewish Hospital. The impact of a hospital-wide implementation of a standardized order set for the management of bacteremic severe sepsis was assessed. Patients managed with the standardized order set received more intravenous fluids in the first twelve hours following onset of hypotension and were more likely to receive appropriate initial antibiotic therapy. In-hospital mortality was also statistically decreased, as was the hospital length of stay for patients managed with the standardized order set.

Conclusion

Protocols appear to be a useful tool for improving processes of medical care in the ICU and patient outcomes. Although the overall quality of evidence supporting the efficacy of protocols may be less than ideal, the reported success following their implementation provides justification for expanded use of these tools for the management of critically ill patients. Complex diseases, such as severe sepsis, often require multiple therapies and interventions to optimize clinical outcomes. Protocols appear to consistently improve the delivery of recommended therapies and as a result may improve patient outcomes. Given that well-designed protocols generally expose patients to no additional risks, and are associated with relatively few acquisition costs, their implementation should become more standard in the ICU setting. However, it is important to update such protocols as new information becomes clinically available.

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Strategies for Implementation of Evidence-based Guidelines for Prevention of Healthcare-associated Infection

S. Labeau, D. Vandijck, and S. Blot

Introduction

Healthcare-associated infections are a serious concern worldwide and are considered the greatest risk that patients face upon hospitalization, with 5 % to 15 % of patients affected [1, 2]. Healthcare-associated infections cause discomfort and disability, and infected patients are at risk for increased morbidity and mortality. Moreover, they are accountable for substantial added costs for the individual as well as for society. Given the burden associated with healthcare-associated infections, and reinforced by the growing focus on improving patient safety over the past few years, the prevention of healthcare-associated infections has become a new healthcare imperative [3].

Over the past decades, strategies for prevention of healthcare-associated infections have evolved from local, hospital-based initiatives to the worldwide dissemination of bundled evidence-based guidelines [3]. Joint efforts of the Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America Standards and Practice Guidelines Committee (IDSA) have recently led to the publication of a compendium of recommendations for preventing the six most common healthcare-associated infections [4]. This compendium differs from most previously published guidelines in that it is typically implementation-focused. Indeed, there is an increasing awareness of the fact that guideline knowledge must be actively implemented in the healthcare setting before it can be expected to actually influence clinician behavior [5, 6].

In this chapter, we summarize the literature on strategies that have been identified as successful for guideline implementation, focusing on the field of infection prevention. The review is not exhaustive, nor does it attempt mathematical data analysis. Its aim is to provide an overview of the insights concerning the most effective ways for healthcare professionals to translate accurately gathered evidence on infection prevention into daily clinical practice.

Guidelines

Clinical guidelines are defined as systematically developed statements to assist decisions about appropriate healthcare for specific clinical circumstances [7]. If applied correctly, clinical guidelines can reduce inappropriate practice variation, speed the translation of research into practice, support quality and safety initiatives, and offer a useful framework for assessing treatment-related costs [8].

Evidence-based guidelines are guidelines which are founded on a critical appraisal of the available scientific evidence, clarifying which interventions are of

proven benefit, and documenting the quality of the supporting data. They alert clinicians to interventions which are not supported by good science, reinforce the importance of critical appraisal, and advise against ineffective and dangerous strategies [9].

With increased interest in the concept of evidence-based medicine since the early 1990s worldwide, various ambitious programs for guideline development have been invested in. Simultaneously, however, numerous more modest and local guideline development initiatives also arose. The subsequent proliferation of recommendations and concerns about their quality and uniformity have led to the foundation of public resources for evidence-based clinical practice guidelines, such as the United States' National Guideline Clearinghouse, and to international collaborations, such as The Guidelines International Network, that released the International Guideline Library, a searchable database which now contains more than 2000 guideline resources [10].

Specifically in the field of infection prevention and infection control, leading international organizations have issued evidence-based guidelines for the prevention and management of specific types of (healthcare-associated) infections [4, 11–15]. Most provide an appraisal of the strength of evidence for each recommendation included. Nowadays, these recommendations are of utmost importance because of the current tendency towards holding hospital employees accountable for their personal responsibilities regarding infection prevention and control and considering healthcare-associated infections as avoidable medical errors. Moreover, in the United States, performance measures of healthcare-associated infection prevention have recently been integrated into regulatory and reimbursement systems, thus reflecting the growing consensus that many healthcare-associated infections are preventable [3].

Adherence to Guidelines

Since the beginning of their successful rise in popularity, guidelines were considered to be the perfect tool for closing the gap between what clinicians do and what scientific evidence supports. Soon, however, it became clear that, once developed, guidelines were far from being self-implementing. The overall pessimistic picture of clinicians' compliance with evidence-based recommendations is illustrated below with a few examples from the field of infection prevention [16–19].

For many years, hand hygiene has been widely recognized as the cornerstone of infection prevention. Although the evidence-based recommendations for performing good hand hygiene are crystal-clear, widespread and readily available, compliance remains a key problem with reported compliance rates of 40 % [18]. Rello et al. investigated physicians' adherence to evidence-based guidelines for the prevention of ventilator-associated pneumonia (VAP) by means of a questionnaire and found an overall self-reported non-adherence rate of 37 % [19]. Ricart et al. used the same questionnaire in a sample of intensive care unit (ICU) nurses and found the non-adherence rate to be 22.3 % [16]. Moreover, as self-reports on behavior are known to be colored by social desirability, it can be presumed that the actual non-adherence rates are even higher. Rickard et al. [17] conducted a survey of practices regarding adherence to the Centers for Disease Control and Prevention (CDC) guidelines for the prevention of intravascular catheter-related infections [11] in 14 ICUs. These authors reported a wide diversity of practices and the absence of consistent adherence to the guidelines.

Numerous reports have been written about the reasons for non-adherence and many theories are available. There is a general consensus that potential barriers and facilitators are the major players involved.

Barriers

Barriers are factors that impede the implementation of change. Cabana et al. conducted an extensive systematic review of the literature from January 1966 to January 1998 to identify barriers to guideline adherence [20]. Out of 76 articles, 120 surveys evaluating 293 potential barriers to physician guideline adherence were reviewed. All barriers abstracted were grouped into common themes, then further organized into groups based on whether they affected physician knowledge, attitude, or behavior, thus setting out a framework for barrier-oriented behavior change. An adaption of this framework is outlined in **Figure 1** [20].

A lack of knowledge is commonly recognized as an elemental barrier to adherence [20, 21]. Recently, surveys evaluating the knowledge of European ICU nurses about evidence-based guidelines for the prevention of VAP and central venous catheter (CVC)-related infection found the overall test scores to be as low as 45.1 % and 44.4 % respectively [22–24], suggesting that low levels of knowledge could contribute to limited adherence to prevention guidelines.

Lack of access to hand washing sinks, insufficient time, skin irritation, ignorance about the problem, and individual preferences or habits have been reported as common barriers to adherence to hand hygiene guidelines, while low staffing and high patient acuity could contribute to making compliance even more difficult [18]. Importantly, the lack of a universally accepted standard for measuring compliance

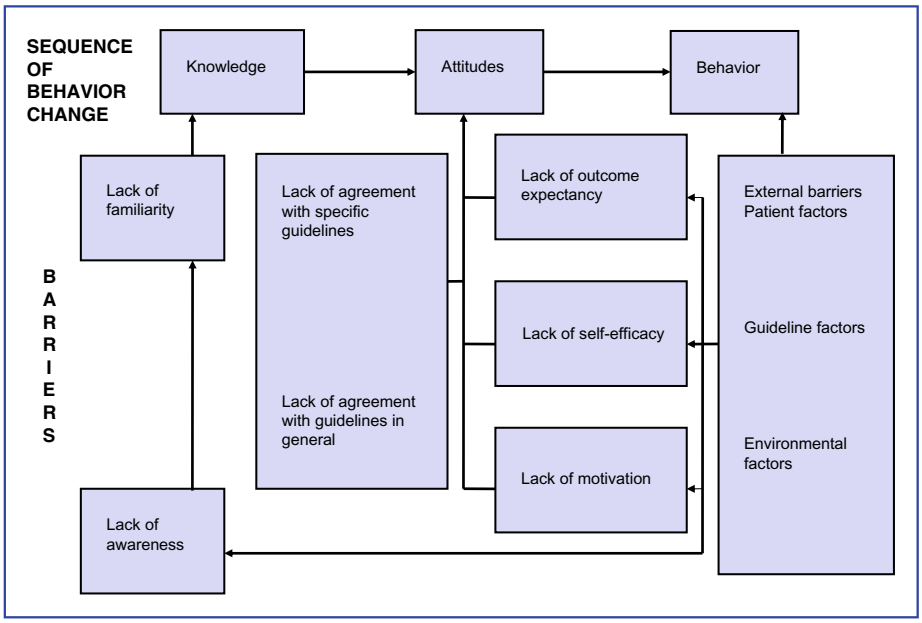

Fig. 1. Global framework for setting out barriers to guideline adherence in relation to behavior change. Modified from [20]

was recognized as an additional major barrier [18]. Disagreement with the interpretation of clinical trials (35 %), unavailability of resources (31.3 %), and costs (16.9 %) were the most common self-reported reasons for non-adherence with evidence-based recommendations for VAP prevention among a sample of physicians who were surveyed by Rello et al. [19], while a sample of ICU nurses who were surveyed using the same questionnaire considered patient-related barriers to be significantly more important (1.8 % vs 8.2 %, odds ratio 4.87; 95 % confidence interval (CI) 2.90 – 8.18) [19].

Facilitators

While barriers impede the implementation process, facilitators enhance behavioral change. Four groups of factors have been identified that facilitate the uptake and the long-term use of clinical guidelines [25]:

1. features of the guidelines, comprising the scientific basis for the guideline and its sources, and the way in which the guideline is presented. A clear, logical and attractive presentation facilitates guideline acceptance and uptake. Also, guidelines that are written with high behavioral specificity and in 'plain English' have a greater chance of being implemented than vague, hard-to-read information;
2. features of the target group, which require the implementer to have a thorough understanding of and adequate sensitivity to the target group's level of knowledge, skills, attitudes, working practices and personalities;
3. features of the social context and the setting, which refer to the expectations and behaviors of patients and healthcare providers, the actual operating culture, the working routines of colleagues, and the views of opinion leaders; and
4. features of the organizational context, including the financial, organizational and structural aspects of implementation, such as the availability of staff and equipment, and legal and regulatory issues.

Information on potential barriers and facilitators can be obtained in various ways, including interviews, surveys, focus groups, Delphi methods, observation, auditing records of routinely collected data, and analysis of documents [26]. Identifying and understanding the barriers and opportunities related to the adherence of evidence-based recommendations is a crucial first step in guideline implementation [25]. When designing an effective guideline implementation framework, local barriers and facilitators always need to be targeted, and the insights of different theories of behavior change integrated [25, 27]. The framework conceived by Cabana et al. (adapted in **Figure 1**), goes beyond merely identifying barriers to guideline adherence, and sets out these barriers in relation to behavior change [20]. This model has been widely used in numerous quality improvement programs, and is still a useful and inspiring outline to tackle non-adherence in the healthcare setting.

Theories of Change

As mentioned above, behavior change theory can provide a framework within which effective guideline implementation strategies can be integrated in order to promote clinician adherence to evidence-based guidelines [27]. Grol [28] studied the different approaches to altering clinical practice, and linked them to different theories of change:

1. educational theories explain change by the desire to learn and to be professionally competent;
2. in epidemiologic theories, humans are considered rational beings who are expected to weigh the available evidence and come to a reasonable conclusion;
3. in marketing theories, behavior change is promoted by exposure to attractive marketing packages;
4. behaviorist theories suggest that change is influenced by numerous external factors which are applied before, during, or after the targeted change;
5. social influence theories highlight the importance of the social group and peers;
6. in organizational theories, altering the system of care is suggested to enhance change; and
7. coercive theories propose the use of pressure and control, such as regulations and legislation, to achieve change.

Implementation Research

The guideline adherence rates mentioned above clearly illustrate that guidelines, once developed, are far from self-implementing. Transferring research findings into healthcare professionals' daily practice is a slow and laborious process [27, 29] that may be facilitated and supported by the findings of implementation research. Implementation research is defined as the scientific study of methods to promote the uptake of research findings, and hence to reduce inappropriate care. It includes the study of influences on healthcare professionals' behavior and interventions to enable a more effective use of implementation-related research findings [30]. Implementation research requires a multidisciplinary collaboration between healthcare professionals [25, 31].

In the scope of evidence-based recommendations, guideline implementation is defined as the phase in the guideline lifecycle in which strategies, systems, and tools are created to operationalize the knowledge and recommendations set forth by the guideline developers [32]. Guideline implementation is thus the final step in translating the scientific basis into clinical practice.

Implementation Interventions and Strategies

An implementation intervention or implementation tool is a single method or technique to assist a proposed change. In the literature, these interventions are also referred to as uptake, adoption, or change interventions. An implementation strategy or implementation program is defined as an integrated set (bundle, package) of implementation interventions [33].

The following classification of implementation strategies has been proposed [1]:

1. clinician education (e.g., workshops, computerized self-study tutorials, ...);
2. patient education (e.g., pamphlets, classes, ...);
3. audit and feedback (e.g., benchmarking, quality reports, ...);
4. clinician reminder systems (e.g., in charts or computer-based, ...);
5. organizational change (e.g., increased staffing, multidisciplinary teams, ...);
6. financial or regulatory incentives for patients or clinicians.

Current insights on implementation interventions and strategies are predominantly based on implementation research that was conducted in the early 1990s [8, 34, 35].

Since that time, the research focus has clearly moved from evaluating the effect of isolated interventions to determining the impact of bundle approaches [3]. Today, it is generally acknowledged that using only one type of implementation intervention is not likely to generate successful results, and that implementation efforts should use a combination of strategies tailored to the setting [21, 27, 36].

Short Historical Overview

The 1990s

As early as in 1994, Haines and Jones denounced the unacceptable delays in the implementation of research findings and promoted a number of approaches which they considered to be effective in speeding up implementation, including the influence of opinion leaders and the use of computer-based decision support systems. These authors concluded that methods to improve the implementation of research findings required further investigation and greater resources devoted to them [37].

Another systematic review on implementation strategies was conducted in 1998, covering the period from 1980 until 1994 and including 61 randomized controlled trials and controlled before-after studies. It assessed the effects of different single and multifaceted interventions to implement guidelines by first comparing different single interventions with no intervention, and then different multifaceted interventions with no intervention. Given the wide range of outcome measures, no standardized outcome measure that could be compared across all studies could be identified. The predominant finding consisted of the fact that there was a considerable variation in effectiveness among the different interventions included. Various strategies were shown to have a potentially beneficial effect, but the authors were unable to pronounce on their effectiveness because of the rather poor methodological quality of many of the studies included, and the need for further investigation [38].

In 1999, a group of implementation experts from Europe and the United States convened at Leeds Castle, England, to identify the best ways to encourage and undertake the implementation of best practices. The subsequent meeting summary expressed the experts' common belief that the approach towards implementing a guideline should be multifaceted [5]. This belief has gained general consensus ever since.

The 2000s

In 2001, the available systematic reviews of interventions that could potentially influence changes in healthcare professionals' behavior were discussed [39]. The authors identified 41 reviews, covering a broad variety of interventions and behaviors. The methodological quality of the included manuscripts was variable. In general, passive implementation approaches, such as passive dissemination, were found to be ineffective and unlikely to change behavior. Active approaches were shown to be more likely to be effective, at least under certain circumstances, but also likely to be more costly. Among the active approaches, educational outreach and reminders are described as promising interventions, and multifaceted strategies targeting different barriers to change are suggested to be more effective than single interventions [39].

In 2004, a systematic review focused on the effectiveness and costs of different guideline development, dissemination and implementation strategies, and included a total of 235 studies, describing 309 comparisons [40]. Frequently assessed single interventions were reminders, dissemination of educational materials, and audit and feedback. No relationship was found between the number of interventions included

in bundle strategies and the strategy's effect. The authors concluded that there was an imperfect evidence base to support decisions about which guideline dissemination and implementation strategies are likely to be efficient under different circumstances, and that there was a need for further research [40].

Current insights

A 2008 synthesis of systematic review findings concerning the effectiveness of guideline implementation strategies covers the period from 1987 to 2007, thus reflecting the most recent insights [36]. Here, 33 reviews concerning 714 primary studies involving 22,512 clinicians in various healthcare settings were analyzed. Implementation strategies were found to be wide-ranging, rarely comparable, and to have variable outcomes. While traditional educational strategies, typically including passive information dissemination, were shown to be constantly ineffective, interactive education strategies, such as those provided by workshops and practical sessions coupled with evaluation processes, were consistently reported as effective, with improvement effects ranging from 1 % to 39 %. Audit and feedback were associated with a range of effects, from a 17 % decline in adherence, through no effect, to a 63 % improvement. Multifaceted strategies consistently resulted in significant improvements in guideline compliance and behavioral change, with a reported improvement ranging up to 60 %; this approach was associated with greater evidence of effectiveness than single intervention strategies. Similar to the 2004 findings by Grimshaw et al. [40], there was no evidence of any relationship between the number of components of a strategy and the strategy's effectiveness. The value of mass media strategies remained inconclusive. Clinicians' behavior seems to be influenced by the construction and content of the guideline, with complex guidelines being inversely related to compliance. Trustworthiness of the developing organization and/or reference group was associated with improved compliance, and so was the level of evidence upon which the guidelines were based. The use of reminders and clinical support systems appeared to be associated with considerable practice enhancements, while the effect of financial incentives was inconclusive. There was no consistent evidence that guideline adherence is promoted by involving local opinion leaders [36].

This review's overall findings are consistent with these of another 2008 systematic review on guideline implementation strategies in allied health professions [21] and reflect the general consensus that today no clear evidence is available to support a specific set of guideline implementation interventions that could be most effective and efficient in the field of healthcare.

Implementation of Infection Prevention Guidelines

The lack of certainty about how guidelines are best implemented also pertains to the field of guidelines for preventing and controlling infection. Only a few resources are available that provide healthcare professionals with clear guidance regarding effective implementation interventions and strategies specifically for infection prevention [3].

Interventional studies

Numerous studies using a broad range of strategies and reporting varying results have been published related to the implementation of evidence-based guidelines for preventing infection.

Among the most appealing examples of successful guideline implementation strategies, are a series of very fine studies using a well-defined set of multifaceted, bundled implementation approaches to reduce CVC-related infection rates in the ICU following the CDC guidelines for preventing catheter-associated infection [11, 41 – 43]. This set, which has been shown to be very effective, consisted of the following five interventions: Education of the local staff; creation of a catheter insertion cart; daily assessment of the need for the catheter to remain *in situ*; implementation of a checklist to ensure adherence to evidence-based CVC-related infection prevention guidelines; and empowerment of the nurses to stop catheter insertion if breaches in the procedure were detected. Over a five-year time period, the rate of CVC-related bloodstream infections decreased from 11.3 to zero per 1,000 catheter days. The authors estimated that the interventions may have prevented 43 CVC-related bloodstream infections, eight deaths, and $1,945,922 in additional costs per year [41]. Using the same five strategies, Pronovost et al. reported the results obtained from a study in 103 ICUs, including 1981 ICU-months of data and 375,757 catheter-days [42, 43]. The authors described a decrease in the median rate of catheter-related bloodstream infections per 1000 catheter-days from 2.7 at baseline to zero at three months after implementation of the study intervention ($p \leq 0.002$), and a decrease in the mean rate per 1000 catheter-days from 7.7 at baseline to 1.4 at 16 to 18 months of follow-up ($p < 0.002$). The regression model demonstrated a significant decrease in infection rates from baseline, with incidence-rate ratios that continuously decreased from 0.62 (95 % CI 0.47 – 0.81) at zero to three months after implementation of the intervention to 0.34 (95 % CI 0.23 – 0.50) at 16 to 18 months [42, 43].

An electronic dashboard, serving as a screen saver on every desktop computer in the ICU, was used to implement bundled evidence-based guidelines for preventing VAP in a surgical ICU [44]. The left side of the screen indicated patient demographics and provided access to the medical records, while measures of the ventilator bundle were indicated on the right hand side of the screen. Green, red and yellow indicators were used to mark the degrees of measures in compliance. Over a one year period, mean compliance with the ventilator bundle improved from 39 to 89 % ($p < 0.001$), and VAP rates decreased from a mean (standard deviation) of 15.2 (7.0) to 9.3 (4.9) per 1000 ventilator days after introduction of the dashboard ($p = 0.01$).

Next to the numerous success stories, a number of studies have been published that demonstrated a failure to implement evidence on infection prevention and control into daily practice. Examples of such less successful implementation reports are provided by Morse and McDonald, where the use of a poster-based education program to improve the recording of date and time of insertion of peripheral venous catheters was shown to have little effect [45], and by De Miguel-Yanes et al., who reported on a failure to implement evidence-based clinical guidelines for sepsis in the emergency department [46].

Single studies may be suggestive and inspiring, but they do not provide the healthcare worker with a global view of which (set of) implementation intervention(s) may be most beneficial.

Systematic review

Recently, more bundled information has been provided by the Stanford-UCSF Evidence-based Practice Center, which reviewed the literature on effective implementation of measures to promote adherence to guidelines for the prevention of VAP, surgical site infection, central line-associated bloodstream infection and cathe-

Table 1. Effective strategies for the implementation of evidence-based guidelines for the prevention of healthcare-associated infection [1]

Healthcare-aassociated infection	Implementation Strategy	Remarks
Surgical site infection	Education + audit & feedback Reminders	Combined Incorporated in computerized order entry system
Central line-associated bloodstream infection	Active educational interventions	Demonstrations & self study tutorials
	Checklist Empowerment of nurses	During catheter insertion To stop line insertion on guideline violation
Ventilator-associated pneumonia	Active educational interventions	Self-study tutorials
Catheter-associated urinary tract infection	Reminders	Printed or computer-based Automatic stop order

ter-associated urinary tract infection [1]. The authors aimed to identify: 1) the implementation strategies that effectively increase adherence to evidence-based preventive interventions for healthcare-associated infections; 2) the critical components of effective quality improvement strategies; and 3) the limitations of current research in this specific area. Sixty-four studies met the inclusion criteria: 28 studies addressed the prevention of surgical site infection, 19 central line-associated bloodstream infection prevention, 12 VAP prevention, and 10 catheter-associated urinary tract infection prevention. Three studies targeted prevention of multiple healthcare-associated infections. The strategies that were demonstrated to be effective in implementing evidence-based guidelines for the prevention of the respective healthcare-associated infections are outlined in **Table 1** and summarized below.

Surgical site infections: The limited data suggest that educational interventions combined with audit and feedback may be effective at improving adherence to evidence-based recommendations for prevention of surgical site infections, specifically appropriate antibiotic prophylaxis. Clinician reminders may also be effective, especially when incorporated into a computerized physician order entry system. No conclusion could be reached regarding the effectiveness of educational interventions alone. The effect of using audit and feedback was not clear.

Central line-associated bloodstream infection: Active educational interventions were shown to reduce the incidence of central line-associated bloodstream infection. These interventions used demonstrations and self-study tutorials to improve adherence to evidence-based prevention guidelines during line insertion. The use of a checklist during the insertion procedure, and empowerment of nurses to stop catheter insertion whenever a violation of the procedure was noticed, resulted in marked reductions in infection rates.

Ventilator-associated pneumonia: Active educational interventions with use of a self-study module for ICU staff, including use of web-based and video tutorials, appeared to be a promising strategy for reducing VAP rates. No conclusion could be reached on the effectiveness of audit and feedback or other implementation strategies on VAP rates.

Catheter-associated urinary tract infection: Printed or computer-based reminders to clinicians appeared to be effective at reducing unnecessary catheter usage. A key element of these studies was the use of an "automatic stop order" mandating discontinuation of the catheter after a specific time period (48 to 72 hours) unless the physician countermanded the order. The effect of other implementation strategies on either infection rate or process measures could not be determined.

In all the studies included, information concerning potential adverse effects of the implementation strategies was extremely scarce, and so was high quality data concerning cost-benefit assessments. The reviewers' conclusion was twofold: First, preliminary data suggest that a number of implementation strategies are worthy of future investigation, and possibly wider implementation; and second, higher quality studies of implementation strategies to implement preventive evidence-based recommendations are urgently needed. Due to the poor quality of the included studies and the limited number of controlled trials, the authors were unable to perform any quantitative analyses, and were thus unable to make any estimate of the effect size expected when implementing these strategies or any firm recommendation [1].

Evaluating the Implementation

Evaluating an implementation consists of assessing whether or not the efforts have been effective when measured against the objective. A good evaluation comprises both the process and the outcome of the strategies used. A process evaluation consists of an examination of the approaches used to achieve the objective. While this process evaluation is important, it is a 'surrogate' endpoint only and the evaluation of outcomes should definitely not be forgotten [47]. Evaluating the outcome is more difficult than evaluating the process, and requires a fair degree of planning. It also requires a budget and assigned personnel to carry out the task [47].

Cost Considerations

Studies and reviews concerning the effectiveness of implementation interventions and strategies are numerous, but economic evaluations of guideline implementation strategies are scarce. Developing and implementing guidelines can, however, be quite costly. Sometimes, implementation costs are even likely to prevail over the potential benefits, and organizations should consider that the implementation of less costly – but also less effective – implementation strategies might be more efficient in their setting [48].

The economic aspects of 63 out of 235 studies on guideline implementation [40] were commented on by Vale et al. [48]; Only 3 studies provided evidence that their guideline was effective and efficient; 38 reported treatment costs only, 12 implementation and treatment costs, 11 implementation costs only, and 2 guideline development, implementation and treatment costs. None of the studies provided complete information on costs. The type of economic evaluation was rarely mentioned, and if it was mentioned, it was sometimes unclear. Seldom were all relevant costs and benefits included. Overall, studies were of poor methodological quality, did not report an economic rationale for the choice of implementation strategies considered, and did not cover all potentially relevant stages of guideline implementation. The multifaceted nature of various implementation strategies in the primary studies, the

broad variety of strategies addressed, and the weak methodology of most evaluations included made it impossible for the reviewers to generate a structured and uniform report of outcomes [48].

A review mentioned earlier that summarized the evidence for the effectiveness of clinical guideline implementation strategies in terms of improved clinical processes, also took into account the effectiveness in terms of cost-benefits [36]. The authors also remarked that, although increased cost-efficiency is an often cited reason for implementing clinical guidelines, few systematic reviews report primary studies which investigated financial outcomes. For most guideline implementation strategies in these reviews, significant cost reductions in clinical practice were reported, but it was not known whether the benefits were offset by the costs of the implementation strategies. This lack of economic evaluation is referred to as a major detractor from the widespread uptake of guidelines, particularly as it has been suggested that, due to the provision of services advocated as 'best practice', healthcare costs may increase [36].

Conclusion

VII

Implementation of change, with a focus on improving patient care, is difficult and requires multidisciplinary collaboration. Today, we know that multifaceted strategies can be effective, but still have little information to guide the choice of strategies, or to optimize the components of such complex programs. As decisions in healthcare are influenced by a broad variety of cultural, organizational, systemic, educational, interpersonal, and individual factors, it seems important to use different strategies when approaching the different groups concerned. Future evaluations are required, to evaluate not only effectiveness, but also the cost-effectiveness of implementation strategies. These evaluations should consider both patient and process outcomes and choose endpoints that adequately reflect their aims.

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Antibiotic Stewardship: Possibilities when Resources Are Limited

D. Curcio

Introduction

Infections caused by multidrug-resistant bacteria continue to challenge physicians in daily practice. There is growing animicrobial resistance among the Gram-positive and Gram-negative pathogens that cause infections in the hospital and in the community [1–3]. Rice recently called these the "ESKAPE" pathogens (*Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumanii, Pseudomonas aeruginosa*, and *Enterobacter* species) [2] to emphasize that they currently cause the majority of world-wide hospital infections and effectively 'escape' the effects of antibacterial drugs.

A number of observations have suggested an association between antimicrobial use and the emergence of bacterial resistance [4]. In this context, controlling antibiotic use and bacterial resistance through interventional programs is of major importance to all professionals involved in infectious diseases. However, these programs are frequently laborious and require long-term commitment from an antibiotic-management team. Optimally, this team should include professionals of different specialities (e.g., infectious disease physician, clinical microbiologist, information system specialist, clinical pharmacist, etc.) and the support and commitment of the hospital administrative director [5]. In developing countries, this infrastructure is uncommon in most hospitals and programs are based on personnel who are willing to devote extra time and effort towards developing and enforcing antibiotic stewardship programs [6] without obtaining adequate compensation.

In the present chapter, we discuss the opportunities for implementing antibiotic stewardship programs in hospitals where resources are limited.

STEP 1-Include the Antibiotic Stewardship Program within the Hospital Infection Control Program

Appropriate antibiotic stewardship programs that include optimal selection, dose, and duration of treatment, as well as control of antibiotic use, will prevent or slow the emergence of resistance among microorganisms [7]. However, other additional factors, such as a lack of infection control policies, may contribute to amplify and disseminate the problem of antimicrobial resistance in hospitals [8, 9]. Once the emergence of multidrug-resistant bacteria is established, a comprehensively applied infection control program (i.e., hand hygiene, isolation precautions and specific transmission-based measures) will prevent the amplification and dissemination of methicillin-resistant *S. aureus* (MRSA), extended-spectrum β-lactamases (ESBL)-

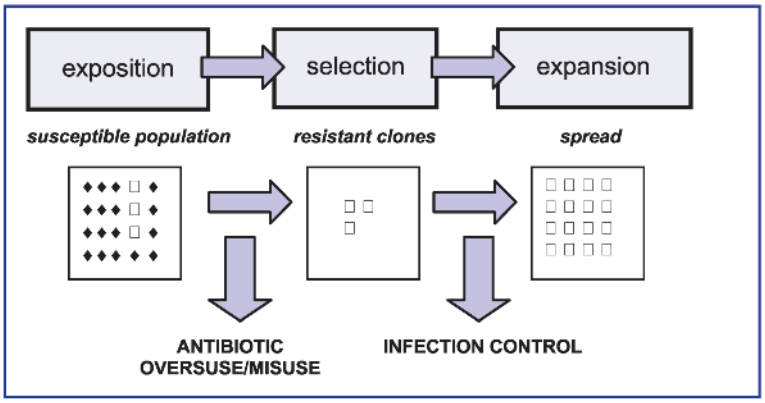

Fig. 1. Dynamic of bacterial resistance in hospitals

producing *Enterobacteriaceae*, *P. aeruginosa*, *A. baumannii* and *Clostridium difficile*, among others [9] (**Fig. 1**).

Eagye et al. [10], in a retrospective, observational case-control-control study, reported that the observed high proportion of meropenem-resistant *P. aeruginosa* was a consequence of ready transmission of an organism already resident in their hospital rather than selective antibiotic pressure promoting its development. Although antibiotic use has been shown elsewhere to promote the development of resistance in *P. aeruginosa*, their population of patients with high-level meropenem resistance had not received carbapenems (or any other class of agent) at a significantly different rate than those with susceptible organisms or no infection at all; in fact, carbapenem administration was nearly zero [10].

Similarly, Giakoupi et al. verified the presence of *K. pneumoniae* carbapenemase-producing (KPC type 2–producing) in 18 Greek hospitals [11]: 96 % of the isolates (166/173) belonged to a single pulsotype, confirming that, although carbapenems and third generation cephalosporins can act as selective factors for carbapenemase genes, resistance to carbapenems in *K. pneumoniae* in Greece seems to be due to the contemporary spread of transferable resistance mechanisms. It also implies that infection control is an important public health strategy for the containment of the KPC-producing mechanism [11].

Although the usage of imipenem, meropenem, and/or ceftazidime is associated with subsequent acquisition of multidrug-resistant *A. baumanii* in critically ill patients [12], its extensive dissemination in hospitals results from modes of transmission via multiple contaminated surfaces and objects and transiently colonized health-care workers' hands [13].

Finally, Monnet et al. reported a dynamic and temporal relationship between the prevalence of MRSA and macrolide, third-generation cephalosporin, and fluoroquinolone use [14]; nevertheless, the best approach in high-prevalence MRSA settings probably involves hand hygiene plus a careful assessment of an institution's particular circumstances, with application of more aggressive procedures such as patient isolation, staff cohorting, and active surveillance cultures when appropriate [15].

In summary, to reduce antimicrobial resistance in hospitals, a good stewardship of antibiotic usage combined with strong infection control is required.

STEP 2-Be Aware of the Different Antibiotic Stewardship Program Strategies

The best strategies for an antibiotic stewardship program have not been definitively established, because there is no randomized, controlled trial in this field [16]. The Infectious Diseases Society of America/Society for Healthcare Epidemiology of America (IDSA/SHEA) guidelines identify two core proactive evidence-based strategies and several supplemental strategies for promoting antimicrobial stewardship (**Table 1**) [5].

The first proactive strategy is either a formulary restriction or a requirement for pre-approval for specific drugs or both. Restriction of antimicrobial use may be obtained either by limited access to available antimicrobials in the hospital through restriction of the hospital formulary, or implementation of a requirement for pre-approval and a justification for prescribing drugs on the restricted list. Both methods have been shown to be effective to reduce the use and costs of restricted antimicrobials [17].

Patterson [18] measured the prevalence of multidrug-resistant *K. pneumoniae* at two hospitals, before and after an acute intervention, which included restrictions on antibiotic use and physician education regarding the association between ceftazidime use and the presence of multidrug-resistant *K. pneumoniae*. Following the intervention, ceftazidime use decreased, and piperacillin-tazobactam use increased at both institutions. The changes were associated with a significant decrease in ceftazidime resistance among *K. pneumoniae* isolates. Similar observations were made in a retrospective analysis of data from 10 hospitals [19]; antimicrobial usage and antimicrobial resistance trends for prominent nosocomial pathogens were compared, as were antimicrobial control programs and policies, across all hospitals. A strong positive correlation was noted between ceftazidime usage and the prevalence of ceftazidime-resistant *P. aeruginosa* and of ceftazidime-resistant *Enterobacteriaceae*. Likewise, control programs and policies were associated with lower prevalence rates of some resistant bacterial strains and less antibiotic usage.

Although restriction of certain antibiotics (e.g., third-generation cephalosporins) is an effective method for controlling outbreaks of multidrug-resistant pathogens, such measures must be undertaken cautiously. A formulary change that restricts

Table 1. Strategies to implement and antibiotic stewardship program. Modified from [5]

Core Strategies
• Formulary restriction and pre-authorization requirements for specific agents
• Prospective audit of antimicrobial use with intervention and feedback to the prescriber
Supplemental Strategies
• Education
• Clinical practice guidelines
• Antibiotic order form
• Streamlining or de-escalation
• Combination therapy
• Dose and route optimization
• Therapeutic substitution
• Cycling
• Mixing – 'diversity'
• Computer decision support

cephalosporins or fluoroquinolones, as well as other antimicrobials, may sometimes promote the emergence of pathogens with new and different resistance profiles. Rahal et al. [20] reported that, in response to an increasing incidence of cephalosporin-resistant *Klebsiella*, a preapproval policy was implemented for cephalosporins. This resulted in an 80 % reduction in hospital-wide cephalosporin use and a subsequent 44 % reduction in the incidence of ceftazidime-resistant *Klebsiella* throughout the medical center, as well as a 71 % reduction in the intensive care unit (ICU). Concomitantly, however, imipenem use increased 141 %, accompanied by a 69 % increase in the incidence of imipenem-resistant *P. aeruginosa*. This untoward restrictive effect of 'squeezing the balloon' may counteract the originally sought-after benefits [20].

In my opinion, however, the major disadvantage of this strategy is that prescribers can have a perceived loss of autonomy when making clinical decisions, which may create conflict and controversy among the different specialties and the infectious diseases physician [21]; in addition, the infectious diseases physician needs to be available for consultation at all times. For these reasons, physicians perceive the prior-approval system as stressful and time-consuming [22].

The second core strategy is performing prospective audit with intervention and feedback to the prescriber. Two randomized controlled trials have shown that this strategy resulted in a reduction of inappropriate use of antimicrobials [23, 24]. Implementation of this strategy has also been shown to maintain its efficacy over the long term (7 years) [25]. The logistics of auditing should be adapted to local needs and resources because, as with formulary restriction, this strategy is time-consuming. For example, a 3-day per week prospective audit with direct interaction with the prescriber may be appropriate in a small community hospital with limited resources and still result in a significant impact on appropriate antibiotic use [26].

We have published two sequential studies using the prospective audit of antimicrobial prescription focused on shifting the leadership of antibiotic use to an infectious diseases consultant [27, 28]. The first study was performed in the general ward and the other in the ICU. In both studies, we reduced vancomycin and third-generation cephalosporin consumption significantly. Even with the limitations of the before and after model used, these findings highlight the concept that infectious disease consultant leadership may by itself produce significant changes in prescribing habits without limiting the physician's prescribing freedom.

Supplemental strategies employed in antibiotic stewardship programs include education of prescribers, implementation of guidelines and clinical pathways, antimicrobial order forms, streamlining or de-escalation, combination therapy, dose optimization, and intravenous-to-oral switch, therapeutic substitution, cycling, mixing and use of computer decision support. In general, several of these strategies are implemented in daily practice simultaneously with one of the two core strategies.

Education: This is essential for any program that is designed to influence prescribing behavior. However, efforts to influence antimicrobial prescribing behavior through passive education (e.g., dissemination of guidelines or handouts), seem to be marginally effective and do not have a sustained effect [29].

Guidelines and clinical pathways: These can improve antimicrobial utilization by multidisciplinary development of evidence-based guidelines that incorporate local microbiology and resistance patterns [5]. In general, compliance with guidelines is poor, ranging from 18 to 33 % [30]. Compliance with the guidelines could be signifi-

cantly improved by periodic updating, close collaboration with prescribing physicians and active dissemination [31].

Antibiotic order forms: An antibiotic order form program was implemented for all inpatient antibiotic orders at an 800-bed hospital to provide an ongoing, concurrent audit of antibiotic use [32]. The prescribing physician provided the clinical indication for the antibiotic order, and individual patient treatment courses were identified. After the introduction of the antibiotic order form, there was a significant decline in the number of antibiotic treatment courses ($p = 0.025$) and in the percentage of patients receiving any antibiotic ($p = 0.007$). The authors concluded that a specialized antibiotic order form is an effective method for antibiotic utilization review and can have a significant impact on a physician's prescribing patterns [32]. In contrast, Bolon et al. found that implementation of an antibiotic order form program did not have its intended effect of improving and reducing vancomycin use in a pediatric setting [33].

De-escalation: The de-escalation strategy (streamlining therapy) is based on the concept that appropriate empirical antimicrobial treatment is associated with better survival in critical ill patients. For that reason, several authors recommend using broad spectrum antibiotics (alone or in combination) for the empirical treatment of serious infections [34–37]. The de-escalation theory proposes that the patient is reassessed on day 3 to define the antibiotic treatment based on the culture results and the clinical response [38]. However, in daily practice, physicians have several reasons to not de-escalate, including the low percentage of positive cultures in the ICU and the difficulty evaluating clinical response in ICU patients [39, 40]. The leadership of infectious diseases physicians may help in this situation to adjust the antibiotic treatment and lead to substantial cost savings without affecting clinical outcomes.

Combination antimicrobial therapy: Safdar et al. reported that combination antimicrobial therapy did not reduce mortality in patients with Gram-negative bacteremia [41] and Dellit et al. noted that there are insufficient data to recommend the routine use of combination therapy to prevent the emergence of resistance [5]. Based on these data, combination antimicrobial therapy has a role only in certain clinical contexts, including empirical therapy for critically ill patients at risk of infection with multidrug-resistant pathogens, to increase the breadth of coverage and the likelihood of adequate initial therapy [5].

Dose optimization: Antimicrobial dose optimization, based on individual patient characteristics, causative organism, site of infection, and pharmacokinetic and pharmacodynamic profile of the drug, is an important component of an antibiotic stewardship program. Dose optimization strategies may include prolonged infusion of β-lactams and higher doses of vancomycin, among others, to ensure that pharmacokinetic pharmacodynamic targets are met. The time that antibiotic concentrations in the serum are above the minimum inhibitory concentration (MIC) (T>MIC) is the pharmacokinetic/pharmacodynamic parameter correlating with the therapeutic efficacy of beta-lactam antibiotics. Jaruratanasirikul et al reported that a 3-h infusion of meropenem resulted in greater T>MICs than those after a bolus injection. For the treatment of infections caused by pathogens with intermediate resistance, they concluded that a 3-h infusion of 2 g of meropenem every 8 h can provide concentrations in serum above the MIC of 16 μg/ml for almost 60 % of an 8-h interval [42]. In a

study of patients with ventilator-associated pneumonia (VAP), Lorente et al. found that the group receiving medication by continuous infusion showed a greater clinical cure rate than the group treated with intermittent infusion (90.47 %, vs 59.57 %, respectively, with OR 6.44 [95 % CI 1.97 to 21.05; $p < 0.001$]), when VAP was due to *P. aeruginosa* [43].

Lodise et al. demonstrated the beneficial clinical impact of a prolonged infusion of piperacillin-tazobactam among critically ill patients with APACHE II scores ≥ 17. The 14-day mortality rate was significantly lower among patients who received extended-infusion therapy (4 h) than among patients who received intermittent-infusion therapy (30 min) – 12.2 % vs 31.6 %, respectively ($p = 0.04$) [44].

The vancomycin MIC creep is a worldwide problem. It is well-established that in respiratory infections and bacteremia due to MRSA, clinical success of treatment is associated with a vancomcyn pharmacodynamic target of ≥ 350 of the area under the curve (AUC)/MIC [45]. When the MRSA MIC is 1 mg/ml, the probability of achieving this AUC/MIC target with the standard dose of vancomycin (1 g/12 h) is between 40 % and 60 %, and when the MRSA MIC is 2 mg/ml the probability is 0 % [45, 46]. For this reason, several authors recommend vancomycin trough concentrations of between 15 and 20 mg/l. In response, some clinicians increased vancomycin dosing to > 2 g/day, which is associated with a higher likelihood of vancomycin-related nephrotoxicity [47]. Therapeutic options other than vancomycin (e.g., linezolid, daptomycin, tigecycline) should be considered in patients with risk factors for infection due to MRSA who have a high vancomycin MIC (i.e., patients with recent exposure to vancomycn) [48].

Intravenous-to-oral switch: This is an effective tactic to decrease the length of stay and health care costs [5].

Therapeutic substitution: This strategy is based on replacing a prescribed antibiotic with another drug known to be effective against the likely multidrug-resistant pathogens. One possible scenario for considering this strategy is a postoperative patient with a suspected ESBL-producing Gram-negative bacilli infection in an institution with high rates of carbapenem-resistant *Enterobacteriaceae*. Alternative treatment for this case may include tigecycline which has excellent *in vitro* activity against ESBL-producing *Enterobacteriaceae* and is approved for the treatment of patients with complicated intra-abdominal infections [49].

Antimicrobial cycling: The role of antimicrobial cycling in antimicrobial stewardship is not clear; insufficient data are available to recommend this strategy for routine use. Antimicrobial cycling involves the deliberate scheduled removal and substitution of specific antimicrobials or classes of antimicrobials within an institution to avoid or reverse the emergence of antimicrobial resistance [50]. As the scheduled antimicrobial is changed on a regular basis, adherence can be difficult with these programs mainly because prescribers may be unaware of the current scheduled antimicrobial [51].

Antimicrobial mixing or diversity: This strategy promotes heterogeneity in antibiotic use as a method to reduce the selection pressure for nosocomial pathogens. Sandiumenge et al. demonstrated that the use of antibiotics with a large epidemiological impact distributed equally among patients (piperacilin-tazobactam, carbapenems, cefepime and fluorquinolones), was associated with a significant reduction in isolates of multidrug-resistant pathogens [52].

Computer-assisted surveillance: Early studies [53] using computer-assisted surveillance and a decision-support system showed promising improvement in antimicrobial use, with more appropriate dosing and fewer adverse drug events. However, subsequent studies have described some difficulties in the routine implementation of this technology and conflicting results have been reported [54]. Some success was observed with the implementation of a web-based approval system of third-generation cephalosporins, resulting in a sustained 50 % reduction in use over a 15-month period and a higher concordance of prescriptions with guidelines [55].

STEP 3-Define the Core Strategy/Key Antibiotics/Areas to Include within the Antibiotic Stewardship Program According to the Institution's Resources

The correct implementation of core antibiotic stewardship program strategies, in addition to several supplemental strategies, requires the evaluation of the patient at the bedside (i.e., before the approval or not of an antibiotic within a formulary restriction strategy). This issue has been identified as a barrier for the antibiotic stewardship program because of the time and effort required and the lack of economic compensation. These could be the reason why authorization of an antibiotic and feedback to the prescriber by telephone or through informal ('curbside') consultations are very common. Attending physicians use this sort of infectious diseases consultation to select an appropriate treatment plan and obtain medical information [56].

To avoid this type of interaction it is mandatory that the core strategy (formulary restriction or prospective audit of prescription) and the form in which it should be implemented are selected according to the institution's resources (e.g., applied to all antibiotic prescriptions or only to prescriptions of 'restricted' antibiotics; hospital-wide or only in the ICU; every day or three times per week, etc.). The characteristics selected for the antibiotic stewardship program must reflect the prescription habits of the institution and assure that infectious disease physicians have enough time to evaluate and discuss the patients with the attending physicians.

Taking into account these considerations, I describe in **Table 2** the 'real world' of antibiotic stewardship program implementation in two different hospitals where prospective audit of the prescription and feedback to the prescriber was the strategy selected (Curcio D; unpublished data). In both hospitals, the duration of an infectious disease physician consultation (which includes review of the clinical chart, patient examination, and feedback to the attending physician with completion of the clinical chart) was 20 – 25 minutes. As you can see in the Table, if Institution A decided to audit all the antibiotic prescriptions, this would be technically impossible with two infectious disease physicians 8 h/day in the hospital. However, they implemented an antibiotic stewardship program to audit only the hospital-wide prescriptions of restricted ('key') antibiotics (third-generation cephalosporins, fluoroquinolones, carbapenems, vancomycin, colistin and new antibiotics, such as linezolid, tigecycline and daptomycin). This strategy insures that the infectious disease physicians can examine and discuss the patients at the bedside, face-to-face with the attending physician, in real time. In Institution B, where only one infectious disease physician works 4 h/day, the best antibiotic stewardship program adapted to the setting was the audit of restricted antibiotic prescriptions only in the ICU, which demanded 95 % of the infectious disease physician's time.

Table 2. Antibiotic stewardship program in the 'real world'. Characteristics of the prospective audit of prescription in two different hospitals and impact of the infectious disease physician's workload.

Variables	Institution A	Institution B
Period of study (months)	12	9
Complexity	Medium	High
University-based	No	Yes
Total beds (n)	150	30
ICU beds (n)	18	10
ID physicians (n)	2	1
ID workload (h/day)	8	4
ID activities		
Assistance of hospitalized pts	Yes	Yes
Assistance of ambulatory pts	Yes	No
Infection control	Yes	Yes
Pts admitted/day (mean, range)	113 (80–150)	28 (21–30)
Pts with antibiotic/day -global- (mean, range)	81 (68–93)	15 (12–18)
Pts with restricted antibiotic/day -global- (mean, range)	28 (23–34)	12 (8–13)
Pts with restricted antibiotic/day -ICU- (mean, range)	12 (9–13)	10 (9–12)
Duration of the ID consultation -gobal- (minutes, mean (range))	20 (18–35)	21 (13–30)
Duration of the ID consultation -ICU- (minutes, mean (range))	25 (21–45)	23 (20–38)
Required time/day to evaluate all pts with antibiotics – gobal – (minutes/hours, mean)	1620/27	315/5.2
Required time/day to evaluate all pts with restricted antibiotics (minutes/hours, mean)	560/9	252/4.2
Required time/day to evaluate all pts with restricted antibiotics – ICU – (minutes/hours, mean)	300/5	230/3.8
Use of prospective audit as ASP strategy	Yes	Yes
Area of the hospital	hospital wide	ICU
Required time/day to apply the ASP strategy by ID	4.5	3.8
Percentage of the ID/day workload	56	95
Frequency	Monday to Friday	Monday to Friday

Institution A=Sanatorio San José, Buenos Aires, Argentina; Institution B=Instituto Sacre Cour, Buenos Aires, Argentina; ICU: intensive care unit; ID: infectious diseases; Pt: patients; APS: antibiotic stewardship program

Among the diverse elements of antibiotic stewardship programs that can be implemented, a proactive core and supplemental strategies adapted to the institution (this is the key point) appear to be the most effective strategies (**Fig. 2**).

Although more data are needed to demonstrate the benefits of these programs, antibiotic stewardship programs have the potential to reduce resistance, health care costs, and drug-related adverse events while improving clinical outcomes.

A systematic review and meta-analysis of antibiotic stewardship programs has recently been performed by the Cochrane collaboration's effective practice and organization of care group [57]. This group selected a total of 66 studies, of which 60 aimed at decreasing antibiotic use. The main reported outcome was optimization of antibacterial use (78 % of studies). Microbiological (prevalence of antibiotic resistant bacteria) or clinical outcomes (length of hospital stay and patient mortality) were reported in only a minority of studies (26 and 15 % respectively).

Martin et al. demonstrated how a policy of formulary restriction and pre-authorization could result in substantial pharmacy cost savings [58]. These programs can provide substantial economic benefits irrespective of the size of the institution.

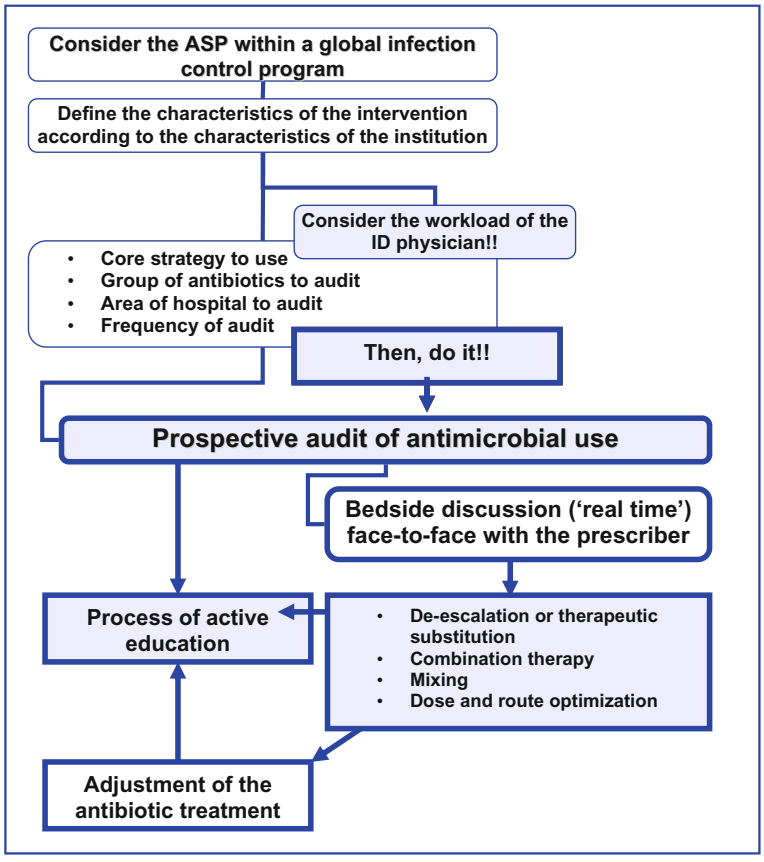

Fig. 2. A practical approach to implement an antibiotic stewardship program (ASP) based on the adaptation of strategies to the resources of the institution. ID: infectious diseases.

STEP 4-Develop and Define Institution-adapted Antibiotic Stewardship Program Performance Indicators

The challenge is to develop an indicator to reflect a local, important, measurable, valid, reliable, and evidence-based measure of the results of the antibiotic stewardship program, taking into account that the most important variable is patient outcomes (i.e., mortality, rate of surgical site infection, need to change the antibiotic treatment to a second line drug, etc.).

Conclusion

In the setting of increasing antimicrobial resistance, antibiotic stewardship programs provide a formalized, practical, and manageable approach to improving the use of antimicrobials in our hospitals, where their use is widespread and often suboptimal. Most publications about antibiotic stewardship programs offer evidence of structure

and theoretical form, without practical sense. In fact, the majority of hospitals, especially in developing countries, lack the resources to implement the different strategies which are described in these publications.

I propose a practical approach to implement an antibiotic stewardship program based on the adaptation of the strategies to the resources of the institution, prioritizing the bedside evaluation of the patient and interaction between colleagues.
The following discussion in an ICU may serve as an example of how this approach works in practice:

The ICU fellow – "This patient has severe community-acquired peritonitis; that's why, according to institutional guidelines, we have prescribed cefepime + metronidazole"

The Chief of the ICU – "But he's from a nursing home and has been receiving fluorquinolones for three weeks before this hospital admission; our computer support system says that a carbapenem is indicated in these cases!"

The infectious disease physician – "That's ok, but, as you know, we have an outbreak of carbapenemase-producing *K. pneumoniae*; therefore, we can reduce carbapenem pressure by using tigecycline in this patient (substitution)"

The Chief of the ICU – "I agree, but what about with the possibility of bacteremia? Tigecycline has only a modest serum concentration. I'd like to use a combination therapy: tigecycline + colistin"

The infectious disease physician – "Ok; but in 72 h we will reassess the patient in order to de-escalate the antibiotic treatment according to the cultures and the clinical response".

This dialogue represents the 'real world' of antibiotic prescription in the hospital, mainly in the ICU; implementation of one core strategy (prospective audit of prescriptions) and several supplemental strategies simultaneously (guidelines, computer support, therapeutic substitution, combination therapy, and de-escalation).

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VIII Metabolic Support

Vitamin D in Critical Illness

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Introduction

Vitamin D is well known for its regulatory effects on calcium and phosphate homeostasis and its role in the maintenance of bone integrity. Over the past decade, there have been data from biochemical and molecular genetic studies that point to vitamin D having a much wider role than just maintenance of calcium and phosphate metabolism. Vitamin D and its synthetic analogues have been shown to have anticancer properties as well as to modulate the immune system. Recently, vitamin D deficiency has been reported in critically ill patients [1, 2]. However, it is still unclear how this deficiency affects patient outcomes in intensive care. The focus of this chapter is to examine the role of vitamin D in the body, with discussion of its effects on mineral and bone metabolism as well as its pleiotropic effects and the role it may play in the pathophysiology of critical illness.

Historical Perspective

The clinical manifestations of rickets were first described in the 17th century by Whistler and Glisson. The sentinel observations of the British medical epidemiologist and missionary, Theodore Palm, were crucial to the discovery and characterization of the physiology of vitamin D and its role in the prevention of rickets. He noted a lower incidence of rickets in children living in the tropics and attributed this to the beneficial effects of sunlight. Sir Edward Mellanby experimentally confirmed this in dogs, where he showed that dogs isolated from sunlight developed rachitic bones. McCollum discovered the compound that is now known as vitamin D. The two major forms of vitamin D (D2 and D3) are shown in **Table 1**. Vitamin D1 is a combination of ergocalciferol and lumisterol in a 1:1 ratio. Vitamin D3 undergoes two sequential hydroxylation steps, 1-hydroxylation in the liver and a subsequent 25-hydroxylation in the kidney resulting in the physiologically active 1 – 25 dihydro-

Table 1. Forms of vitamin D

Form	Chemical name	Characteristics
Vitamin D2	Ergocalciferol	Made in plants, fungi and invertebrates, not produced in vertebrates. Precursor is ergosterol
Vitamin D3	Cholecalciferol	Made in the skin of humans when sunlight reacts with 7-dehydrocholesterol and converts it to cholecalciferol.

xycholecalciferol ($1,25(OH)_2D_3$). Only a small fraction of $1,25(OH)_2D_3$ circulates in the plasma as the free fraction, most of it is bound to vitamin D binding proteins.

Circadian Rhythm of Vitamin D

Cholecalciferol, being a secosterol is subject to circadian variation just like cortisol. Studies of $1,25(OH)_2D_3$ levels in normal volunteers have demonstrated a small, but significant diurnal variation in levels [3]. In post-menopausal women, however, a significant circadian rhythm in $1,25(OH)_2D_3$ levels has been observed with a nadir level in the morning followed by a rise to a plateau level (14 % > nadir) during the day [4].

Pleiotropic Effects of Vitamin D

$1,25(OH)_2D_3$ exerts its molecular effects by binding to the vitamin D receptor [5, 6]. Vitamin D receptors are nuclear receptors and binding of $1,25(OH)_2D_3$ to the vitamin D receptor results in target gene transcription. These receptors are ubiquitous as demonstrated by the response in most tissues to administration of $1,25(OH)_2D_3$. Further research into the mechanism of action of these receptors brought to fore the more subtle, pleiotropic effects of this hormone, which are distinctly different from its effects on bone and mineral homeostasis (**Fig. 1**.).

Vitamin D and the Musculoskeletal System

As noted, $1,25(OH)_2D_3$ acts as the ligand for vitamin D receptor and the hormone-receptor complex results in calcemic and phosphatemic effects. Low calcium stimulates secretion of parathyroid hormone (PTH) and $1,25(OH)_2D_3$ by the kidney resulting in calcium absorption in the kidney and in the intestines. Phosphate absorption in the intestine is stimulated by $1,25(OH)_2D_3$. In addition, osteoblasts secrete fibroblast growth factor 23 (FGF 23), a phosphaturic hormone to regular phosphate and calcium metabolism relative to $1,25(OH)_2D_3$. FGF 23 lowers the levels of $1,25(OH)_2D_3$ and suppresses the absorption of phosphate from the kidneys. The $1,25(OH)_2D_3$-vitamin D receptor complex also controls production of $1,25(OH)_2D_3$ by feedback loops – most of the mineral effects of $1,25(OH)_2D_3$ are attenuated by inactivating the DNA binding function of vitamin D receptors [5]. Osteoblasts also synthesize phosphate-regulating endopeptidase homolog, X-linked (PHEX), which regulates protein degradation to reduce FGF 23 synthesis, thus allowing continued renal phosphate reabsorption. PHEX levels are also regulated by $1,25(OH)_2D_3$, which represses its expression. Mutations in PHEX lead to development of X-linked hypophosphatemia. Thus, $1,25(OH)_2D_3$ regulates calcium and phosphate homeostasis by regulating PTH, FGF 23 and PHEX.

Various anabolic and catabolic genes involved in bone formation and resorption are also regulated by $1,25(OH)_2D_3$. The anabolic genes include: a) *RP5*, b) *Runx2*, c) *TRPV 6* and d) *Npt2c*. Catabolic genes regulated include a) *PTH* and b) *RANKL*. Hence, $1,25(OH)_2D_3$ plays a pivotal role not only in regulating the minerals that are critical for bone formation but also by altering the expression of various genes needed for bone remodeling [5].

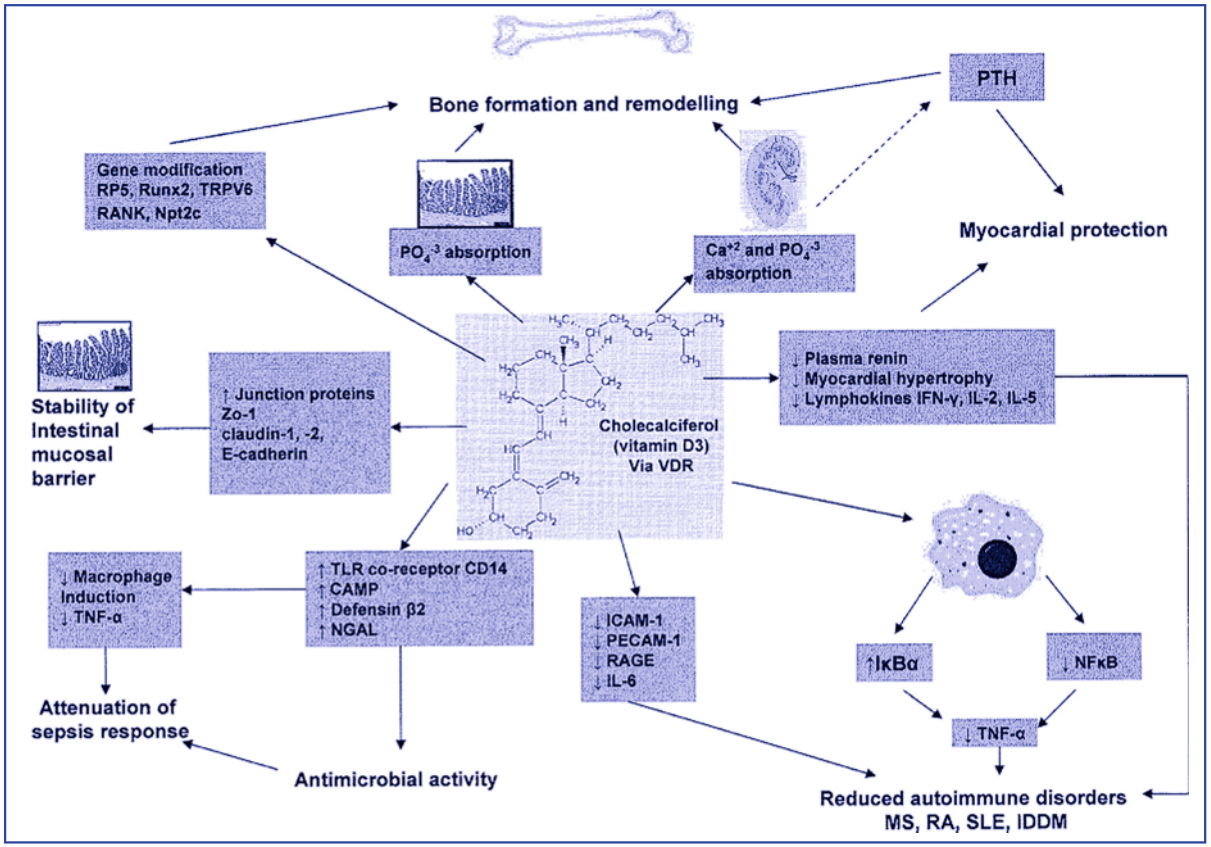

Fig. 1. Pleiotropic effects of cholecalciferol. CAMP: cathelicidin antimicrobial peptide; ICAM: intercellular adhesion molecule; IDDM: insulin-dependent diabetes mellitus; IFN: interferon; IL: interleukin; MS: multiple sclerosis; NF-κB: nuclear factor kappa B; NGAL: neutrophil gelatinase-associated lipocalin; PECAM: platelet endothelial cell adhesion molecule; PTH: parathyroid hormone; RA: rheumatoid arthritis; RAGE: receptor of advanced glycation end products; RANK: receptor activator of NF-κB: SLE: systemic lupus erythematosis; TLR: Toll-like receptor; TNF: tumor necrosis factor; VDR: vitamin D receptor

Vitamin D deficiency leads to rickets in children or osteomalacia in adults and myopathy. In a recent meta-analysis, Bischoff-Ferrari et al. [7] showed that the incidence of falls in ambulatory or institutionalized individuals with stable health was reduced by 22 % following therapy with vitamin D. After analyzing 5 randomized controlled trials involving 1237 participants, the authors concluded that 15 patients would have to be treated to prevent one fall. The authors postulate that $1,25(OH)_2D_3$ binds to the active vitamin D receptor in the skeletal muscle tissues, stimulating protein synthesis and improving skeletal muscle function. This particular finding has significant implications for patients undergoing rehabilitation after a serious illness, particularly those who have a long stay in the intensive care unit (ICU).

Vitamin D and Cardiovascular Disease

Vitamin D receptors have a broad distribution including vascular smooth muscle [6], endothelium [8], and cardiomyocytes [9]. There is increasing evidence that vitamin D deficiency is an important contributory factor in the causation of cardiovascular disease. Tishkoff et al. [10] demonstrated the importance of calcitriol in modulating and maintaining the function of cardiac myocytes in vitamin D receptor-knockout mice. Simpson and colleagues [11] showed that there was significant myocardial hypertrophy in mice following ablation of the vitamin D receptor signaling system. Vitamin D has also been shown to reduce plasma renin activity [12] and prevent release of inflammatory cytokines from lymphocytes [13]. Levels of vitamin D have also been shown to inversely correlate with coronary arterial calcification [14]. In a recently published study involving 1739 patients, Wang et al. demonstrated an increased incidence of cardiovascular disease in vitamin D-deficient patients [15]. The postulated mechanisms include the direct beneficial effects of vitamin D as well as reduction in the deleterious effects of PTH by feedback inhibition of the hormone. Further studies are needed to determine whether intervention with calcitrol supplementation reduces the incidence of cardiovascular disease. Zittermann et al. [16] showed that low calcitriol levels following cardiac transplantation were associated with higher one-year mortality in cardiac transplant recipients.

Vitamin D and the Immune System

Early interest in vitamin D as an immune modulator was sparked by the discovery of vitamin D receptors on monocytes. Both T helper 1 (Th1) and Th2 cells are direct targets of $1,25(OH)_2D_3$. The expression of vitamin D receptors on CD4+ T cells is increased five-fold after activation [17]. The proliferation of purified Th cells and production of interferon (IFN)-γ, interleukin (IL)-2 and IL-5 is reduced by $1,25(OH)_2D_3$. In Th2 cells, the production of IL-4 is reduced. Bemiss et al. [18] demonstrated in mice that IL-2 suppression was one of the important effects of $1,25(OH)_2D_3$ and significantly reduced mortality. Cantorna et al. demonstrated that $1,25(OH)_2D_3$ upregulated IL-4 and prevented the development of experimental autoimmune encephalomyelitis in mice [19]. $1,25(OH)_2D_3$ has also been shown to reduce the expression of tumor necrosis factor (TNF)-α by increasing IκBα and decreasing nuclear factor-kappa B (NF-κB) activity in macrophage cell lines, thereby significantly reducing inflammation [20]. Calcitriol also inhibited the non-stimulated and lipopolysaccharide (LPS)-stimulated expression of pro-inflammatory and pro-atherosclerotic parameters, including intercellular adhesion molecule (ICAM)-1, platelet endothelial cell adhesion molecule (PECAM)-1, receptor of advanced glycation

end products (RAGE), and IL-6 on human umbilical vein cords, by affecting the activity of NF-κB and p38 mitogen-activated protein kinase (MAPK) pathways [21]. *In vitro*, $1,25(OH)_2D_3$ inhibits the differentiation of monocytes to dendritic cells, thereby reducing their ability to stimulate T cells [22].

Evidence for the role of vitamin D in immune modulation is also present in clinical studies. Reduced calcitriol levels have been shown to correlate with the development of many autoimmune disorders, including type 1 diabetes mellitus, multiple sclerosis, rheumatoid arthritis, systemic lupus erythematosus (SLE) and inflammatory bowel disease (IBD) [23]. Exacerbations of multiple sclerosis have been reported in spring when vitamin D levels are low [24]. This was confirmed in 187,000 patients who were evaluated over a period of 10 to 20 years; patients with higher intake of vitamin D had a 40 % lower frequency of multiple sclerosis than those with lower intakes [25]. Similar findings have been reproduced in 2 large series of patients with rheumatoid arthritis and type 1 diabetes mellitus [26, 27]. Moreover, a two-week treatment with $1,25(OH)_2D_3$ reduced the progression and severe symptoms of arthritis in murine models of human disease [28]. A recent study of patients with asthma from Quebec has shown that vitamin D receptor variants are strongly associated with the disease [29].

Vitamin D and Sepsis

As a logical extension of the immunomodulatory effects of vitamin D, the question arises whether vitamin D could influence the development or progression of sepsis. $1,25(OH)_2D_3$ is an immune system modulator and induces expression of Toll-like receptor (TLR) co-receptor CD14 [30, 31]. $1,25(OH)_2D_3$ acts as a ligand for the vitamin D receptor that is expressed in epithelial tissues and cells of the immune system. Wang et al. demonstrated that while $1,25(OH)_2D_3$ did not possess any antibacterial activity, it can induce cathelicidin antimicrobial peptide (*camp*) and defensin β2 (*defB2*) genes [32]. This release of antimicrobial activity in neutrophils may contribute to innate immune responses. $1,25(OH)_2D_3$ also stimulated expression of neutrophil lipocalin (NGAL), which has been demonstrated to be a bacteriostatic agent [33]. These actions are significant because CAMP has been demonstrated to restore antimicrobial activity against resistant pathogens in patients with cystic fibrosis. Among the pathogens that were inhibited were mucoid and nonmucoid strains of *Pseudomonas aeruginosa*, *Stenotrophomonas maltophila* and *Achromobacter xylosoxidans* [34]. In mice injected with lethal doses of LPS, CAMP also blocked macrophage induction, decreased the sepsis response and enhanced survival [35]. Cathelicidin also binds to LPS and neutralizes it [36], and inhibits release of TNF-α, tissue factor and nitric oxide (NO) in response to LPS [36, 37]. Moller et al. found that $1,25(OH)_2D_3$ modulated the response to sepsis-induced coagulation disturbances in rats in a cecal ligation and puncture model; platelet counts were significantly higher in rats treated with $1,25(OH)_2D_3$ [38]. Liu et al. showed that microbial binding to TLRs stimulated macrophages, which induced expression of vitamin D receptors, increased conversion of $25\text{-}(OH)D_3$ to $1,25(OH)_2D_3$, and thereby increased the levels of cathelicidin to promote intracellular killing of mycobacteria [39]. This explains the mechanism by which sunburn is a treatment for cutaneous tuberculosis/lupus vulgaris.

Recently, there has been considerable interest in 3-hydroxy-3-methyl-glutaryl-CoA (HMGCoA) inhibitors for their pleiotropic effects in patients with sepsis [40]. There are data to suggest that there may be some synergy between the pleiotropic

effects of statins and those of vitamin D. In a recent meta-analysis, Hatzigeorgiou and Jackson showed that the incidence of hip fractures was significantly reduced in patients who received statins than in those who did not and their hip bone mineral density significantly better [41]. In patients with acute ischemic heart disease, the use of atorvastatin was also associated with an increase in 25 (OH) cholecalciferol levels [42]. The same effect was replicated in dyslipidemic patients who received rosuvastatin [43]. It is possible that some of the pleiotropic effects of statins in patients with sepsis could be mediated by increased levels of 25 (OH) and 1,25 $(OH)_2$ cholecalciferol.

Miscellaneous Effects of Vitamin D

$1,25(OH)_2D_3$ has also been shown to be important for the maintenance of intestinal mucosal integrity and maintenance of genomic stability [44, 45]. Animal studies have demonstrated reparative [46] and protective effects [47] of vitamin D on the nervous system.

Vitamin D in Critical Illness

There is a dearth of significant data in large numbers of critically ill patients. Cholecalciferol deficiency has been demonstrated in a small series of chronic critically ill patients [1]. $1,25(OH)_2D_3$ levels were demonstrated to be low at the time of admission in another study [2]. A recent report from an ICU in Australia demonstrated an association between low levels of 25 (OH) cholecalciferol and adverse outcomes [48]. The etiology of vitamin D deficiency in these patients is multifactorial with lack of exposure to sunlight, renal impairment, relative nutritional deficiency, malabsorption of nutrients, and effects of cytokines and inflammatory mediators all contributing in various measures to this phenomenon. The causal relationship between low cholecalciferol levels and outcomes has not been proven in any of the above studies. But these findings become more relevant in light of the increasing volume of evidence linking low cholecalciferol levels with adverse outcomes. A recent study in the general population found a 26 % increase in all-cause mortality in those in the lowest quartile of 25 (OH) cholecalciferol levels when compared to the highest quartile with a population attributable risk of 3.1 % [49].

Challenges for the Intensivist

Large studies examining the role of vitamin D and its association with propensity to sepsis, organ dysfunction and mortality are lacking in critically ill patients. Consequently, firm recommendations on routine supplementation are premature at this stage. More fundamental questions remain unanswered. For example, should we measure $25\text{-}OHD_3$ or $1,25(OH)_2D_3$? $25\text{-}OHD_3$, although not the biologically active hormone, has a half life of 2 – 3 weeks and therefore is a more reliable indicator of the vitamin D status of the patient. On the other hand, $1,25(OH)_2D_3$, the biologically active form, circulates in the plasma at a concentration 1000 fold lower than $25\text{-}OHD_3$ and has a half life of only 4 – 6 hours. Thus, it may be a less reliable indicator of the vitamin D status than $25\text{-}OHD_3$. Moreover, $1,25(OH)_2D_3$ is influenced by PTH levels, whilst $25\text{-}OHD_3$ is not. However the physiological basis of the role of vitamin D in immunity and sepsis is based on $1,25(OH)_2D_3$ levels rather than $25\text{-}OHD_3$.

Thus, more data are required to determine the appropriate endpoint and the range which may be observed in various critically ill patients. Moreover, when the prevalence of vitamin D deficiency is so high in the community, it is unclear whether a reliable signal will be generated which might suggest correlations with organ dysfunction and mortality.

The best time to collect blood for estimation of vitamin D levels following admission to ICU is also uncertain. As noted, there may be a circadian rhythm in certain groups of patients. In the study by Van den Berghe et al. a large proportion of the patients had low cholecalciferol levels on admission to the ICU [2]. These authors found that TNF-α levels inversely correlated with vitamin D levels; whether these reflect a pre-morbid deficiency or are secondary to fluid resuscitation is unclear. We hypothesized that acute administration of large quantities of fluids could significantly influence vitamin D levels, if the sample collection happened around the time of fluid resuscitation. Preliminary results from a study to examine this hypothesis, have shown that acute fluid loading does significantly lower cholecalciferol levels (unpublished data). It may, therefore, be prudent in these patients to wait a few days following admission before estimating cholecalciferol levels to assess vitamin D status.

Pharmacokinetic and pharmacodynamic dose response data also need to be generated in critically ill patients. These issues need clear answers before any clear pathophysiological associations between vitamin D status and organ dysfunction can be made and before decisions regarding the role of supplementation in critically ill patients can be established.

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IX Anticoagulant Therapies

Update on Antithrombin for the Treatment of Burn Trauma and Smoke Inhalation Injury

S. Rehberg, D.L. Traber, and P. Enkhbaatar

Introduction

A severe imbalance of systemic and alveolar hemeostasis, as evidenced by an increase in pro-coagulant and a decrease in anti-fibrinolytic activities, represents a hallmark of burn trauma and smoke inhalation injury [1]. The resulting hypercoagulable state is established within the initial 24 h after the injury and is characterized by high levels of activated factor VII, thrombin-antithrombin complexes, plasminogen activator inhibitor type-1 (PAI-1), and low levels of protein C as well as antithrombin [2]. Plasma levels of antithrombin decrease by 50 % in burn patients within the first five days and represent an independent predictor of length of hospital stay and mortality [1, 3]. However, the host response to burn trauma as well as to smoke inhalation injury, is not only restricted to coagulation disorders, but also includes a marked activation of the inflammation cascade [4]. Both the systemic inflammatory response syndrome (SIRS) and the pro-coagulatory imbalance in hemostasis ultimately result in multiple organ failure (MOF) and increased mortality rates.

In this context, it has been reported repeatedly that there is an extensive cross-talk between coagulation and inflammation pathways [5]. Briefly summarized, the initial phase after the injury leads to the release of inflammatory cytokines from activated lymphocytes, macrophages, and endothelium. These cytokines further contribute to endothelial damage and activate nuclear factor-kappa B (NF-κB), which in turn promotes the production of tissue factor [5]. Tissue factor is the most potent initiator of the extrinsic coagulation cascade and thereby induces thrombin formation. Thrombin augments the inflammatory response, worsens injury [6] and ultimately leads to fibrin formation [7]. This mechanism may be of particular importance, because it represents the link between inflammation and coagulation [6]. As a consequence, anti-inflammatory effects of several anticoagulant and fibrinolytic compounds, such as heparin, tissue factor pathway inhibitor, antithrombin, activated protein C (APC), recombinant soluble thrombomodulin, urokinase plasminogen activator or tissue plasminogen activator, have been investigated in recent years [6].

Based on its central role in the regulation of the coagulation-anticoagulation-system [8], its deficiency after burn injury [1], and its multiple anti-inflammatory properties [9], antithrombin may represent a very promising approach for the treatment of burn trauma and acute lung injury following smoke inhalation. Therefore, the present chapter reviews the current knowledge on the anticoagulant and anti-inflammatory effects of antithrombin with a special focus on the coagulation-independent anti-inflammatory properties. In addition, the potential benefits of antithrombin in experimental and clinical studies investigating its use for the treatment of burn and smoke inhalation injury are critically discussed.

Antithrombin

Antithrombin is a plasma-derived, single chain glycoprotein with a molecular weight of 58 kDa that is produced in the liver. The physiological plasma levels of this serine protease inhibitor are around 150 μg/ml corresponding to about 1 IU/ml [8, 10]. Notably, there are two isoforms of antithrombin, an alpha- and a beta-isoform. The beta-isoform lacks one carbohydrate side chain compared with the alpha-isoform and has a higher affinity for heparin and heparan sulfate proteoglycans (HSPG). While the beta-isoform only represents 5–10 % of the total antithrombin in the plasma, it is concentrated in the vessel wall. In addition, the beta-isoform is a more potent inhibitor of FXa and FIXa than the alpha-isoform [8].

For therapeutic purposes, antithrombin is available in a plasma-derived and in a recombinant form produced from transgenic goat milk [11]. Compared to plasma-derived antithrombin concentrates, recombinant human antithrombin is associated with a higher affinity to heparin and a shorter *in vivo* half-life. An advantage of the recombinant form is that the risk of infusion-transmitted infections is avoided.

Therapeutic Effects of Antithrombin

The therapeutic effects of antithrombin can be subdivided into three main categories: Anticoagulant, associated coagulation-dependent anti-inflammatory effects, and anti-inflammatory properties that are not based on the inhibition of coagulation factors (coagulation-independent). **Figure 1** provides a simplified overview of the anti-inflammatory effects of antithrombin.

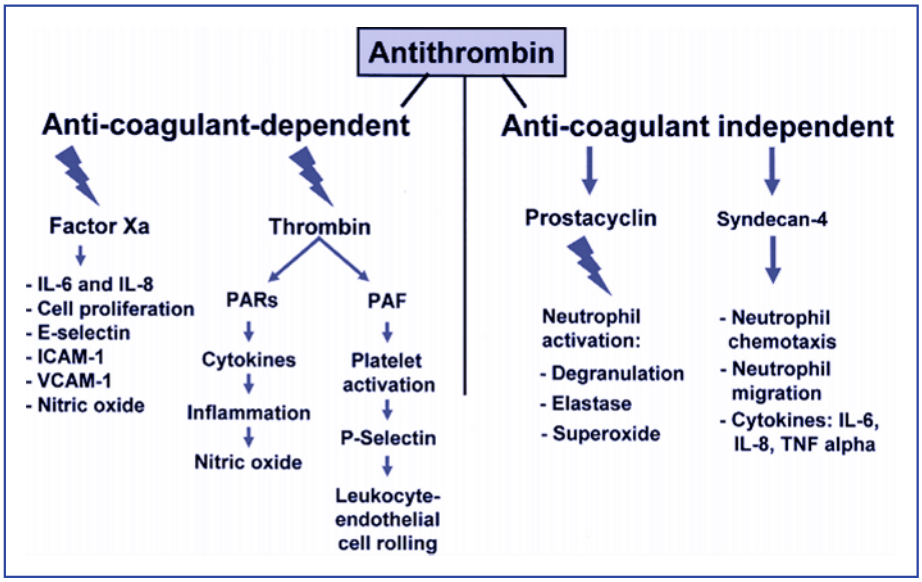

Fig. 1. Coagulation-dependent and coagulation-independent anti-inflammatory effects of antithrombin. ICAM-1: intercellular adhesion molecule 1; IL: interleukin; PAF: platelet activating factor; PARs: protease-activated receptors; TNF alpha: tumor necrosis factor alpha; VCAM-1: vascular cell adhesion molecule 1

Anticoagulant Effects

Antithrombin plays a central role in the regulation of the coagulation cascade. Although its primary action consists of the inhibition of thrombin (FIIa) and FXa, antithrombin also inhibits FIXa, FXIa, FXIIa and, in the presence of heparin, FVII [6, 8, 9]. Antithrombin binds stoichiometrically and irreversible to its target proteases forming equimolar complexes that are removed from the circulation by the reticuloendothelial system [12]. For thrombin inhibition, binding to heparin is a prerequisite. But antithrombin also provides anticoagulatory effects in the absence of heparin, which are slower than those with heparin [8].

This broad spectrum capacity of antithrombin to control the coagulation cascade renders it the most important serpin in homeostasis. Accordingly, even small decreases in antithrombin levels can lead to serious systemic (after burn injury or sepsis) or local (after acute lung injury) hemostatic imbalance and impairment of the microcirculation ultimately resulting in organ failure [6].

Anti-inflammatory effects dependent on the coagulation system

The coagulation-dependent anti-inflammatory properties of antithrombin result from the inhibition of coagulation factors, such as thrombin, FXa or FVIIa, which themselves are associated with a number of pro-inflammatory effects. Thrombin, for example, binds to three of the four protease-activated receptors (PAR 1 – 3) on endothelial cells [5, 13], leading to transmembrane signalling of these G-protein coupled receptors and increased expressions of P-selectin (resulting in the adhesion of neutrophils) or platelet-activating factor (causing platelet aggregation) [14]. In addition, thrombin stimulates neutrophil/monocyte adhesion and regulates cytokine (interleukin [IL]-6 and IL-8) transcription and release [13]. Last but not least, thrombin contributes to leukocyte rolling and sticking [15], which represents a central mechanism of vascular leakage.

The second protease of the coagulation pathway inhibited by antithrombin, FXa, binds to effector cell protease receptor-1 and thereby stimulates the production of IL-6, IL-8, monocyte chemotactic protein-1, E-selectin, soluble as well as vascular cell adhesion molecules [13]. Notably, in an *in vitro* study using human umbilical vein endothelial cells all of these pro-inflammatory effects of FXa were inhibited by antithrombin [16]. In addition, binding of FVIIa to tissue factor results in an increased production of transcription factors, pro-inflammatory cytokines, like IL-1ß or IL-8, chemokines and collagenases [17]. In summary, the ability of antithrombin to block the stimulation of inflammatory pathways by inhibition of these coagulation factors already results in a potent anti-inflammatory effect.

Coagulation-independent anti-inflammatory effects

The first descriptions of the coagulation-independent anti-inflammatory effects of antithrombin were published in the late 1980s. In this context, Taylor and colleagues reported an increase in mean arterial pressure as well as a reduction in organ failure and mortality in a baboon model of *Escherichia coli*-induced sepsis that could not be solely explained by inhibition of the coagulation cascade [18]. About ten years later – in 1998 – Uchiba et al. postulated that the coagulation-independent anti-inflammatory effects of antithrombin were based on two different mechanisms, namely the release of prostacyclin from endothelial cells and a direct interaction of

antithrombin with leukocytes and endothelial cells [19, 20]. For both of these effects the binding of antithrombin with its heparan binding site to HSPGs on the surface of the interacting cells seems to be critical [8, 9]. Within the HSPGs, the syndecan-4 receptor is increasingly reported as the 'antithrombin receptor'. Syndecan-4 is a G-protein coupled transmembrane HSPG bearing extracellular glykosaminoglycans [21]. Binding of antithrombin to the syndecan-4 receptor leads to inhibition of the intracellular signal transduction cascade initiated by endotoxin or other stimuli. Thereby, antithrombin prevents the stimulation of NF-κB transcription and the subsequent increase in IL-6, IL-8, tumor necrosis factor (TNF) alpha, and tissue factor [22], resulting in a downregulation of the inflammatory response.

As mentioned before, antithrombin also induces the release of prostacyclin after binding to endothelial cells [20]. The anti-inflammatory properties of prostacyclin include inhibition of platelet aggregation and reduction in the synthesis of pro-inflammatory cytokines, release of reactive oxygen species (ROS), and neutrophil activation [7, 23, 24]. The central role of prostacyclin in the anti-inflammatory effects of antithrombin was verified by demonstrating that these beneficial effects of antithrombin were eliminated by the addition of indomethacin, a cyclooxygenase inhibitor, to the treatment [23].

Syndecan-4 has also been shown to mediate the inhibitory effects of antithrombin on endotoxin-induced endothelial adherence of neutrophils [25]. The ability to inhibit leukocyte rolling and adhesion represents a profound anti-inflammatory mechanism of antithrombin [23], because this interaction between leukocytes and endothelial cells results in endothelial damage, vascular leakage, transmigration of inflammatory cells, and, ultimately, in an impairment of the microcirculation and organ damage. In addition, the release of prostacyclin and the downregulation of P-selectin expression, as evident in lipopolysaccharide (LPS)-stimulated endothelial cells, have been suggested to reduce the adhesion of leukocytes [26, 27].

Whereas the latter mechanisms are based on the interaction of antithrombin with the endothelium, Dunzendorfer and colleagues reported additional, direct effects of antithrombin on leukocytes. The authors investigated neutrophil migration in Boyden chambers and discovered that antithrombin inhibited the migration of neutrophils towards IL-8, GRO-alpha and N-formyl-L- methionyl-L-leucyl-L-phenylalanine (fMLP) via a CXCR1-related signalling pathway [28]. These results even suggest a physiological role of antithrombin by preventing leukocytes from premature activation. In this context, the same group reported inhibitory effects of antithrombin on chemokine-stimulated migration of monocytes and lymphocytes that were also mediated by the syndecan-4 receptor and subsequent activation of protein kinase C and Rho signalling [29]. In addition, Komura and colleagues suggested that antithrombin reduces LPS-induced TNF-α production of monocytes by inhibiting the increase in early growth response factor-1[30].

Several investigators have postulated that higher doses of antithrombin (250 IU/kg) are necessary to provide anti-inflammatory effects than to inhibit coagulation [31, 32]. In contrast, in a recent experiment of combined 40 % total body surface area (TBSA) burn and smoke inhalation injury in sheep, our research group was able to demonstrate that maintaining antithrombin plasma levels at baseline values reduced neutrophil activation and transmigration as well as pulmonary transvascular fluid flux and improved gas exchange [33]. However, there are several major differences between our and previous studies: First, the previous studies were performed in rodent models of endotoxemia, while we used a large animal model of combined burn and smoke inhalation injury. In addition, antithrombin was admin-

istered as a continuous infusion of 6 IU/kg/h in our study, while the above cited studies used bolus infusions of 250 IU/kg. Therefore, future studies need to clarify the role of different animal models, different injuries, and different modes of administration.

A very interesting finding about antithrombin was recently reported by Hofstra and colleagues [34]. In a rat model of *Streptococcus pneumoniae*-induced lung injury, the nebulization of 500 IU/kg plasma-derived antithrombin not only attenuated lung injury, but also reduced bacterial outgrowth, as evidenced by a reduced number of colony forming units per ml bronchoalveolar lavage fluid. Notably, administration of other anticoagulants, such as APC, heparin or danaparoid, was not associated with these anti-inflammatory effects. The authors concluded that antithrombin might be associated with a direct antimicrobial effect by competing with bacterial toxins for binding to endothelial cell proteoglycans [35].

Interactions with Heparin

The interaction between heparin and antithrombin represents a double-edged sword in the treatment of disease states associated with activated coagulation as well as inflammation (**Fig. 2**). On the one hand, heparin markedly increases, by 600–2,000-fold depending on the individual coagulation factor, the ability of antithrombin to inhibit proteases of the coagulation cascade [36]. By binding to antithrombin with a unique pentasaccharide sequence, heparin induces a conformational change in the antithrombin molecule that enhances its abilities to inhibit FXa, and other serine proteases. To promote the inhibition of thrombin by antithrombin, heparins with longer polysaccharide chains are required, because heparin needs to interact with the antithrombin and the thrombin molecule simultaneously [8].

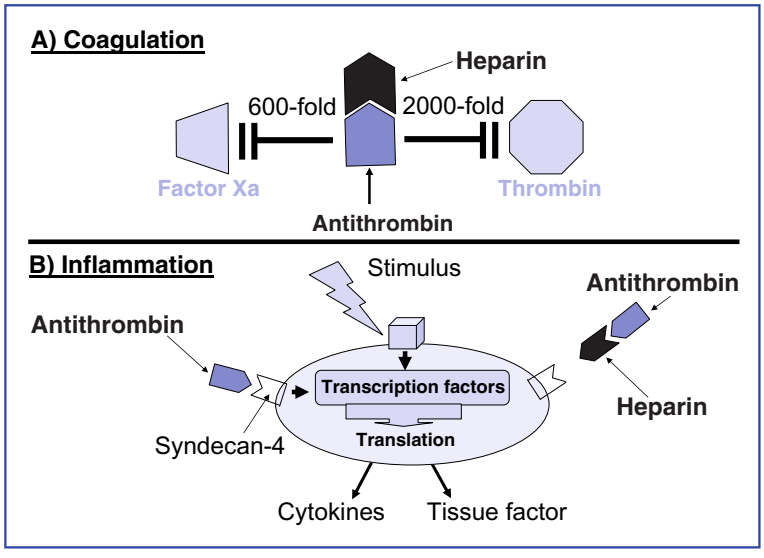

Fig. 2. Interactions between antithrombin and heparin. A) Heparin increases the ability of antithrombin to inhibit Factor Xa and thrombin 600- and 2000-fold, respectively. B) However, anti-inflammatory effects of antithrombin, like the inhibition of the intracellular signal transduction cascade and the resulting release of different cytokines and tissue factor, are eliminated by heparin.

On the other hand, the coagulation-independent anti-inflammatory effects of antithrombin are significantly reduced or even eliminated by heparin. The reason for this finding is that heparin and HSPGs compete for the same pentasaccharide binding site of antithrombin. Accordingly, pre-treatment with heparinase III completely prevented the binding of antithrombin to cultured endothelial cells [37]. In this context, it is also very important to consider that one molecule of pentasaccharide is able to inactivate several antithrombin molecules in terms of cellular interaction [29]. This finding might explain why even low-dose heparin used for thrombosis prophylaxis reduced the potential beneficial effects of high-dose antithrombin in a randomized, controlled multicenter trial investigating the effects of high-dose antithrombin in critically ill patients [38]. In contrast, a pre-defined subgroup analysis in patients not receiving heparin revealed a significant improvement in 90-day survival as compared to placebo.

Antithrombin for the Treatment of Burn Trauma and Smoke Inhalation Injury

Experimental Studies

Our research group has investigated the pathophysiology and potential treatment strategies for burn as well as acute lung injuries in different ovine models for more than three decades. The effects of antithrombin on acute lung injury following smoke inhalation and *Pseudomonas aeroginosa*-induced pneumonia were reported by Murakami and colleagues [39]. The injury was characterized by severe airway obstruction due to fibrin cast material, an increase in pulmonary transvascular fluid flux, and a reduction in the PaO_2/FiO_2 ratio. The continuous intravenous infusion of 4.35 IU/kg/h human recombinant antithrombin started 1 h after the injury not only kept the antithrombin levels at baseline values, but also reduced pulmonary obstruction and edema. In addition, treated animals had higher urine outputs and mean arterial pressures than control animals.

The majority of studies, however, have been performed in our internationally established ovine model of a 40 % TBSA cutaneous 3rd degree flame burn combined with 48 breaths of cold (< 40 °C) cotton smoke. Following this injury, antithrombin levels fall to 30 % of the baseline level. The local administration of either 290 IU recombinant human antithrombin or 10,000 IU heparin via nebulization every 4 h did not significantly improve pulmonary gas exchange. In addition, aerosolized antithrombin administration did not affect the reduced systemic plasma levels of antithrombin, which represent an independent risk factor for mortality in burn patients [1]. However, the combination of both treatment strategies improved pulmonary oxygenation and reduced airway obstruction and pulmonary transvascular fluid flux evaluated by measuring the lung lymph flow [40]. Due to the inhibition of the anti-inflammatory effects of antithrombin by heparin, the attenuation of pulmonary injury was mainly mediated by the anticoagulant effects of antithrombin that prevented fibrin deposition in the airway thus reducing tracheobronchial cast formation. To reduce the interference between antithrombin and heparin and thereby increase the anti-inflammatory effects of antithrombin, we substituted the aerosolization with an intravenous administration of 2.4 IU/kg/h recombinant human antithrombin (started 1 h post injury) and combined it with nebulization of 10,000 IU of heparin every 4 h. Again, lung injury, including pulmonary gas exchange, edema and lung lymph flow, was attenuated compared to placebo-treated animals [41].

Comparing these two studies, the combination of intravenous antithrombin and aerosolized heparin was associated with a more pronounced decrease in pulmonary transvascular fluid flux and lung water content, but with a lower PaO_2/FiO_2 ratio compared to the combined nebulization of heparin and antithrombin. In addition, neutrophil accumulation in lung tissues was significantly reduced, supporting our hypothesis that systemic administration of recombinant human antithrombin with only local interference of aerosolized heparin exerts potent anti-inflammatory properties in the systemic circulation. Notably, coagulation times were not affected by this treatment strategy, suggesting that the amount of aerosolized heparin that entered the systemic circulation was negligible. Due to lower antithrombin levels in the bronchoalveolar lavage fluid the reduction in fibrin deposition and subsequent improvement in pulmonary gas exchange were not as pronounced with the intravenous antithrombin therapy as with the combined nebulization of anticoagulants. Nevertheless, compared to placebo-treated control animals the latter therapeutic approach significantly reduced cast formation and increased PaO_2/FiO_2 ratios.

To further evaluate the potential of recombinant human antithrombin for the treatment of combined burn and smoke inhalation injury, we recently investigated single treatment with a continuous infusion of a higher dose of recombinant human antithrombin (6 IU/kg/h started 1 h after injury) in our ovine model [33]. Antithrombin activity was maintained at baseline levels and pulmonary gas exchange improved as compared to untreated control animals. Notably, the increase in pulmonary transvascular fluid flux was almost completely blocked and the number of neutrophils in the lymph was significantly reduced in antithrombin-treated as compared to untreated animals. In agreement with this finding, the activation of neutrophils isolated from the peripheral blood, represented by combined staining of CD11b and syndecan-4, was significantly lower than in the control group. In addition, recombinant human antithrombin treatment was associated with a reduced positive net fluid balance (fluid accumulation) demonstrating that systemically administered recombi-

Table 1. Experimental studies

Model	Compound, dose, administration	Results
Smoke inhalation and pneumonia in sheep [39]	Continuous infusion of 4.35 IU/kg/h rhAT started 1 h after injury	AT baseline levels were maintained, reduction in pulmonary edema and obstruction, increase in urine output
40 % TBSA burn and smoke inhalation injury in sheep [40]	290 IU rhAT aerosolized every 4 h, alone or combined with 10,000 IU aerosolized heparin every 4 h	rhAT alone did not improve gas exchange; combination with heparin reduced airway obstruction and improved pulmonary function
40 % TBSA burn and smoke inhalation injury in sheep [41]	continuous infusion of 2.4 IU/kg/h rhAT (started 1 h post injury) combined with 10,000 IU aerosolized heparin every 4 h	Combined treatment improved gas exchange, reduced airway obstruction, pulmonary edema and neutrophil accumulation in the lung
40 % TBSA burn and smoke inhalation injury in sheep [33]	continuous infusion of 6 IU/kg/h rhAT (started 1 h post injury)	Improvement of pulmonary gas exchange, reduction of airway obstruction, pulmonary and systemic fluid accumulation as well as neutrophil activation and transmigration

AT: antithrombin; rhAT: recombinant human antithrombin; TBSA: total body surface area

nant human antithrombin may affect the microvascular permeability. Although, the exact mechanism of this latter effect is not completely understood, we speculate that recombinant human antithrombin may reduce vascular leakage by inhibiting neutrophil accumulation, excessive nitric oxide (NO) formation, and expression of vascular endothelial growth factor (VEGF).

In summary, based on these experimental studies (**Table 1**), antithrombin seems to have a broad therapeutic potential in combined burn and smoke inhalation injury. Nevertheless, future studies are needed to reveal the most beneficial treatment approach to improve long-term morbidity and survival.

Clinical Studies

In contrast to experimental studies, clinical trials investigating the use of antithrombin in the treatment of burn and smoke inhalation injury have mainly focused on the burn and associated coagulation disorders or wound healing rather than on smoke inhalation injury (**Table 2**).

Table 2. Clinical studies

Design	Treatment	Results
Case report about a patient with 68 % TBSA burn [42]	9 infusions of AT (human) concentrate (50 – 100 IU/kg) during the first 4 days after injury	No excessive bleeding or prolongation of wound healing occurred
Pilot study with 18 patients with burn injuries [43]	Infusions of AT (human) concentrate every 8h during the first 3 days post injury	Reduction in wound healing time, trend towards fewer autograft procedures and a shorter hospital stay
Open pilot study with 32 patients with thermal injuries [44]	Median dose 97 IU/kg/dose AT (human) concentrate	Fewer episodes of pneumonia, trend toward improved oxygenation (PaO_2/FiO_2 ratio) and reduced airway resistance
2 children with > 50 % TBSA burns [45]	10 infusions of AT (human) concentrate (106 IU/kg) in the first 4 days post injury	Well tolerated, lack of bleeding during eschar removal
Pilot study in children with burn injuries [46]	Infusions of AT (human) concentrate every 8h during the first 3 days post injury	Reduction in the time of microcirculation recovery compared to control
201 consecutive patients with severe burn injuries [3]	continuous infusion of AT (human) concentrate to maintain AT activity of 70 – 120 %	38 – 41 % developed AT deficiency within the first 5 days; AT deficiency was an independent predictor of length of hospital stay and mortality
Prospective study in 45 patients with severe thermal burn injury [47]	none	AT levels on day one represent a prognostic marker for mortality
Randomized, controlled study in 31 burned patients [48]	65 IU/kg/d AT (human) concentrate during the first 4 days post injury	Reduction in multiple organ failure and mortality, no treatment related adverse effects

AT: antithrombin; TBSA: total body surface area

Unfortunately, clinical evidence is prevailingly restricted to case reports and pilot studies.

Kowal-Vern and colleagues reported the first evidence for the safety of antithrombin in burned patients in a case report of a 40 year old man with a 68 % TBSA burn without identified inhalation injury [42]. The patient received nine infusions of plasma-derived antithrombin concentrate (50 – 100 IU/kg each) during the first four days after injury. Plasma levels of antithrombin were increased from 45 % on admission to 120 ± 25 % during the next four days, but there was no excessive bleeding during the 11 grafting procedures and no prolongation in wound healing.

Following up on their observations, the same group conducted two pilot studies in patients with thermal injuries [43, 44]. In the first study in 18 patients, the infusion of human antithrombin concentrate every 8 h during the first three days post-injury led to a reduced wound healing time and a tendency towards fewer autograft procedures as well as a shorter hospital stay as compared to untreated patients [43]. The second trial included 32 patients with ≥ 20 % TBSA burns and is the only clinical study so far that reports the effects of antithrombin on pulmonary function [44]. Nine patients received bolus infusions of human antithrombin concentrate every 8 h during the first 3 days after injury. The mean dose administered was 97 IU/kg/dose. The treatment was associated with a lower incidence of pneumonia, a reduction in ventilatory duration, and higher PaO_2/FiO_2 ratios from day 4 – 6 as compared to the control group. In patients with combined inhalation injury (antithrombin: 4; control 12), antithrombin led to a significant reduction in airway resistance.

The safe administration of antithrombin in children was reported in a case report and a small pilot study. Ten infusions of human antithrombin concentrate (106 IU/kg each) during the first 4 days post-injury were well tolerated in two children with > 50 % TBSA burns [45]. Notably, in one patient, bleeding during eschar removal (all four extremities) was only 40 ml. The safety of antithrombin was supported by a small pilot study in children with burn injuries who received infusions of human antithrombin concentrate during the first 3 days post-injury. In addition, the time of microcirculation recovery was significantly lower in antithrombin-treated than in control patients [46].

The largest study on antithrombin for the treatment of burn injuries, including 201 consecutive patients with severe buns, showed that 38 – 40 % of the patients developed antithrombin deficiency within the first 5 days after injury. Statistical analyses revealed antithrombin deficiency as an independent predictor of length of hospital stay and mortality emphasizing the potential role of antithrombin administration as a therapeutic approach in burned patients [3]. Two recent studies from the group of Lavrentieva and colleagues further emphasize the relevance and efficiency of antithrombin supplementation following severe burn injuries. In a prospective study on 45 patients with severe thermal burn injury and an associated 28-day mortality of 33 %, the investigators reported a significant correlation between the presence of disseminated intravascular coagulation (DIC) and mortality (OR = 0.1). In addition, among others, antithrombin plasma levels on day 3 were identified as a prognostic marker of intensive care unit (ICU) mortality [47]. The second study by this group represents the first randomized, controlled study of the use of antithrombin in 31 burned patients. The average administered dose of antithrombin was 65 IU/kg/d for the first four days after injury. While no treatment-related adverse effects were observed, antithrombin reduced the incidence of multiple organ failure, as represented by lower Sequential Organ Failure Assessment (SOFA) Scores, and 28-day mortality [48].

Conclusion

Based on the current experimental and clinical data, administration of antithrombin in patients with isolated burn or combined burn and smoke inhalation injuries seems to be safe in respect to bleeding complications. In addition, the availability of recombinant human antithrombin avoids the risk of infusion transmitted infections. Antithrombin seems to provide beneficial effects on wound healing, microcirculatory blood flow, vascular leakage, pulmonary, cardiovascular and multi-organ function as well as on survival. However, the proper 'operating instructions' for the administration of antithrombin are still lacking [49]. First, it still needs to be determined whether the restoration of physiological or induction of supra-physiological plasma activities of antithrombin represents the most beneficial therapeutic approach in respect to the benefit-risk-ratio; accordingly, the dose needs to be adjusted. Second, the time point to start the treatment is critical. Administration of antithrombin at the wrong time point in the course of the physiological coagulatory and inflammatory response of the body (e.g., too early) can also result in detrimental effects [50]. Third, in case of smoke inhalation injury without concomitant cutaneous burn, the most effective way of administration, i.e., systemically by intravenous infusions or locally by nebulization, has not yet been investigated. Last but not least, all the previous aspects of potential antithrombin therapy need to be adapted to the general therapeutic concept for the individual patient (e.g., heparin administration, pre-existing bleeding disorders, or therapeutic anticoagulation). In summary, the results of the discussed experimental and clinical studies suggest beneficial effects of antithrombin in the treatment of burn and smoke inhalation injury. However, randomized, controlled clinical trials are warranted to verify this hypothesis.

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Update on Physiological Anticoagulant Factor Concentrates in Patients with Sepsis

M. Levi and T. van der Poll

Introduction

Patients with severe sepsis have systemic activation of the inflammatory system and of coagulation. Increasing evidence points to an extensive cross-talk between these two systems, whereby inflammation not only leads to activation of coagulation, but coagulation also considerably affects inflammatory activity [1]. The intricate relationship between inflammation and coagulation may have major consequences for the pathogenesis of microvascular failure and subsequent multiple organ failure, as a result of severe infection and the associated systemic inflammatory response. Molecular pathways that contribute to inflammation-induced activation of coagulation and modulation of inflammation by coagulation factors have been precisely identified. Endothelial-bound anticoagulant mechanisms, in particular the protein C system, tissue factor pathway inhibitor (TFPI) and the antithrombin system, play important roles in this respect [2]. These findings have resulted in the development of physiological anticoagulant factor concentrates for (adjunctive) treatment in patients with sepsis. In this chapter, we briefly provide new insights from preclinical research with these anticoagulant factors in sepsis and an update of recent clinical findings.

Inflammation-induced Effects on Physiological Anticoagulant Factors

Activation of coagulation and deposition of fibrin as a consequence of inflammation can be considered instrumental in containing inflammatory activity to the site of injury or infection, rendering this relationship physiologically efficient. However, inflammation-induced coagulation may also contribute to disease, as illustrated by the coagulopathy that is associated with severe infection, including sepsis [3]. The main mediators of inflammation-induced activation of coagulation are pro-inflammatory cytokines. Several studies have shown, for example, the importance of interleukin (IL)-6 in the initiation of coagulation activation and the role of tumor necrosis factor-α (TNF-α) and IL-1 in the regulation of physiological anticoagulation.

Procoagulant activity is regulated by three important anticoagulant pathways: Antithrombin, the protein C system and TFPI. Interestingly, all three anticoagulant systems are in principal located at the endothelial surface, where they can direct both anticoagulant and anti-inflammatory functions (**Fig. 1**). During inflammation-induced activation of coagulation, the function of all three pathways can be impaired [1].

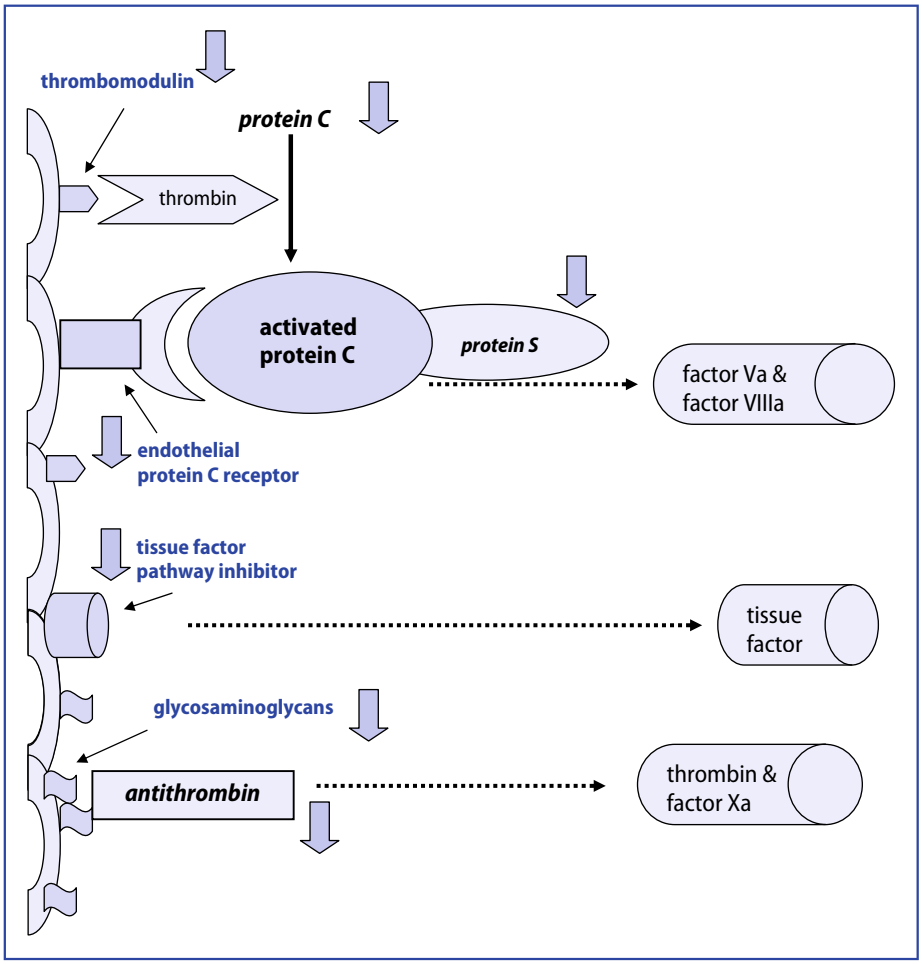

Fig. 1. Schematic representation of the three important physiological antiocoagulant mechanisms and their point of impact in the coagulation system. In sepsis, these mechanisms are impaired by various mechanisms (blue arrows). The protein C system is dysfunctional due to low levels of zymogen protein C, downregulation of thrombomodulin and the endothelial protein C receptor, and low levels of free protein S due to acute phase-induced high levels of its binding protein, C4b-binding protein. There is a relative insufficiency of the endothelial cell-associated tissue factor pathway inhibitor. The antithrombin system is defective due to low levels of antithrombin and impaired glycosaminoglycan expression on perturbed endothelial cells.

The Antithrombin System

The serine protease inhibitor, antithrombin, is the main inhibitor of thrombin and factor Xa. Without heparin, antithrombin neutralizes coagulation enzymes in a slow, progressive manner. Heparin induces conformational changes in antithrombin that result in at least a 1000-fold enhancement of antithrombin activity. Thus, the clinical efficacy of heparin is attributed to its interaction with antithrombin. Endogenous glycosaminoglycans, such as heparan sulfates, on the vessel wall also promote anti-

thrombin-mediated inhibition of thrombin and other coagulation enzymes. During severe inflammatory responses, antithrombin levels are markedly decreased owing to impaired synthesis (as a result of a negative acute phase response), degradation by elastase from activated neutrophils, and – quantitatively most importantly – consumption as a consequence of ongoing thrombin generation [1]. Pro-inflammatory cytokines can also cause reduced synthesis of glycosaminoglycans on the endothelial surface, which will also contribute to reduced antithrombin function, since these glycosaminoglycans can act as physiological heparin-like cofactors of antithrombin [4].

The Thrombomodulin-protein C System

Activated protein C (APC) appears to play a central role in the pathogenesis of sepsis and associated organ dysfunction. There is ample evidence that insufficient functioning of the protein C pathway contributes to the derangement of coagulation in sepsis [5]. The circulating zymogen protein C is activated by the endothelial cell-bound thrombomodulin once this is activated by thrombin [6]. APC acts in concert with its co-factor, protein S, and is able to proteolytically degrade the coagulation essential co-factors, Va and VIIIa; hence, APC is an effective anticoagulant. The endothelial protein C receptor (EPCR) not only accelerates the activation of protein C several-fold, but also serves as a receptor for APC: binding of APC to this receptor may amplify its anticoagulant and anti-inflammatory effects [7]. A recent study has demonstrated that exposure of cultured endothelial cells to APC results in the release of microparticles that contain EPCR, but the relevance of that observation for coagulation or inflammation is not yet clear [8].

In patients with severe inflammation, this system malfunctions at virtually all levels. First, plasma levels of the zymogen protein C are low or very low, due to impaired synthesis, consumption, and degradation by proteolytic enzymes, such as neutrophil elastase [2]. Furthermore, a significant downregulation of thrombomodulin, caused by pro-inflammatory cytokines such as TNF-α and IL-1, has been demonstrated, resulting in diminished protein C activation [9]. Low levels of free protein S may further compromise an adequate function of the protein C system. In plasma, 60 % of the co-factor protein S is complexed to a complement regulatory protein, C4b binding protein (C4bBP). Increased plasma levels of C4bBP as a consequence of the acute phase reaction in inflammatory diseases may result in a relative protein S deficiency, which further contributes to a procoagulant state during sepsis. Although it has been shown that the β-chain of C4bBP (which mainly governs the binding to protein S) is not very much affected during the acute phase response, support for this hypothesis comes from studies showing that the infusion of C4bBP in combination with a sublethal dose of *Escherichia coli* into baboons resulted in a lethal response with severe organ damage due to disseminated intravascular coagulopathy (DIC) [10]. Finally, but importantly, the EPCR has shown to be downregulated in sepsis, which may further negatively affect the function of the protein C system. Apart from these effects, sepsis may cause a resistance toward APC by other mechanisms, which are partly dependent on a sharp increase in factor VIII levels (released from endothelial cells), but partly occur by as yet unidentified mechanisms [11].

Tissue Factor Pathway Inhibitor

A third inhibitory mechanism of thrombin generation involves TFPI, the main inhibitor of the tissue factor-factor VIIa complex. The role of TFPI in the regulation of inflammation-induced coagulation activation is not completely clear. Experiments showing that administration of recombinant TFPI (thereby achieving higher than physiological plasma concentrations of TFPI) blocks inflammation-induced thrombin generation in humans, and the observation that pharmacological doses of TFPI are capable of preventing mortality during systemic infection and inflammation suggest that high concentrations of TFPI are capable of markedly modulating tissue factor mediated coagulation [12, 13].

Effects of Natural Anticoagulant Systems on Inflammation

Rather than being a one-way direction of inflammation leading to coagulation, the two systems interact intensely, whereby coagulation can also modulate inflammatory activity. Binding of coagulation proteases (such as thrombin or tissue factor) or anticoagulant proteins (such as APC) to specific cell receptors on mononuclear cells or endothelial cells may affect cytokine production or inflammatory cell apoptosis. This cross-talk between the two systems is relevant for many disease states, including various manifestations of vascular disease and the systemic inflammatory response syndrome, leading to organ dysfunction and mortality in sepsis or other conditions [1].

Antithrombin possesses anti-inflammatory properties, many of which are mediated by its actions in the coagulation cascade. Most importantly, thrombin inhibition by antithrombin blunts the activation of many inflammatory mediators. For example, thrombin activates platelets and endothelial cells, which in turn contribute to local inflammation [14]. Activated platelets secrete inflammatory mediators, such as IL-1, which stimulate leukocyte activity. In particular, recruitment and adhesion of neutrophils and monocytes to blood vessels within the microcirculation promote inflammation.

Increasing evidence suggests that antithrombin possesses potent anti-inflammatory properties independent of its anticoagulant activity [14]. Most of these effects have been demonstrated *in vitro* or *in vivo* at high concentrations. Nevertheless, these mechanisms may be important in clinical settings that are driven by a combined activation of inflammation and coagulation. Perhaps most importantly, antithrombin induces prostacyclin release from endothelial cells. Prostacyclin inhibits platelet activation and aggregation, blocks neutrophil tethering to blood vessels, and decreases endothelial cell production of various cytokines and chemokines [15].

Additional anti-inflammatory actions of antithrombin are mediated by direct interaction with leukocytes and lymphocytes. Antithrombin binds to receptors, such as syndecan-4, on the cell surfaces of neutrophils, monocytes, and lymphocytes and blocks the interaction of these cells with endothelial cells. Inhibition of leukocyte-endothelial cell interactions by antithrombin may be mediated by prostacyclin release, downregulation of P-selectin, or prevention of leukocyte activation. Thus, antithrombin directly hinders leukocyte migration and adhesion to endothelial cells, which in turn impacts the severity of capillary leakage and subsequent organ damage. Given the wide-ranging impact of antithrombin on coagulation and inflammation, there are multiple potential clinical applications of antithrombin in different clinical settings that encompass thrombotic states generally not associated with

inflammation (e.g., pregnancy) and coagulation-related disease states with powerful pro-inflammatory elements (e.g., sepsis).

There is compelling evidence that besides their role as an important regulator of coagulation activity, components of the protein C system also have an important function in modulating inflammation [16]. APC acts as an important mediator in the systemic inflammatory response in sepsis as demonstrated in experiments showing that blocking the protein C pathway in septic baboons exacerbated the inflammatory response. In contrast, administration of APC ameliorated the inflammatory activation after intravenous infusion of *E. coli*. Similar experiments in rodents showed identical results and demonstrated a beneficial effect of APC on inflammatory effects in various tissues. Support for the notion that APC has anti-inflammatory properties comes from *in vitro* observations, demonstrating an APC binding site on monocytes, that may mediate downstream inflammatory processes [17], and from experiments showing that APC can block nuclear factor-kappa B (NF-κB) nuclear translocation, which is a prerequisite for increases in pro-inflammatory cytokines and adhesion molecules. These *in vitro* findings are supported by *in vivo* studies in mice with targeted disruption of the protein C gene. In these mice with genetic deficiencies of protein C, endotoxemia was associated with a more marked increase in pro-inflammatory cytokines and other inflammatory responses compared with wild-type mice [18].

It is likely that the effects of APC on inflammation are mediated by the EPCR, which may mediate downstream inflammatory processes [19]. Binding of APC to EPCR influences gene expression profiles of cells by inhibiting endotoxin-induced calcium fluxes in the cell and by blocking NF-κB nuclear translocation [17]. The EPCR-APC complex itself can translocate from the plasma membrane into the cell nucleus, which may be another mechanism of modulation of gene expression, although the relative contribution of this nuclear translocation and cell surface signaling is unclear at present [5]. Some studies also suggest that EPCR binding of APC can result in activation of protease activated receptor (PAR)-1 and, thereby, affect cytokine responses [20]. In contrast, other experiments demonstrated that a significant physiological role for PAR-1 activation by APC was less likely. Like APC, EPCR itself may have anti-inflammatory properties. Soluble EPCR, the extracellular domain of the cell-associated EPCR shed from the cell surface by the action of an inducible metalloproteinase, can bind to proteinase 3, an elastase-like enzyme. The resulting complex binds to the adhesion integrin macrophage 1 antigen (Mac-1). Of considerable interest, the crystal structure of EPCR is remarkably similar to the structure of the major histocompatibility complex (MHC) class 1/CD1 family of proteins, the majority of which are involved in inflammation [21]. Blocking the EPCR with a specific monoclonal antibody aggravates both the coagulation and the inflammatory response to *E. coli* infusion [22].

Apart from the effect of APC on cytokine levels, a remarkable effect of the agent on leukocyte chemotaxis and adhesion of circulating leukocytes to the activated endothelium has been demonstrated [23]. This notion was confirmed in a hamster endotoxemia model at concentrations of recombinant human APC (rhAPC) that preclude a significant anticoagulant effect [24]. The localized effect of rhAPC in the lung has also been shown for these anti-inflammatory mechanisms [25]. A potential mechanism may be that APC inhibits the expression of platelet-derived growth factor in the lung. APC was also shown to protect against the disruption of the endothelial cell barrier in sepsis, probably by interfering with EPCR and PAR-1 on endothelial cells [26].

Finally, APC is capable of inhibiting endothelial cell apoptosis, which also seems to be mediated by binding of APC to EPCR and seems to require PAR-1 [20]. Signaling through this pathway can affect Bcl-2 homolog protein, which can inhibit apoptosis, and further suppresses p53, which is a pro-apoptotic transcription factor [27].

Clinical Application of Natural Anticoagulant Factor Concentrates

In view of the central role of physiological anticoagulants at the interface between coagulation and inflammation, therapies aimed at restoring or improving the natural inhibition of coagulation and thereby modulating inflammatory activity have been developed and evaluated in clinical trials. Potential agents include antithrombin concentrate, rhAPC, soluble thrombomodulin, and recombinant TFPI (rTFPI).

Antithrombin Concentrate

Antithrombin replacement therapy has been used in patients with severe sepsis and DIC since the 1980s. The rationale for this adjunctive treatment strategy is based on the notion that natural anticoagulant pathways are defective in patients with a severe systemic inflammatory response upon infection and this may play a central role in the systemic generation of thrombin and subsequent formation of microthrombi, which may in turn contribute to the pathogenesis of organ dysfunction [28]. Indeed, plasma levels of antithrombin are (very) low in patients with sepsis and are independent predictors of clinical outcome. A substantial decrease in the level of circulating antithrombin has been demonstrated to be a very early phenomenon in sepsis, lending support to the idea that this protease inhibitor is involved in the pathogenesis of the disease. In addition, experimental studies suggest that antithrombin may not only have anticoagulant properties, but also may modulate inflammatory responses [29]. Previous studies have shown that the strong interaction between coagulation and inflammation may indeed be a suitable point-of-impact of new adjunctive strategies in patients with severe sepsis. Antithrombin concentrate has been evaluated in a number of small clinical trials. All trials show some beneficial effect in terms of improvement of a DIC score, shortening of the duration of DIC, or even improvement in organ function. Since all trials, however, used highly variable criteria for assessing these outcomes, it is hard to compare results. In the more recent clinical trials, very high doses of antithrombin concentrate were used to attain supraphysiological plasma levels and the beneficial results in these trials seem to be more distinct. Some trials showed a modest reduction in mortality in antithrombin-treated patients; however, the effect never reached statistical significance. Aggregate results suggested at least a trend towards a reduction in mortality from 47 % to 32 % (odds ratio 0.59, 95 % confidence interval 0.39 – 0.87) [30]. A large randomized controlled clinical trial in 2314 patients with severe sepsis (Kybersept trial), however, did not demonstrate a difference between treatment with antithrombin for four days versus placebo [31]. An interesting subanalysis of patients in the KyberSept trial evaluated antithrombin treatment for severe sepsis with or without DIC [32]. In this analysis, 563 patients with severe sepsis who did not receive heparin and who had sufficient data for DIC determination were evaluated. Using the criteria of the International Society on Thrombosis and Hemostasis (ISTH), 229 (41 %) of these patients had DIC. Among these patients with DIC, those who received antithrombin treatment (n = 114) had a significantly reduced 28-day mortality rate compared with those who

received placebo (n = 115; 25 % vs 40 %, respectively, p = 0.02). In contrast, among patients without DIC, 28-day mortality rates were similar in patients who received antithrombin (n = 172) or placebo (n = 162; 22 % mortality in both treatment groups). Thus, entithrombin treatment may potentially benefit patients with severe sepsis and DIC.

Interestingly, the overall subgroup of patients that did not receive concomitant heparin (which was at the discretion of the attending physician) in the Kybersept trial had a clear trend towards a better survival at 28 days, which was statistically significant at 90 days. Apparently, the combination of antithrombin concentrate and administration of heparin does not work very well. Interestingly, this conclusion was already suggested in the very first clinical trial of antithrombin in patients with DIC 25 years ago, but may have been forgotten over time [33]. The fact that intravenous infusion of antithrombin did not alter mortality in patients with sepsis may possibly be due to the fact that the antithrombin effect may have been obscured by concurrent heparin treatment, considering that heparin, which is a highly sulfated version of heparan sulfate, has been found, like other soluble glycosaminoglycans, to antagonize the anti-inflammatory and microcirculatory effects of antithrombin [34]. Heparan sulfate polysaccharides are ubiquitously expressed as heparan sulfate polyglycans (HSPGs) on cell surfaces such as the endothelium. Direct binding of bacteria to HSPGs on the alveolar epithelium has been described; however, this phenomenon has not been reported for HSPGs on the endothelium, nor has it been substantiated *in vivo* [35]. Glycosaminoglycans have been shown to interfere with antibacterial properties of the antimicrobial cathelicidin, LL-37. The same phenomenon could play a role with heparin. Glycosaminoglycans have been described as playing an important pro-inflammatory role by participating in almost every stage of leukocyte transmigration through the vessel wall. This holds true especially for HSPGs. Endothelial HSPGs facilitate adhesion of leukocytes to the inflamed endothelium by binding to L-selectin expressed by leukocytes. HSPGs also play a role in endothelial transcytosis and subsequent presentation of chemokines such as IL-8, which is important for leukocyte activation and subsequent production of integrins that tighten leukocyte binding to the endothelium [36]. Moreover, HSPGs facilitate leukocyte transmigration through the vessel wall, possibly by binding proteins that regulate vascular permeability, such as kininogen. To cross the endothelial basement membrane, leukocytes secrete various proteases such as heparanase, which releases growth factors that are normally associated with basement membrane HSPGs. These growth factors play a role in the establishment of an acute and chronic inflammatory reaction by modulating angiogenesis and tissue remodelling [36].

Recombinant Human Activated Protein C

The efficacy of rhAPC in terms of reducing 28-day mortality is shown in **Table 1** [37]. The initial evidence for a beneficial role of the APC system in septic patients, which was crucial for the licensing of this treatment in the USA and in Europe, came from two randomized controlled trials. First, in a dose-ranging clinical trial, 131 patients with sepsis were enrolled [38]. Included patients received rhAPC by continuous infusion at doses ranging from 12 μg/kg/h to 30 μg/kg/h, or placebo. Based on D-dimer plasma levels, the optimal dose of rhAPC was determined to be 24 μg/kg/hr. There was a clear trend towards a lower mortality in patients receiving higher doses of rhAPC. In these patients, a 40 % reduction in the relative risk of mortality was shown, although this was not statistically significant (due to the size of the

Table 1. Efficacy (28-day mortality) and safety of recombinant human activated protein C (rhAPC) in adult patients with severe sepsis.

	N	28-day mortality	Severe bleeding	Intracranial hemorrhage
Bernard et al. (phase II) [38]	131	28.9 % in rh-APC group vs 24.1 % in placebo group ($p = 0.27$)	4.0 % in rh-APC group vs 5.0 % in placebo group ($p = 0.99$)	none
PROWESS (phase III) [39]	1690	24.7 % in rhAPC group vs 30.8 % in placebo group ($p = 0.005$)	3.5 % in rhAPC group vs 2.0 % in placebo group ($p = 0.06$)	0.2 % in rhAPC group vs 0 % in placebo group (NS)
ADDRESS (phase III in patients with relatively low disease severity) [41]	2640	18.5 % in rhAPC group vs 17.0 % in placebo group (NS)	3.9 % in rhAPC group vs 2.2 % in placebo group ($p = 0.01$)	0.5 % in rhAPC group vs 0.4 % in placebo group (NS)
XPRESS (adjunctive heparin in patients receiving rhAPC for severe sepsis) [42]	1994	28.3 % in heparin group vs 31.9 % in placebo group ($p = 0.08$)	5.2 % in heparin group vs 3.9 % in placebo group ($p = 0.16$)	1.0 % in heparin group vs 0.7 % in placebo group (NS)
ENHANCE (open label, all patients received rhAPC) [45]	2378	25.3 %	6.5 %	1.5 %

NS = not significant

trial). The potential benefit of rhAPC was also shown for duration of mechanical ventilation, shock and length of ICU stay as well as for days free of systemic inflammatory response.

Based on these encouraging results in the phase II trial, a large multicenter efficacy trial was performed (the recombinant human PROtein C Worldwide Evaluation in Severe Sepsis, PROWESS study) [39]. This trial was prematurely stopped at the second interim analysis because of a significant reduction in mortality in the rhAPC-treated patients. A total of 1728 patients were included and randomized in this study, of whom 1690 were eligible for analysis. Of these patients, 840 were randomized to receive rhAPC at a dose of 24 μg/kg/h for 96 hours and 850 patients received placebo. Mortality was 24.7 % in the rhAPC group compared with 30.8 % in the placebo group (relative risk reduction 19.4 %, 95 % confidence interval, 6.6 to 30.5). A later analysis of the mortality of the patients in this trial one year after inclusion still showed a statistically significant benefit in rhAPC-treated patients. Interestingly, patients who could be classified as having sepsis in combination with DIC, according to the ISTH DIC scoring system, had a relatively greater benefit from rhAPC treatment than patients who did not have overt DIC [40]. The relative risk reduction in mortality of patients with sepsis and DIC who received rhAPC was 38 %, in comparison with a relative risk reduction of 18 % in patients with sepsis who did not have DIC. This seems to underscore the importance of coagulation derangement in the pathogenesis of sepsis and the point of impact that restoration of microvascular anticoagulant pathways may provide in the treatment of sepsis.

An extensive analysis of subgroups in this phase III clinical trial was performed. Essentially, administration of rhAPC proved to be of benefit in virtually all defined subgroups, including age, type and site of infection. The efficacy of APC was most prominent in the subgroups of patients with a relatively high disease severity, whereas in patients with a lower disease severity the drug appeared less effective. To prospectively analyze this issue, the Administration of Drotrecogin alfa (activated) in Early Severe Sepsis (ADDRESS) trial was performed in 2640 patients with sepsis and a relatively low disease severity (defined as a single sepsis-associated organ failure or an APACHE II score below 25) [41]. The initial sample size of this trial was 11,400 patients; however, the trial was prematurely stopped after a second interim analysis according to the predefined futility rules. The 28-day mortality rates were 18.5 % in the rhAPC group and 17.0 % in the placebo group ($p = 0.34$). Disappointingly, in patients with two or more organ failures (who had entered the trial because of an APACHE score less than 25), the 28-day mortality rate was not lower in patients treated with rhAPC compared with those who received placebo (20.7 % versus 21.9 %, not significant), although a direct comparison with PROWESS is not possible due to many differences in the patient populations between the two studies [37]. Nevertheless, based on the ADDRESS study, treatment with rhAPC seems not to be indicated in patients with sepsis and a relatively low disease severity.

Another issue that was raised in PROWESS was the potential interaction of APC with heparin. Patients treated with the combination of rhAPC and heparin appeared to have a higher mortality, although it was quite clear that since the decision to administer heparin was not random, this result may have been strongly biased. Nevertheless, the Food and Drug Administration (FDA) requested an additional trial to evaluate the concomitant administration of rhAPC and heparin. The Xigris and Prophylactic HepaRin Evaluation in Severe Sepsis (XPRESS) trial enrolled 1994 patients with severe sepsis (and two or more organ failures) who all received rhAPC and were subsequently randomized to unfractionated heparin, low molecular weight heparin or placebo [42]. The study was designed as a non-inferiority trial with 28-day mortality as its primary endpoint. The results of the trial did not meet the non-inferiority assumption but showed a small survival advantage in the group of patients treated with rhAPC and heparin (28.3 % versus 31.9 % in the group treated with rhAPC and placebo, $p = 0.08$). Interestingly, a subgroup analysis of this study demonstrated that the difference between the two groups was mainly driven by the subset of patients who were already receiving heparin before entering the trial. In fact, patients who were randomized to placebo actually stopped their heparin and in this group there was an excess mortality. The mechanism underlying this result is not entirely clear; however, it has been suggested that cessation of heparin is associated with a rebound hypercoagulability. Overall, the incidence of ischemic stroke was significantly smaller in the heparin group than in the placebo group (0.5 % versus 1.8 %, $p = 0.01$). The conclusion from this trial was that adding prophylactic heparin to treatment with rhAPC is not harmful but that heparin administration in patients with severe sepsis should not be interrupted or only with caution.

Currently, there is ample debate on the role of rhAPC in the treatment of sepsis. Clearly, the pivotal phase III clinical trial (PROWESS) showed a reduction in 28-day mortality and this study formed the basis for the approval of this therapy by regulatory agencies in the USA, Europe, and other parts of the world. Consequently, the use of rhAPC in patients with severe sepsis and multiple organ failure, and in the absence of major risk factors for bleeding, has been advocated in guidelines for the

treatment of sepsis. However, meta-analyses of published literature conclude that the basis for treatment with rhAPC, even in patients with a high disease severity, is not very strong or even insufficient [43]. The series of negative trials in specific populations of patients with severe sepsis (as reviewed above) has added to the skepticism regarding the use of rhAPC. In view of these equivocal results many clinicians believe that one placebo-controlled trial is not enough to support the use of this agent in patients with severe sepsis, whereas, in contrast, others believe it is ethically not justified to withhold rhAPC from patients with severe sepsis and multiple organ failure and to expose these patients to placebo. Moreover, there is uncertainty regarding the bleeding risk associated with rhAPC administration in patients with severe sepsis. The bleeding rate in the clinical trials seems to be acceptable [44], but it may be that in the 'real world' the risk of bleeding, including intracranial bleeding, is higher [45]. Finally, the very high cost of rhAPC may have added to the critical attitude of many clinicians towards use of this treatment; indeed, implementation of this strategy was shown to be related to the rate of reimbursement of this expensive agent [46]. Taken together, there is considerable uncertainty and doubt surrounding the exact place of rhAPC in patients with severe sepsis and this equipoise has convinced the manufacturer of this agent to start a new placebo-controlled trial in patients with severe sepsis and septic shock [47]. Certainly, the result of this new trial will be helpful to more precisely assess the effectiveness and safety of APC in the treatment of patients with severe sepsis.

Soluble Thrombomodulin

Recombinant human soluble thrombomodulin binds to thrombin to form a complex that inactivates thrombin's coagulant activity and activates protein C, and, thus, is a potential drug for the treatment of patients with DIC. Several preclinical studies in experimental sepsis models have shown that soluble thrombomodulin is capable of improving the derangement of coagulation and my restore organ dysfunction [2]. In a phase III randomized double-blind clinical trial in patients with DIC, administration of soluble thrombomodulin had a significantly better effect on bleeding manifestations and coagulation parameters than heparin, but the mortality rate at 28 days was similar in the two study groups [48]. Currently, soluble thrombomodulin is being evaluated in a phase II/III clinical study in patients with sepsis and DIC.

Recombinant Tissue Factor Pathway Inhibitor

rTFPI has been extensively tested. An increase in levels of TFPI was successful in reducing mortality in experimental and initial clinical studies of severe systemic inflammation [13, 49], although no beneficial effect on survival was observed in a large study in patients with severe sepsis [50]. Recently, the efficacy and safety of recombinant TFPI was investigated in patients with severe pneumonia and organ dysfunction in a large multicenter randomized-controlled trial. Preliminary presentation of the data indicated that there was no survival benefit of TFPI over placebo. In the same trial, the safety of TFPI was established as this treatment was not associated with serious adverse events or major bleeding complications.

Conclusion

Systemic inflammation, such as in sepsis, will invariably lead to activation of the coagulation system but components of the coagulation system may markedly modulate the inflammatory response. Increasing evidence points to extensive cross-talk between the two systems at various points, with pivotal roles of physiological anticoagulant factors. Restoration of impaired physiological anticoagulant pathways by administration of these agents, as plasma-derived concentrates or recombinant proteins, has theoretically beneficial properties and has demonstrated to be effective in experimental sepsis. Clinical trials in patients with sepsis show variable results; nevertheless, this treatment modality deserves further study to more precisely establish a potential beneficial adjunctive role in the management of sepsis.

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X Anemia and Blood Transfusions

Venous Oxygen Saturation as a Physiologic Transfusion Trigger

B. Vallet, E. Robin, and G. Lebuffe

Introduction

Venous oxygen saturation is a clinical tool which integrates the whole body oxygen uptake-to-delivery (VO_2-DO_2) relationship. In the clinical setting, in the absence of pulmonary artery catheter (PAC)-derived mixed venous oxygen saturation (SvO_2), the central venous oxygen saturation ($ScvO_2$) is increasingly being used as a reasonably accurate surrogate [1]. Central venous catheters (CVCs) are simpler to insert, and generally safer and cheaper than PACs. The CVC allows sampling of blood for measurement of $ScvO_2$ or even continuous monitoring if an oximetry catheter is being used. The normal range for SvO_2 is 68 to 77 % and $ScvO_2$ is considered to be 5 % above these values [2].

A decrease in hemoglobin (Hb, g/dl) is likely to be associated with a decrease in DO_2 when cardiac output (CO) remains unchanged, since $DO_2 = CO \times CaO_2$, where CaO_2 is arterial oxygen content and is $\approx Hb \times SaO_2 \times 1.34$ (where SaO_2 is the arterial oxygen saturation in %; and 1.34 is the oxygen-carrying capacity of Hb in mlO_2/g Hb), when one ignores the negligible oxygen not bound to Hb [1]. A decrease in Hb is one of the four determinants responsible for a decrease in SvO_2 (or $ScvO_2$), alone or in combination with hypoxemia (decrease in SaO_2), an increase in VO_2 without a concomitant increase in DO_2, or a fall in cardiac output.

When DO_2 decreases, VO_2 is maintained (at least initially) by an increase in oxygen extraction (O_2ER) since $O_2ER = VO_2/DO_2$. As $VO_2 \approx (SaO_2 - SvO_2) \times (Hb \times 1.34 \times CO)$ and $DO_2 \approx SaO_2 \times Hb \times 1.34 \times CO$, O_2ER and SvO_2 are thus linked by a simple equation: $O_2ER \approx (SaO_2 - SvO_2)/SaO_2$ or even simpler: $O_2ER \approx 1 - SvO_2$. Assuming $SaO_2 = 1$ [3], if SvO_2 is 40 %, then O_2ER is 60 %.

Because it integrates Hb, cardiac output, VO_2 and SaO_2, the venous oxygen saturation therefore helps to assess the VO_2-DO_2 relationship and tolerance to anemia during blood loss.

Venous Oxygen Saturation as a Physiologic Transfusion Trigger

When DO_2 decreases beyond a certain threshold, it induces a decrease in VO_2. This point is known as the critical DO_2 (DO_2crit), below which there is a state of VO_2-DO_2 dependency also called tissue dysoxia. In humans, dysoxia is usually present when SvO_2 falls below a critical 40 – 50 % (SvO_2crit); this may, however, also occur at higher levels of SvO_2 when O_2ER is impaired. Usually efforts in correcting cardiac output (by fluids or inotropes), and/or Hb and/or SaO_2 and/or VO_2 must target a return of SvO_2 ($ScvO_2$) from 50 to 65 – 70 % [4]. In sedated critically ill patients in

whom life support was discontinued, the DO_2crit was found to be approximately 3.8 to 4.5 mlO_2/kg/min for a VO_2 of about 2.4 mlO_2/g/min; O_2ER reached an O_2ERcrit of 60 % [5] with SvO_2crit being ≈ 40 %.

In a landmark study by Rivers et al. [6], patients admitted to an emergency department with severe sepsis and septic shock were randomized to standard therapy (aiming for a central venous pressure [CVP] of 8 – 12 mmHg, mean arterial pressure (MAP) ≥ 65 mmHg, and urine output ≥ 0.5 ml/kg/h) or to early goal-directed therapy where, in addition to the previous parameters, an $ScvO_2$ of at least 70 % was targeted by optimizing fluid administration, keeping hematocrit ≥ 30 %, and/or giving dobutamine to a maximum of 20 μg/kg/min. The initial $ScvO_2$ in both groups was low (49 ± 12 %), suggesting a hypodynamic condition before resuscitation was started. From the 1st to the 7th hour, the amount of fluid received was significantly larger in the early goal-directed therapy patients (≈ 5,000 ml vs 3,500 ml, $p < 0.001$), fewer patients in the early goal-directed therapy group received vasopressors (27.4 vs 30.3 %, p = NS), and significantly more patients were treated with dobutamine (13.7 vs 0.8 %, $p < 0.001$). It is noticeable that the number of patients receiving red blood cells (RBCs) was significantly larger in the early goal-directed therapy group than in the control group (64.1 vs 18.5 %) suggesting that the strategy of targeting a $ScvO_2$ of at least 70 % was associated with more decisions to transfuse once fluid, vasopressors, and dobutamine had been titrated to improve tissue oxygenation. In the follow-up period between the 7th and the 72nd hour, mean $ScvO_2$ was higher, mean arterial pH was higher, and plasma lactate levels and base excess were lower in patients who received early goal-directed therapy. Organ failure score and mortality were significantly different in patients receiving standard therapy compared to early goal-directed therapy patients. This was the first study to demonstrate that initiation of early goal-directed therapy to achieve an adequate level of tissue oxygenation by DO_2 (as judged by $ScvO_2$ monitoring) could significantly reduce mortality.

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In a prospective observational study [7], we tested how well the $ScvO_2$ corresponded to the French recommendations for blood transfusion and to the anesthesiologist's decision to transfuse. The French recommendations for blood transfusion were presented during a consensus conference organized in 2003 by the French Society of Intensive Care Medicine (Société de Réanimation de Langue Française, SRLF) [8]. These recommendations are based on plasma Hb concentration and associated clinical state (**Table 1**), and apart from in cardiac and septic patients, the threshold Hb value for blood transfusion is 7 g/dl. Sixty high risk surgical patients in whom

Table 1. The French recommendations for blood transfusion in critically ill patients are based on a recent consensus by the French Society of Intensive Care Medicine (*Société de Réanimation de Langue Française*; SRLF) using threshold values for hemoglobin (Hb) together with the clinical context to indicate blood transfusion [8].

Threshold value of Hb (g/dl)	Clinical context
10	• Acute coronary syndrome
9	• Ischemic heart disease • Stable heart failure
8	• Age > 75 • Severe sepsis
7	• Others

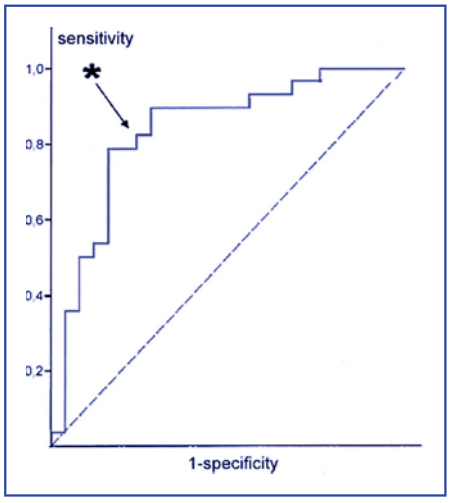

Fig. 1. ROC curve analysis illustrating the usefulness of $ScvO_2$ measurement before blood transfusion in order to predict a minimal 5 % increase in $ScvO_2$ after BT. The threshold value for $ScvO_2$ with the best sensitivity and best specificity was 69.5 % (*sensitivity: 82 %, specificity: 76 %; area under the curve: 0.831 $\pm$ 0.059). Adapted from [7] with permission

the need for a blood transfusion was discussed postoperatively were included in the study [7]. They were eligible for study inclusion if they were hemodynamically stable and equipped with a CVC. The decision to transfuse was taken by the anesthesiologist in charge of the patient. The anesthesiologist was aware of the SRLF recommendations; if requested, he/she was provided with the $ScvO_2$ value that was obtained at the same time as the blood was sampled for the Hb concentration. The following parameters were registered: Age, a history of cardiovascular disease, presence of sepsis, number of blood units transfused, agreement with the SRLF recommendations. A decision to transfuse was made in 53 of the 60 general and urologic surgical patients. $ScvO_2$ and Hb were measured before and after blood transfusion, together with hemodynamic parameters (heart rate, systolic arterial pressure). Patients were retrospectively divided into two groups according to the $ScvO_2$ before blood transfusion ($<$ or $\geq$ 70 %); each of these groups was further divided into two groups according to agreement or not with the SRLF recommendations for blood transfusion. The $ScvO_2$ threshold value of 69.5 % (sensitivity 82 %; specificity 76 %) was validated with a receiver operator characteristic (ROC) curve analysis (**Fig. 1**).

Overall, demographic characteristics were similar (age, weight, number of blood units transfused) among the groups. Blood transfusion provided a significant and approximately similar increase in hemoglobin concentration for all patients in the four groups but the $ScvO_2$ value increased significantly only in patients with $ScvO_2$ $<$ 70 % before blood transfusion (**Fig. 2** and **Table 2**). The heart rate and systolic arterial pressure did not help in the decision to transfuse.

The conclusions of this observational study were as follows: 1) Twenty of the 53 patients (37.7 %) received a blood transfusion against SRLF recommendations; 2) thirteen of these 20 patients (65 %) had an $ScvO_2$ $<$ 70 % and nevertheless seemed to benefit from the blood transfusion (according to the VO_2/DO_2 relationship), and one may speculate that the fact that they did not comply with the SRLF recommendations for blood transfusion could have contributed to a "lack of blood transfusion" in these patients; indeed, according to the $ScvO_2$ (which remained largely below 70 %) blood transfusion may even have been insufficient (n = 2 blood units) in this

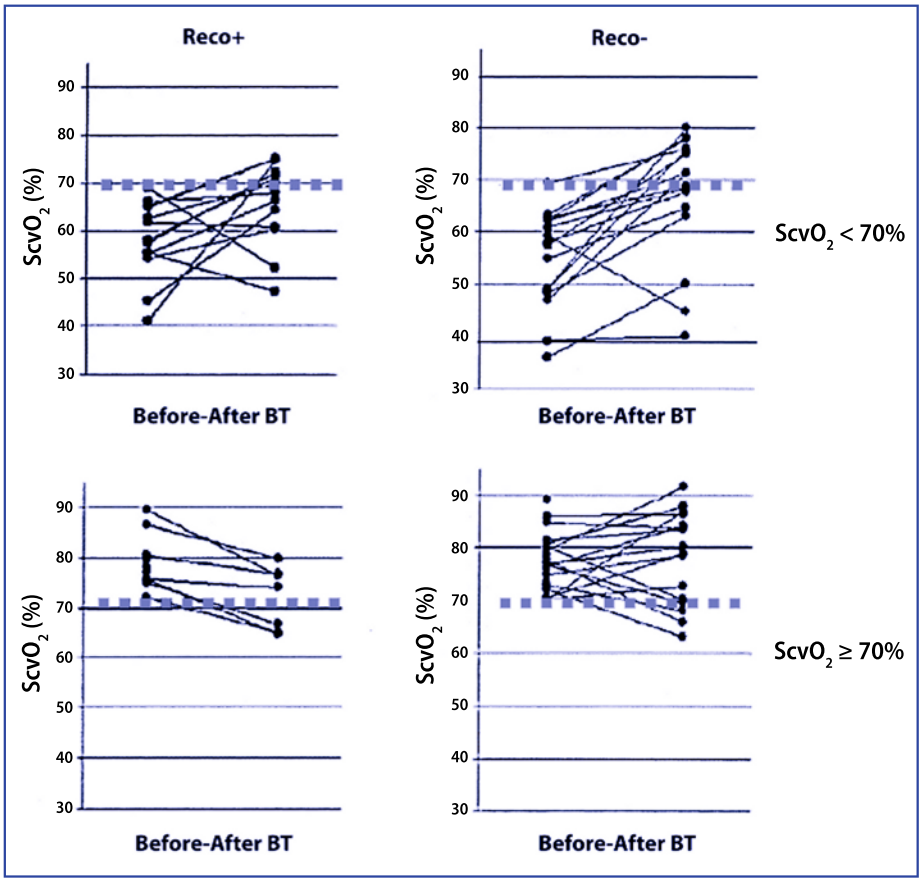

Fig. 2. Individual evolutions in $ScvO_2$ before and after blood transfusion (BT) according to agreement (Reco+) or not (Reco-) with the SRLF recommendations for transfusion and according to the $ScvO_2$ before transfusion (< or ≥ 70 %). Adapted from [7] with permission

sub-group; 4) 54.5 % of the patients (18/33) met the SRLF recommendation had an $ScvO_2 \geq 70$ % and received a blood transfusion although VO_2/DO_2 may have been adequate; one may speculate that transfusion in these patients could have contributed to an "excess of blood transfusion".

Following the study by Rivers et al. [6] and our own observations [7] we can conclude that $ScvO_2$ appears to be an interesting parameter to help with transfusion decisions in hemodynamically unstable patients with severe sepsis or in stable high-risk surgical patients equipped with a CVC. $ScvO_2$ can be proposed as a simple and universal physiologic transfusion trigger. This suggestion merits a controlled randomized study in which patients would be separated into two treatment groups: 1) A control group in which the decision to transfuse would be made according to Hb threshold values (similar to those presented by the SRLF); 2) an $ScvO_2$ goal-directed group in which the decision to transfuse would be made according to an $ScvO_2$ value < 70 % as soon as the Hb value was less than 10 g/dl (hematocrit < 30 %) providing that the CVP was 8 to 12 mmHg.

Table 2. Central venous O_2 saturation ($ScvO_2$), hemoglobin (Hb), heart rate (HR) and systolic arterial pressure (SAP) values (median [CI 95 %]) in 53 hemodynamically stable postoperative patients who received blood transfusion (BT), divided into two groups according to their $ScvO_2$ before blood transfusion (< or ≥ 70 %); and then into four groups according to agreement or not with the SRLF recommendations for transfusion.

	$ScvO_2$ < 70 %		$ScvO_2$ ≥ 70 %		
SRLF recommendations	Yes (n = 15)	No (n = 13)	Yes (n = 18)	No (n = 7)	Kruskal-Wallis test (p <.05)
$ScvO_2$ preBT	57.4 [48.2 – 62.0]	58.0 [55.3 – 65.0]	76.9 [72.0 – 80.8]	75.7 [75.0 – 86.4]	p < 0.001
$ScvO_2$ postBT	68.7* [63.0 – 75.6]	67.8* [60.7 – 72.0]	78.7 [70.0 – 84.2]	74,0* [65.0 – 76.7]	p < 0.01
Hb preBT	7.4 [7.1 – 7.9]	7.8 [7.4 – 8.7]	7.5 [7.3 – 8.1]	8.1 [7.5 – 8.2]	ns
Hb postBT	9.4** [8.7 – 9.7]	10.0** [9.4 – 10.6]	10.1** [9.3 – 10.6]	9.8* [9.4 – 10.7]	ns
HR preBT	88 [78 – 90]	96 [93 – 120]	92 [85 – 105]	95 [81 – 112]	ns
HR postBT	92 [84 – 97]	95 [89 – 100]	89 [78 – 104]	96 [78 – 100]	ns
SAP preBT	118 [101 – 141]	130 [120 – 150]	128 [114 – 150]	130 [124 – 151]	ns
SAP postBT	133 [119 – 140]	120 [106 – 140]	141* [128 – 161]	140* [133 – 175]	p = 0.047

Ns: non-significant; * p < 0.05; **p < 0.01; Wilcoxon test for values before (preBT) vs after transfusion (postBT). Adapted from [7]

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The Concept of Physiologic Transfusion Trigger

In an 84-year-old male Jehovah's Witness undergoing profound hemodilution, the DO_2crit was 4.9 mlO_2/kg/min for a VO_2 of about 2.4 mlO_2/kg/min; the Hb value at the DO_2crit was 3.9 g/dl [9]. This Hb value can be defined as the critical Hb value. Consistent with these results, in young, healthy, and conscious (which means higher VO_2) volunteers undergoing acute hemodilution with 5 % albumin and autologous plasma, DO_2crit was found to be less than 7.3 mlO_2/kg/min for a VO_2 of 3.4 mlO_2/kg/min [10] and an Hb value of 4.8 g/dl. The same investigators studied healthy resting humans to test whether acute isovolemic reduction of blood hemoglobin concentration to 5 g/dl would produce an imbalance in myocardial oxygen supply and demand, resulting in myocardial ischemia [11]. Heart rate increased from 63 ± 11 (baseline measured before hemodilution began) to 94 ± 14 beats/min (a mean increase of 51 ± 27 %; p < 0.0001), whereas MAP decreased from 87 ± 10 to 76 ± 11 mmHg (a mean decrease of 12 ± 13 %; p < 0.0001), mean diastolic blood pressure decreased from 67 ± 10 to 56 ± 10 mmHg (a mean decrease of 15 ± 16 %; p < 0.0001), and mean systolic blood pressure decreased from 131 ± 15 to 121 ± 16 mmHg (a mean decrease of 7 ± 11 %; p = 0.0001). Electrocardiographic (EKG) changes were monitored continuously using a Holter EKG recorder for detec-

tion of myocardial ischemia. During hemodilution, transient, reversible ST-segment depression developed in three asymptomatic subjects at hemoglobin concentrations of 5 g/dl. The subjects who had EKG ST-segment changes had significantly higher maximum heart rates (110 to 140 beats/min) than those without EKG changes, despite having similar baseline values. The higher heart rates that developed during hemodilution may have contributed to the development of an imbalance between myocardial oxygen supply and demand resulting in EKG evidence of myocardial ischemia. An approach to the myocardial oxygen balance is offered by the product systolic arterial pressure × heart rate which should remain below 12,000. For heart rate = 110 beats/min, if systolic arterial pressure is 120 mmHg, systolic arterial pressure × heart rate = 13,200 and may be considered too high for the myocardial VO_2.

In 20 patients older than 65 years and free from known cardiovascular disease, Hb was decreased from 11.6 ± 0.4 to 8.8 ± 0.3 g/dl [12]. With stable filling pressures, cardiac output increased from 2.02 ± 0.11 to 2.19 ± 0.10 l/min/m^2 ($p < 0.05$) while systemic vascular resistance (SVR) decreased from 1796 ± 136 to 1568 ± 126 dynes/s/cm^5 ($p < 0.05$) and O_2ER increased from 28.0 ± 0.9 to 33.0 ± 0.8 % ($p < 0.05$) resulting in stable VO_2 during hemodilution. While no alterations in ST segments were observed in lead II, ST segment deviation became slightly less negative in lead V_5 during hemodilution, from -0.03 ± 0.01 to -0.02 ± 0.01mV ($p < 0.05$). The authors concluded that isovolemic hemodilution to a hemoglobin value of about 8.8 g/dl was the limit that could be tolerated in these patients [12].

In 60 patients with coronary artery disease receiving chronic beta-adrenergic blocker treatment and scheduled for coronary artery bypass graft (CABG) surgery, Hb was decreased from 12.6 ± 0.2 to 9.9 ± 0.2 g/dl ($p < 0.05$) [13]. With stable filling pressures, cardiac output increased from 2.05 ± 0.05 to 2.27 ± 0.05 l/min/m^2 ($p < 0.05$) and O_2ER from 27.4 ± 0.6 to 31.2 ± 0.7 % ($p < 0.05$), resulting in stable VO_2. No alterations in ST segments were observed in leads II and V_5 during hemodilution. Individual increases in cardiac index and O_2ER were not linearly related to age or left ventricular ejection fraction [13].

Healthy young volunteers were also tested with verbal memory and standard computerized neuropsychologic tests before and twice after acute isovolemic reduction of their Hb concentration to 5.7 ± 0.3 g/dl [14]. Heart rate, MAP, and self-assessed sense of energy were recorded at the time of each test. Reaction time for Digit-Symbol Substitution Test (DSST) increased, delayed memory was degraded, MAP and energy level decreased, and heart rate increased (all $p < 0.05$). Increasing PaO_2 to 406 ± 47 mmHg reversed the DSST result and the delayed memory changes to values not different from those at the baseline Hb concentration of 12.7 ± 1.0 g/dl, and decreased heart rate ($p < 0.05$) although MAP and energy level changes were not altered with increased PaO_2 during acute anemia. In that study, the authors confirmed that acute isovolemic anemia subtly slows human reaction time, degrades memory, increases heart rate, and decreases energy levels [14].

Subsequent studies identified the cause of the observed cognitive function deficits in impaired central processing as quantified by measurement of the P300 latency. The P300 response was significantly prolonged when unmedicated healthy volunteers were hemodiluted from hemoglobin concentrations of 12.4 ± 1.3 to 5.1 ± 0.2 g/dl [15]. The increased P300 latencies could be reversed to values not significantly different from baseline when inspired oxygen concentration was increased from 21 (room air) to 100 %. These results suggest that P300 latency is a variable that is sensitive enough to predict subtle changes in cognitive function. Accordingly, increase in the P300 latency above a certain threshold may serve as a monitor of inadequate

cerebral oxygenation and as an organ-specific transfusion trigger in the future. Spahn and Madjdpour recently commented [16] that Weiskopf et al. [15, 17] have opened a "window to the brain" with respect to monitoring the adequacy of cerebral oxygenation during acute anemia.

These observations and results clearly indicate that there is no 'universal' Hb threshold that could serve as a reliable transfusion trigger and that transfusion guidelines should take into account the patient's individual ability to tolerate and to compensate for the acute decrease in Hb concentration. Useful transfusion triggers should rather consider signs of inadequate tissue oxygenation that may occur at various hemoglobin concentrations depending on the patient's underlying disease(s) [18].

Conclusion

Physiologic transfusion triggers should progressively replace arbitrary Hb-based transfusion triggers [19]. The same conclusions were drawn by Orlov et al. in a recent trial using a global oxygenation parameter for guiding RBC transfusion in cardiac surgery [20]. The use of goal-directed erythrocyte transfusions should render the management of allogeneic red cell use more efficient and should help: 1) in saving blood and avoiding unwanted adverse effects; and 2) in promoting and optimizing the adequacy of this life-saving treatment [16]. These 'physiologic' transfusion triggers can be based on signs and symptoms of impaired global (lactate, SvO_2 or $ScvO_2$) or, even better, regional tissue (EKG ST-segment, DSST or P300 latency) oxygenation; they do, however, have to include two important simple hemodynamic targets: heart rate and MAP or systolic arterial pressure.

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Tissue Protective Activities of Erythropoietin

N.S.A. Patel, M.M. Yaqoob, and C. Thiemermann

Introduction

Erythropoietin (EPO) is a 165 amino acid glycoprotein hormone (30.4 kDa) member of the type 1 cytokine superfamily that is produced primarily by renal cortical and outer medullary type 1 fibroblasts [1] in response to tissue hypoxia under the control of the oxygen-sensitive transcription factor hypoxia-inducible factor-1 (HIF-1). EPO binds to a preformed EPO receptor homodimer $(EPOR)_2$ present on the cell membrane of erythrocyte progenitors. On activation of $(EPOR)_2$ a molecular cascade begins with the phosphorylation of Janus tyrosine kinase 2, which ultimately results in inhibition of programmed cell death, principally involving Akt and the *Bcl-2* gene family, resulting in the survival and maturation of erythroid progenitor cells to erythrocytes [2]. The overall effect is a compensatory adaptation to tissue hypoxia by enhancing the oxygen-carrying capacity of the blood [3], and thus may be therapeutically useful for the treatment of anemia associated with chronic kidney disease or chemotherapy [4–6].

Over the last two decades, our understanding of the actions of EPO has shifted from a belief that the hormone act exclusively on erythroid progenitor cells to the knowledge that this agent exerts significant protection in conditions such as hemorrhagic shock and ischemia/reperfusion injury [7–12]. Ischemia/reperfusion injury is the principal cause of acute kidney injury (AKI), a condition that affects about 5 % of all hospitalized patients. There is no specific therapy for AKI and it is associated with high mortality despite significant advances in preventive strategies and support measures. Many clinical settings are associated with ischemia/reperfusion injury. These include surgical procedures (e.g., bypass surgery), transplantation, trauma-hemorrhage and septic shock, among others. From a pathophysiologic perspective, ischemia and associated tissue hypoxia lead to cell death, which is mediated by fundamental alterations in cellular homeostasis. While no single factor has been identified as the critical mediator of cell death, depletion of cellular energy stores plays a major role [13]. Re-establishment of blood flow to an organ following ischemia (reperfusion) is essential for the recovery and survival of the previously ischemic tissue. However, reperfusion itself is often harmful, as highly reactive molecules are produced that add injury to the previously ischemic organ (termed reperfusion injury). Furthermore, reperfusion can also result in systemic alterations caused by the release/generation of vasoactive and/or pro-inflammatory mediators and cytokines (e.g., tumor necrosis factor [TNF], high mobility group box protein [HMGB-1]) within the previously ischemic tissue [14]. These provoke a systemic inflammatory response syndrome (SIRS) which may cause additional, remote organ injury (e.g., acute respiratory distress syndrome [ARDS]) [15, 16]. The purpose of this

chapter is to review the experimental and clinical evidence for a tissue protective benefit of EPO following tissue injury and the potential mechanisms of these protective actions.

EPO and Tissue Protection

An ischemic insult within the central nervous system (CNS) was the first model used to demonstrate the powerful tissue protective properties of EPO. EPO (100 pg/ml) was used experimentally to protect cultured hippocampal and cerebral cortical neurons from glutamate neurotoxicity [17] in a dose-dependent manner. This protection was completely reversed by co-application of a soluble EPOR capable of binding with EPO. Infusion of EPO into the lateral ventricles of gerbils subjected to occlusion of the common carotid arteries prevented ischemia-induced learning disability and prevented the degeneration of hippocampal CA1 neurons [11]. Similarly, an infusion of soluble EPOR into animals that were only given a mild ischemic insult, that was insufficient to produce any damage by itself, caused CA1 neuronal degeneration. These studies not only indicate that the survival of neurones following an ischemic insult is dependent on the formation of endogenous EPO, but also that exogenous EPO may protect the brain and other tissues against ischemia/reperfusion injury.

In 2004, the expression of EPORs was discovered in the rat heart [18] and a year later in the human heart [19]. Prior to this knowledge, work on the heart was well underway and it had already been shown that EPO can reduce the increase in caspase activation and the subsequent apoptotic cell death caused by hypoxia and oxidative stress in rat ventricular myoblasts (H9C2 cells) [7, 20]. The potential protective role of EPO in a rat model of myocardial infarction has been assessed. The results showed that the administration of EPO (5,000 units/kg i.p. daily for 7 days) attenuated cardiomyocyte loss by approximately 50 % [8]. Similarly, we have reported that the administration of low doses of EPO (300 units/kg i.v.) acutely upon reperfusion reduced the infarct size caused by coronary occlusion and reperfusion in the rat [7]. These observations suggest that there is a potential therapeutic role for EPO in the treatment of myocardial ischemia and infarction, as well as in other organs, by preventing apoptosis and attenuating post-infarct deterioration in hemodynamic function.

Although it had been recognized for many years that EPO was produced in the adult kidney, it was not until 1999 that the EPOR was reported to be expressed in tubular epithelial cells [21]. When rats were subjected to 45 minutes of bilateral renal ischemia there was significant renal dysfunction and damage to the tubular architecture. However, this process was prevented by administration of EPO 24 hours prior to the ischemic insult, which was attributed to attenuation of apoptosis [22]. This beneficial effect of EPO was secondary to inhibition of the activities of caspase-3, -8 and -9 in the proximal tubule [12].

EPO is able to stimulate the proliferation of a number of cells, including endothelial and tubular epithelial cells [23]. Circulating bone marrow-derived endothelial progenitor cells (EPCs) promote vascular reparative processes. EPO has been shown to be a mediator for the mobilization and proliferation of EPCs [24]. We have demonstrated that pre-conditioning mice with EPO (for three days) using a protocol that has been shown to mobilize EPCs [9] was associated with a greater degree of renal protection in a model of renal ischemia/reperfusion injury (30 minutes ischemia and 24 hours reperfusion) when compared to the administration of a single dose of EPO at the time of reperfusion [10].

The evidence in favor of a direct anti-inflammatory effect of EPO is continually increasing, thus reclassifying EPO as a multifunctional tissue-protective cytokine. Data indicate that EPO may be of benefit in certain disease models in which excessive inflammation plays a key role. For instance, a recent study has demonstrated that EPO administration within 2 hours of a lipopolysaccharide (LPS) insult prevented apoptosis, excessive nitric oxide (NO) production, peroxynitrite formation and tissue hypoxia, but without any significant alterations in tissue neutrophilia, nuclear factor-kappa B (NF-κB) activation, or increased serum levels of pro-inflammatory chemokines and HMGB-1 [25]. Much of these data are consistent with previous findings which have shown that EPO prevents the expression of inducible NO synthase (iNOS) induced by interferon (IFN)-γ and LPS [26]. In a model of zymosan-induced non-septic shock, EPO attenuated the degree of systemic injury, and this effect was attributed to a reduced nitrotyrosine and poly (ADP-ribose) polymerase (PARP) staining in the tissue of target organs, and a reduction in the level of circulating cytokines (TNF and interleukin [IL]-1) in the plasma [27]. We have recently reported that the administration of EPO after severe hemorrhage (e.g., on resuscitation) reduced the organ injury and dysfunction caused by hemorrhagic shock. This beneficial effect of EPO was associated with a reduced activation of apoptosis secondary to prevention of the activation of caspases -3, -8 and -9 [7]. Most notably, EPO reduced the joint injury and chronic inflammation in a rat model of type II collagen-induced arthritis. It is likely that the anti-inflammatory effects of EPO in this model of chronic inflammation are – at least in part – secondary to prevention of tissue injury (both apoptosis and necrosis), which in turn would result in the reduced formation of pro-inflammatory cytokines in the circulation [28]. Finally, inflammatory cells [29, 30] have been shown to express EPOR; thus, EPO may play important roles in modulating the inflammatory response to injury.

Many of these observed effects of EPO are dependent on Janus tyrosine kinase 2 activation (mediated by the EPOR) and the translocation of NF-κB [31]. Although, direct anti-inflammatory effects of EPO have not been reported, EPO may reduce the inflammation associated with shock and ischemic injury through a reduction in apoptotic cell death [32].

Tissue Protection and Clinical Trials

Considering all of the above pre-clinical data, recombinant EPO (rhEPO) is an attractive molecule for evaluation in several human disease conditions. The first condition in which rhEPO was evaluated as a potential therapy was human stroke [33]. The aim of this first trial was to determine whether rhEPO would be safe, because of the possibility that it would increase the hematocrit and subsequently increase the likelihood of further transient ischemic attacks. Patients were infused rhEPO at a rate of 33000 units/50 ml/30 min within the first 8 hours after the onset of symptoms, and again 24 and 48 hours later. During the 30-day follow up period, hematocrit, hemoglobin and red blood cell (RBC) counts all remained normal despite such a high infusion of EPO (100000 units over 3 days). This trial clearly demonstrated that rhEPO was well tolerated; moreover, clinical outcome, as determined by neurologic scoring and magnetic resonance imaging (MRI), was improved at 1 month.

Trauma is the leading cause of mortality and morbidity in the Western world, accounting for the highest number of deaths in Americans under the age of 34 [34]. In critically ill trauma patients, anemia is very common. The CRIT study high-

lighted this very well, demonstrating that critically ill trauma patients were more likely to be transfused than critically ill non-trauma patients (55.4 % vs 44.1 %) and received a greater number of blood transfusions (5.8 ± 5.5 units vs 4.6 ± 4.9 units) [35]. This led to the hypothesis that treatment with pharmacological doses of rhEPO might decrease the exposure of patients to allogeneic blood and increase the hemoglobin level in critically ill patients. This was essentially the start point for three randomized studies (EPO-1, -2 and -3) involving 160, 1302 and 1460 patients, respectively. EPO-1 demonstrated a reduction in RBC transfusion that correlated with an increase in hemoglobin concentration in critically ill patients treated with rhEPO [36]. These findings were later confirmed in the second, larger trial, EPO-2 [37]. Interestingly, this second trial demonstrated a survival benefit in critically ill trauma patients randomized to receive rhEPO treatment (at day 29, placebo mortality 8.9 % vs rhEPO 4.1 % and at day 42, placebo mortality 10.4 % vs rhEPO 4.8 %). However, the significance of this was not very clear, as the study did not collect specific information on trauma-specific variables that could have potentially affected patient outcome in the trauma cohort. In the third randomized study (EPO-3), admission groups were prospectively identified and randomization was stratified according to trauma, medicine non-trauma, and surgery non-trauma [38]. Patients were treated with rhEPO (40,000 units/kg) or placebo once a week for 3 weeks. As with the previous study a survival benefit was identified in critically ill trauma patients receiving rhEPO (day 29, placebo mortality 6.7 % vs rhEPO 3.5 %, day 42, placebo mortality 7.2 % vs rhEPO 3.7 %, and day 140, placebo mortality 9.2 % vs rhEPO 6.0 %). However, on this occasion there was no reduction in RBC transfusion in patients treated with rhEPO despite an increase in hemoglobin concentration, which actually resulted in an increase in clinically relevant thrombovascular events (placebo 12.5 % vs rhEPO 16.4 %). The data from EPO-3, therefore suggest that the survival benefit was independent of any transfusion effects [39].

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Erythropoiesis versus Tissue Protection

The signaling cascades initiated by EPOR are very complex and their importance for the cellular effects of EPO described above is not fully understood. Evidence suggests that there are a number of diverse conformations of the EPOR that may potentially activate different intracellular pathways [40]. This led to the speculation that the receptor conformation achieved by EPO and its subsequent activation of signaling pathways may depend entirely on the extracellular binding site of EPO. There has now been considerable interest in the common β chain (β_C) subunit (CD131) and its functional/physical association with EPOR since IL-3 and granulocyte-macrophage colony-stimulating factor (GM-CSF) receptors also share this β_C, and both cytokines enhance EPO-dependent *in vitro* erythropoiesis by primary hematopoietic progenitors and factor-dependent cells [41–43]. Co-immunoprecipitation studies from cells expressing both EPOR and β_C with antibody against β_C and blotted with antibody against EPOR showed that EPOR and β_C co-immunoprecipitated [44, 45]. Subsequent studies have identified that the powerful tissue protective properties of EPO require the expression of CD131 and essentially a low affinity, heterodimeric EPOR-CD131 receptor, which may possibly exert a different signaling cascade than the classical $(EPOR)_2$ [46].

Recently, an 11-amino acid peptide composed of the adjacent amino acids forming the aqueous face of helix B of the EPO molecule (pyroglutamate helix B surface

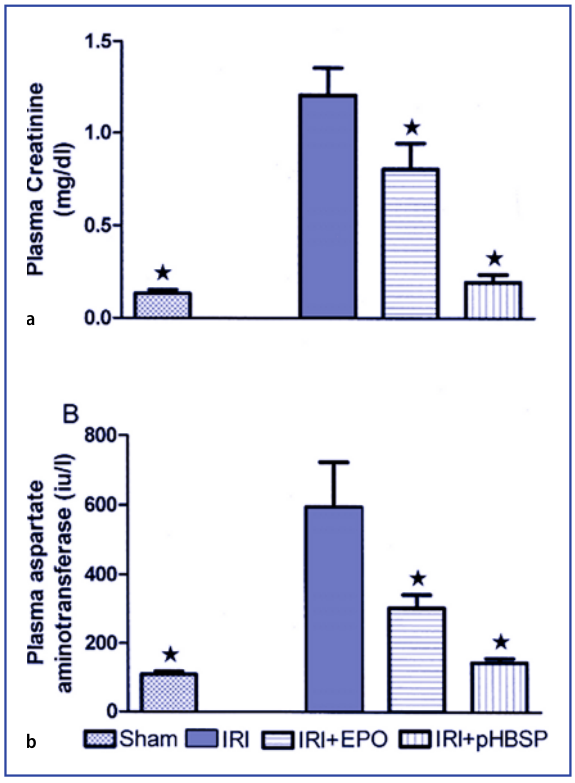

Fig. 1. Renal dysfunction in mice treated with erythropoietin (EPO) or pyroglutamate helix B surface peptide (pHBSP) following 30 minutes ischemia and 24 hours reperfusion. Plasma creatinine (a) and plasma aspartate aminotransferase (b) levels were measured subsequent to sham-operation (Sham) or renal ischemia/reperfusion injury (IRI) and administration of either 1000 units/kg EPO (IRI + EPO) for 3 days prior to ischemia, or 8 nmol/kg pHBSP (IRI + pHBSP) at 1 minute, 6 hours and 12 hours into reperfusion. Renal IRI caused significant renal dysfunction, as measured by plasma creatinine, and significant renal injury, as measured by plasma aspartate aminotransferase, when compared to sham-operated animals. The administration of EPO significantly attenuated both the renal dysfunction and injury when compared to animals subjected to IRI only. However, the administration of pHBSP abolished both the renal dysfunction and injury when compared to animals subjected to IRI only. Data are expressed as means ± SEM for 8–21 observations. *$p < 0.05$ *vs* IRI. (Modified from [10] and [47]).

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peptide [pHBSP]) has been found to be tissue protective, but totally lacking of any potentially adverse activities mediated by $(EPOR)_2$. In a rat model of wound healing, full thickness punch biopsy wounds were placed on the dorsum of rats [47]. Rats that were administered pHBSP (24 nmol/kg subcutaneously) healed faster than saline-treated control rats. Additionally, in a mouse model of ischemia/reperfusion injury with 30 minutes ischemia and 24 hours reperfusion, administration of pHBSP at 1 minute, 6 hours and 12 hours after the onset of reperfusion produced dose-dependent renoprotection, with animals treated with the highest dose (8 nmol/kg i.p.) exhibiting nearly normal serum creatinine levels 24 hours post-injury [47]. **Figure 1** demonstrates that the degree of protection observed with pHBSP was improved compared to previous observations of EPO in this model [10].

Conclusion

The identification/characterization of agents that protect organs from the pathophysiological consequences of ischemia/reperfusion injury (both local tissue injury/dysfunction and secondary systemic effects) is of considerable importance. Such compounds may be given as prophylactic treatment prior to the ischemic episode or

as therapeutic intervention after an ischemic episode. It has been evident for many years that a factor, or factors, must antagonize the powerful tissue destructive effects of ischemia/reperfusion injury and the additional local and systemic injury caused by the release of pro-inflammatory mediators. In the last decade, several key lines of evidence have strongly supported the view that endogenous EPO may play a crucial role in dampening this excessive tissue injury.

Systemic administration of EPO has been found (by us and others) to be active in a large number of animal models associated with ischemia/reperfusion injury, including stroke [11], myocardial infarction [7, 8], AKI [10, 12], hemorrhagic shock [7], and SIRS [27]. However, several large clinical trials of EPO carried out to assess potential utility of normalizing the marginally low hemoglobin concentrations in patients with breast or head and neck cancers unexpectedly found an increase in mortality within the EPO arm due to tumor progression or significant thrombosis [48–50]. Additionally, a surgical trauma trial that showed increased survival in the EPO arm also showed that this was at the expense of a 40 % increase in clinically significant thromboses [38]. Thus, although administration of EPO has potentially valuable tissue protective effects, clinical trials have shown that EPO administration is accompanied by significant adverse complications. Notably, these complications appear to be more frequent with high doses of EPO, such as used in the tissue protection proof-of-concept trials. There is, therefore, a need for novel EPO analogs, lacking erythropoietic activity, for the treatment of ischemia/reperfusion injury.

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XI Renal Disease and Therapy

Doppler-Based Renal Resistive Index: A Comprehensive Review

M. Darmon, D. Schnell, and F. Zeni

Introduction

Renal sonography is performed routinely to assess renal and collecting system morphology. B-mode sonography provides valuable information on anatomic features including kidney size (longitudinal diameter and parenchyma thickness) and appearance (kidney margins and echogenicity of the parenchyma, cortex, medulla, and papillae); presence and degree of hydronephrosis; and presence of stones, calcification, cysts, or solid masses. However, B-mode sonography does not evaluate kidney function. Renal Doppler, in contrast, helps to assess renal perfusion and renal function of native or transplanted kidneys (**Fig. 1**). Renal Doppler is valuable for

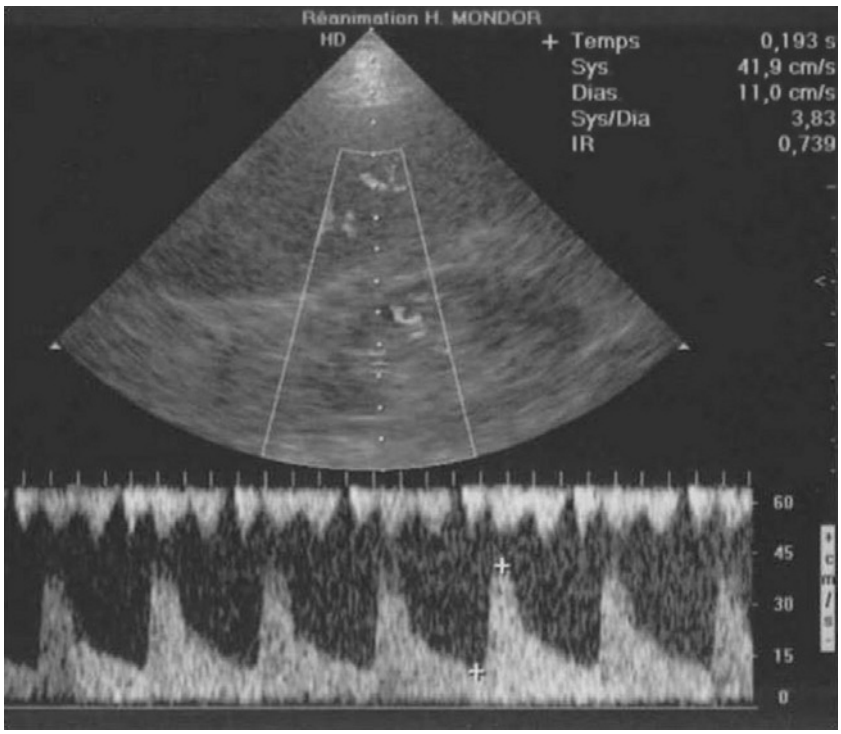

Fig. 1. Example of an intrarenal arterial Doppler waveform

assessing large arterial or venous abnormalities and has been suggested for evaluating changes in intrarenal perfusion due to diseases of the renal parenchyma [1–5]. The Doppler-based renal resistive index is a recently suggested tool for assessing changes in renal perfusion in critically ill patients [6–8] and for predicting acute kidney injury (AKI) in patients with severe sepsis [9]. However, many factors influence the renal resistive index and should be taken into account when interpreting resistive index values in critically ill patients [10].

This purpose of this chapter is to describe the technical requirements for Doppler assessment of the small intrarenal vessels, factors influencing the arterial Doppler waveform, suggested applications, and controversies.

Technique

Duplex Doppler assessment of the small intrarenal vessels, although not technically difficult, must be performed with great care in order to obtain high-quality data [11]. In most studies of renal Doppler, 2- to 5-MHz transducers were used [11]. Gray-scale sonography allows location of the kidneys and detection of signs of chronic renal damage. Although assessment of both kidneys is preferable, the right kidney is generally more accessible, and it may be necessary to limit the investigation to this side [12]. Color-Doppler or power-Doppler sonography allows vessel localization and a semi-quantitative evaluation of renal perfusion (**Table 1**) [12]. The arcuate arteries (at the cortico-medullary junction) or interlobar arteries (adjacent to the medullary pyramids) are then insonated with pulsed wave Doppler using a 2- to 5-mm Doppler gate [11]. The waveforms should be optimized for the measurements using the lowest pulse repetition frequency without aliasing (to maximize waveform size), the highest gain without obscuring background noise, and the lowest wall filter [11]. A spectrum is considered optimal if three to five consecutive similar-appearing waveforms are noted [11].

To characterize the intrarenal Doppler waveform, most investigators have used the resistive index (or Pourcelot Index). Three to five reproducible waveforms are obtained, and resistive indexes from these waveforms are averaged to compute the mean resistive index for each kidney. This easily calculated parameter is defined as:

$$\text{Resistive index} = [\text{peak systolic shift} - \text{minimum diastolic shift}]/\text{peak systolic shift}$$

Resistive indexes can, therefore, range from 0 to 1. The resistive index is normally < 0.70 [11]. In several studies, the mean resistive index (± SD) in healthy subjects ranged from 0.58 (± 0.05) to 0.64 (± 0.04) [5, 13, 14]. The normal resistive index range may be age dependent. Thus, resistive index values greater than 0.70 have been described in healthy children younger than 4 years of age [15] and in individuals older than 60 years who had normal renal function [16]. When the resistive index is measured for both kidneys, the side-to-side difference is usually less than 5 % [17].

Table 1. Color-Doppler for semi-quantitative evaluation of intrarenal vascularization [12]

Stage	Quality of renal perfusion by color Doppler
0	Unidentifiable vessels
1	Few vessels in the vicinity of the hilum
2	Hilar and interlobar vessels in most of the renal parenchyma
3	Renal vessels identifiable until the arcuate arteries in the entire field of view

Since resistive index depends in part on the minimum diastolic shift, it may be influenced by the heart rate [18]. Therefore, a formula has been developed to correct the resistive index value for heart rate: Corrected resistive index = observed resistive index – 0.0026 × (80 – heart rate) [18]. However, the influence of heart rate *per se* on resistive index remains unclear [19] and the correction formula has not been validated.

Physiological Significance of the Renal Resistive Index

Although renal Doppler has been the focus of many studies, the physiological significance of the resistive index long remained obscure. As suggested by its name, the resistive index was initially considered an indicator of renal vascular resistance [11, 20–22]. Several hemodynamic and physiological factors influence the intrarenal arterial Doppler waveform patterns and, therefore, the resistive index value (**Table 2**). Several studies established that vascular compliance is crucial to the interpretation of resistive index values [10, 23, 24]. In an *in vitro* study, the relationship between vascular resistance and resistive index was linear when vascular compliance was normal but became progressively weaker when vascular compliance decreased [23]. Studies in *ex vivo* rabbit kidney models have confirmed the crucial importance of vascular compliance when interpreting resistive index [10, 24]. In addition, although a relationship was found between resistive index and pharmacologically induced changes in renal vascular resistance in these studies, the observed resistive index changes were modest and occurred only with non-physiologic increases in renal vascular resistance [24]. Last, changes in pulse pressure index [(systolic pressure – diastolic pressure/systolic pressure)] had direct and dramatic effects on resistive index values [24].

Another factor shown in *ex vivo* studies to influence resistive index values is interstitial pressure [10]. An increase in interstitial pressure reduces the transmural pressure of renal arterioles, thereby diminishing arterial distension and, consequently, decreasing overall flow and vascular compliance. Studies of *ex vivo* rabbit kidney models have helped to determine how changes in vessel cross-sectional area occur in response to interstitial pressure elevation and how these changes asymmetrically affect renal circulation during systole and diastole, thereby increasing the resistive index value [10]. In addition to interstitial pressure, intra-abdominal pressure may influence the resistive index. Thus, incremental changes in intra-abdominal pressure correlated linearly with resistive index in a porcine model [25].

Table 2. Factors influencing the Doppler-based renal resistive index [10, 23, 24, 54]

Physiological factors	Vascular compliance (arterial stiffness) Vascular resistances Pulse pressure Renal blood flow Heart rate Age
Pathological factors	Interstitial pressure Ureteral pressure Intra-abdominal pressure

Doppler-Based Renal Resistive Index in Selected Renal Diseases

Non-obstructive Renal Diseases

Studies started in 1990 evaluated the performance of Doppler-based resistive index measurement as a tool for assessing renal function [26]. A preliminary study evaluated correlations between Doppler-based resistive index values and renal biopsy findings in patients with renal diseases requiring renal biopsy [26]. In this preliminary work, patients with interstitial, tubular, or vascular nephritis had markedly increased resistive index values (mean, 0.73 to 0.87); patients with isolated glomerular disease had normal resistive index values (mean, 0.58) [26]. However, subsequent studies only partially confirmed these findings. Thus, in non-transplanted patients, the resistive index failed to distinguish among five groups of predefined renal parenchymal diseases [21]. In a recent study, the resistive index correlated mainly with the degree of arteriosclerosis in renal biopsy specimens [27]. In renal transplant recipients, although no correlation was found between resistive index and semi-quantitative histological scores, resistive index elevation was significantly associated with the severity of tubular injury 6 months after transplantation [28]. In addition, weak but significant correlations were found between resistive index and the degree of interstitial fibrosis ($r^2 = 0.07$; $p < 0.0001$), tubular atrophy ($r^2 = 0.07$; $p < 0.0001$), chronic allograft nephropathy ($r^2 = 0.07$; $p < 0.0001$), and chronic allograft arteriopathy ($r^2 = 0.11$; $p < 0.0001$) [28]. These findings suggest that, although the resistive index does not allow separation of underlying renal diseases, it may help to evaluate the severity of vascular and tubulo-interstitial lesions in transplanted and native kidneys. In keeping with this possibility, several studies found that the resistive index contributed to predict recovery from hemolytic and uremic syndrome [4], to detect renal involvement in systemic sclerosis [29], to predict renal outcomes in lupus nephritis [30], and to evaluate the progression of chronic renal diseases [31–33].

Several studies have evaluated the usefulness of resistive index measurement for assessing renal function after renal transplantation [2, 3, 28, 34–42]. Preliminary reports suggested that resistive index elevation might be highly specific of acute rejection [2, 3, 35]. However, as with non-transplanted patients, subsequent studies indicated that resistive index might be useful as a non-specific marker for renal dysfunction but was neither sensitive nor specific for detecting acute rejection [36–39]. Nevertheless, several studies reported that resistive index elevation predicted poor long-term outcomes [28, 40] and accurately predicted early vascular and non-vascular renal complications (e.g., AKI, rejection, and obstructive kidney disease) [41, 42].

Obstructive Renal Diseases

Sonography is sensitive for diagnosing renal obstruction, which is detected as dilatation of the collecting system. However, pyelocaliectasis does not necessarily indicate obstructive renal disease [43]. Studies evaluating the performance of Doppler-based resistive index measurement for diagnosing renal obstruction found high resistive index values in patients with obstructive renal disease [5, 44–46]. In a study of 70 kidneys with pyelocaliectasis, resistive index values greater than 0.70 indicated renal obstruction with 92 % sensitivity and 88 % specificity [44]. An *ex vivo* study clarified the mechanisms of the elevated resistive index associated with ureteral obstruction [10]. However, despite these promising findings and the physiological plausibility of resistive index elevation in obstructive disease, recent studies suggest that Doppler-based resistive index values may be very specific but fairly insensitive [19,

47, 48]. Discrepancies in resistive index sensitivity for detecting obstruction may be ascribable to poor sensitivity of the Doppler-based resistive index for detecting mild obstruction, as no patients with mild obstruction were included in the early studies [49].

A Promising Tool in Critically Ill Patients?

Renal Doppler is rapid, non-invasive, and repeatable and may, therefore, hold promise for monitoring renal function or renal perfusion in critically ill patients [7]. A growing number of studies are being performed to investigate this possibility.

In patients managed in the intensive care unit (ICU) for septic shock, resistive index elevation during the first few hours was associated with the development of renal dysfunction [9]. Resistive index measurement may help to detect non-obstructive AKI. In several studies, resistive index values discriminated reliably between acute tubular necrosis and prerenal failure [50–52]. However, few patients in these studies were critically ill, and no subsequent studies have been performed to confirm these findings.

Doppler-based resistive index measurement may not only help to assess renal function, but may also serve to monitor renal perfusion. In recent studies, the resistive index was used to assess the effect of low-dose dopamine on renal perfusion [8]. The impact of gradual changes in mean arterial pressure on resistive index has also been studied in patients receiving norepinephrine [6]. However, both studies considered that resistive index faithfully reflected renal vascular resistance, although, as explained above, many factors may affect the resistive index (e.g., changes in renal perfusion, vascular resistance, and vascular compliance; and interstitial edema). Therefore, no firm conclusions can be drawn from the results of these studies [10, 23, 24]. Similarly, a recent study showed that Doppler-based estimates of renal blood flow correlated weakly with implanted flow probe measurements of renal blood flow [53]. In this study, even renal blood flow changes greater than 20 % were missed by the Doppler-based measurements [53].

Conclusion

Despite promising findings from preliminary studies, conflicting data in the literature and discouraging observations from clinical practice have prompted some physicians to discard renal Doppler measurements. Previous studies have demonstrated that renal Doppler neither constitutes a substitute for renal biopsy nor provides reliable information on renal perfusion. This limited value of resistive index may be related to the many physiological, hemodynamic, and disease-related factors that influence the intrarenal arterial Doppler waveform patterns. Nevertheless, renal Doppler holds promise for investigating and monitoring critically ill patients. Conceivably, early detection of renal Doppler changes may improve the early diagnosis of AKI. Furthermore, monitoring the renal hemodynamic response to a fluid challenge or to vasopressors might prove useful for optimizing the treatment. However, experience with critically ill patients is scant and our understanding of factors influencing changes in resistive index in this setting is limited. The role for renal Doppler as a monitoring tool in the ICU will remain unclear until additional studies are conducted, including an evaluation of the performance of resistive index for detecting

intrinsic acute renal failure and a description of resistive index variations in response to hemodynamic changes in critically ill patients.

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Atrial Natriuretic Peptide in Postoperative Acute Renal Failure

S.-E. Ricksten and K. Swärd

Introduction

Acute renal dysfunction is a common postoperative complication following cardiac or major vascular surgery [1–4]. Ten to twenty percent of patients with acute renal dysfunction after cardiovascular surgery may develop dialysis-dependent acute renal failure, with a reported mortality of 30–60 % [1–4]. Dialysis-dependent acute renal failure has been considered an independent risk factor for early mortality in such patients [5, 6]. The pathogenesis of postoperative acute renal failure is believed to be predominantly a consequence of renal hypoperfusion and ischemia, particularly of the renal medulla [7, 8]. The renal medullary concentrating mechanism, requiring large amounts of oxygen, in combination with the relatively low medullary blood flow, renders the renal medulla hypoxic, with low tissue PO_2 levels, already under normal conditions [7]. The renal medulla, particularly the outer portion, is, therefore, sensitive to acute renal ischemia. Perioperative acute renal failure may also be related to factors including nephrotoxin exposure (heme pigments, inflammatory cytokines), embolism, and aortic cross-clamping. In spite of recent advances, outcomes from cardiovascular surgery-related acute renal failure have not changed substantially in the last decades and novel treatment strategies for prevention/treatment of perioperative acute renal dysfunction are, therefore, urgently needed.

The Discovery of the Atrial Natriuretic Peptide System

Bruno Kisch in 1956 [9] and Jamieson and Palade in 1964 [10] described electron-microscopic evidences of small, dense granules in guinea-pig and human atrial cardiocytes. In 1981, de Bold and co-workers [11] demonstrated "a rapid and potent natriuretic response to intravenous injection of atrial myocardial extract in rats". There was a 30-fold increase in sodium and chloride excretion, while urine volume rose 10-fold. Two years later, Flynn at al. [12] identified that the amino acid structure of the atrial natriuretic factor from rat atrial muscle was a 28-amino acid peptide with diuretic and natriuretic activity, and it was named atrial natriuretic peptide (ANP). This sequence is highly homologous between species. In 1984, Kangawa and Matsuo described the complete amino acid sequence of human ANP [13].

The natriuretic peptide system is primarily an endocrine system that maintains fluid and pressure homeostasis by modulating cardiac and renal function. ANP and brain natriuretic peptide (BNP) are released continuously from the heart and the rate of release increases in response to atrial and ventricular stretch, respectively, and will cause vaso- and venodilation, natriuresis, and inhibition of the sympathetic

nervous system and the renin–angiotensin–aldosterone axis [14]. The natriuretic peptides are ligands to high-affinity natriuretic peptide receptors and the vasodilatory action of ANP is mediated by cellular accumulation of cyclic guanosine monophosphate (cGMP) through the activation of membrane-bound particulate guanylyl cyclase [14].

Renal Effects of ANP in Humans

Renal Blood Flow

In humans, variable effects of ANP on renal blood flow have been demonstrated. This is not surprising, since the dilatory effects of ANP on venous capacitance vessels and resistance vessels may to a variable degree decrease cardiac output and systemic vascular resistance, with a consequent fall in renal perfusion pressure, which in turn may modify a potential renal vasodilatory effect of ANP. The effects of ANP on renal hemodynamics and function have been studied in healthy volunteers [15–18] and in patients with normal renal function after cardiovascular surgery [19–21]. Investigators reported that there was no change [15, 19, 20] or a decrease [16–18] in renal blood flow when plasma levels of ANP were increased 5 to 10 times by ANP infusion at a rate of 25–75 ng/kg/min. In the majority of these studies, renal vascular resistance was calculated and did not change after ANP [19–21], while one study found an increase in renal vascular resistance with ANP [18].

Glomerular Filtration Rate

In healthy volunteers and in post-cardiovascular surgery patients with normal renal function, the majority of studies have shown that the natriuretic response to ANP is associated with an increase in glomerular filtration rate (GFR) [15, 18–21]. At the infusion rates mentioned above, GFR and filtration fraction increased by 5–35 % and 20–60 %, respectively [15, 18–21]. These data together suggest that in humans with normal renal function, ANP causes a decrease in preglomerular vascular resistance and an increase in postglomerular vascular resistance. These findings in humans are in line with results from animal studies showing that ANP dilated preglomerular (afferent) arteriols and constricted post-glomerular (efferent) arterioles, leading to increased hydraulic pressure within glomerular capillaries [22].

Tubular Effects of ANP

The increase in GFR alone cannot account for the pronounced natriuresis and diuresis induced by ANP. The finding that ANP increases fractional sodium excretion by 50–200 % in healthy volunteers and in postoperative cardiovascular patients, strongly suggests that ANP also directly alters tubular sodium and water reabsorption [15, 16, 18–21]. There is extensive evidence from experimental studies that ANP inhibits sodium transport in the inner medullary collecting duct via binding to natriuretic receptors and production of cGMP, and that ANP exerts an inhibitory action on angiotensin II-induced antinatriuresis at the proximal tubules [14]. Furthermore, ANP inhibits the tubular actions of arginine vasopressin and aldosterone [14].

Effects of ANP on Renal Oxygen Consumption

It is well-known that tubular sodium reabsorption is a major determinant of renal oxygen consumption (VO_2) [23]. It has recently been shown that there is a positive correlation between tubular reabsorption and renal VO_2 in humans and that GFR correlates positively with tubular sodium reabsorption and renal VO_2 [21, 24, 25]. In other words, an increase in GFR will increase the tubular sodium load, which, in turn will increase tubular sodium reabsorption and renal VO_2. ANP promotes preglomerular vasodilatation and postglomerular vasoconstriction, thereby increasing GFR, which would increase the renal oxygen demand. On the other hand, experimental data suggest that ANP inhibits tubular sodium reabsorption in the medullary collecting duct, which would decrease renal VO_2 [26]. In patients with cirrhosis and refractory ascites, ANP induced an increase in GFR, which was accompanied by a natriuresis and a decrease in renal VO_2, attributed to an inhibitory effect of ANP on the elevated levels of anti-natriuretic substances in this condition [27]. Conversely, Sward et al. demonstrated that the ANP-induced increase in GFR and filtration fraction in postoperative patients with normal renal function, was accompanied by a 26 % increase in renal VO_2, in contrast to furosemide which decreased renal VO_2 by 23 % [21]. Thus, the potential energy-conserving, tubular effect of ANP was offset by the increase in GFR and tubular sodium reabsorption in patients with normal renal function.

Effects of ANP on Renal Blood Flow and GFR in Postoperative Acute Renal Failure

In a pharmacodynamic dose-finding study, Valsson et al. [28] studied 12 patients with early ischemic acute renal failure caused by postcardiac surgical heart failure, who required inotropic and vasoactive agents and intra-aortic balloon pump (IABP) counterpulsation [28]. The infusion of ANP at a rate of 25 – 50 ng/kg/min caused a 30 – 40 % increase in renal blood flow and GFR, with no change in filtration fraction, and a 30 % reduction in renal vascular resistance (**Fig. 1**).

In other words, in ischemic acute renal failure, ANP preferentially induces a reduction in pre-glomerular resistance, as also reflected by a minimum change in the filtration fraction, in contrast to the effects of ANP in patients with normal renal function. The ANP-induced increase in GFR in these patients would increase renal VO_2, which would potentially be balanced by the proportional increase in renal blood flow, due to the dilation of the afferent arterioles. However, the precise effects of ANP on renal VO_2 and the renal oxygen supply/demand relationship in patients with ischemic acute renal failure require further evaluation.

The renal vasodilatory effect of ANP on the afferent arterioles in clinical ischemic acute renal failure was demonstrated during a short-term infusion (hours) of ANP. Sward et al. studied the effects of ANP withdrawal on renal blood flow and GFR after long-term (2 – 9 days) treatment of patients with ischemic acute renal failure after complicated cardiac surgery, who required inotropic and vasoactive agents and IABP counterpulsation [29]. Discontinuation of a long-term infusion of ANP at a rate of 50 ng/kg/min substantially reduced GFR (-32 %) and renal blood flow (-31 %) and increased renal vascular resistance (93 %). In this situation, the re-institution of ANP increased renal blood flow and GFR by 30 – 40 % and reduced renal vascular resistance by 40 %, with no change in filtration fraction. These effects of

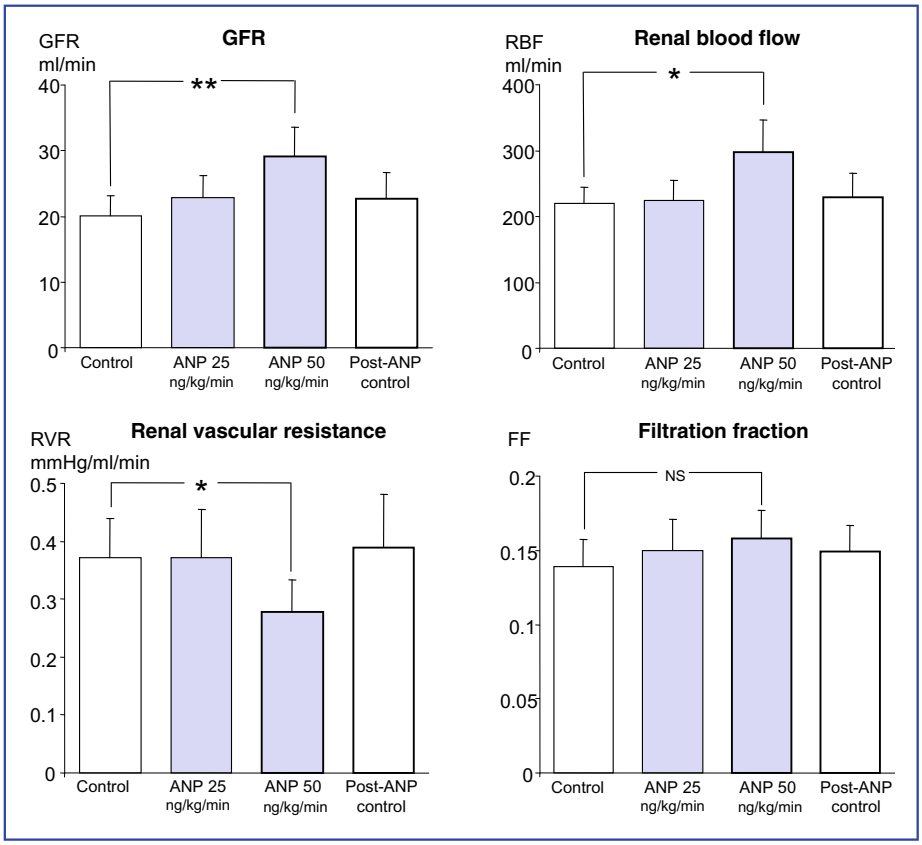

Fig. 1. Renal effects of atrial natriuretic peptide (ANP) infusion (25 and 50 ng/kg/min) in patients with early ischemic acute renal failure after complicated cardiac surgery. ANP induced renal vasodilation preferentially of the afferent arterioles as both glomerular filtration rate (GFR) and renal blood flow (RBF) increased with no change in filtration fraction. Modified from [28] with permission.

XI

ANP were almost identical to those described by Valsson et al. [28] during acute administration in a similar group of patients and further support the findings of an ANP-induced renal vasodilation of the afferent arterioles. Thus, the acute renal vasodilatory effects of ANP are maintained during long-term infusion, suggesting that tachyphylaxis to ANP does not develop during prolonged administration of ANP. This is in striking contrast to the recently described renal tolerance to low-dose dopamine in ICU patients with early acute renal dysfunction [30].

Effects of ANP on Renal Outcome in Acute Renal Failure

Despite encouraging results related to the beneficial effects of ANP in experimental acute renal failure, two recent multicenter, prospective randomized trials in patients with acute renal failure of various etiology treated with the ANP-analog anaritide [31, 32] failed to show any significant beneficial effects on renal outcome. Anaritide did not reduce the need for dialysis or improve dialysis-free survival in this hetero-

geneous group of patients with acute renal failure [31]. However, in a subgroup of patients with oliguria, anaritide administration was associated with an improvement in dialysis-free survival rates from 8 % in the placebo group to 27 % in the anaritide group [31]. The same research group then conducted a prospective, randomized, double-blind, placebo-controlled study of anaritide in patients with oliguric acute renal failure of various etiologies [32]. In this later study, there was no difference in the primary outcome variable, dialysis-free survival through day 21, in the two groups. At day 14 of the study, however, 64 % and 77 %, respectively, of the anaritide and placebo groups had been treated with dialysis ($p = 0.054$).

The failure to demonstrate a clear-cut beneficial effect of anaritide in acute renal failure in these two studies could be explained by the use of a dose of anaritide that was too high (200 ng/kg/min). Ninety-four percent of the anaritide group vs 45 % of the placebo group became hypotensive, i.e., had a systolic blood pressure < 90 mmHg. Hypotension may jeopardize renal perfusion, particularly in acute renal failure that is characterized by a loss of autoregulatory capacity [33]. Valsson et al. showed that the optimal dose of ANP is 50 – 100 ng/kg/min with respect to renal blood flow and GFR [19, 28]. At a dose of 100 ng/kg/min or higher, GFR and renal blood flow decline towards pre-treatment level in conjunction with a fall in mean arterial blood pressure [19]. Another limitation of the studies by Allgren et al. [31] and Lewis et al. [32] was that the duration of the anaritide infusion was only 24 hours. The development of severe acute tubular necrosis and reversion of this process take several days or weeks. As a result, any potentially efficacious agent should probably be administered for a substantially longer period than 24 hours to prevent dialysis-dependent acute renal failure.

In a prospective, blinded, randomized, placebo-controlled trial, Sward et al. [34] evaluated whether long-term infusion of ANP (50 ng/kg/min) could reduce the probability of dialysis and improve dialysis-free survival in patients with ischemic acute renal failure after cardiac surgery complicated by circulatory shock, who required significant inotropic and vasoactive support. The primary endpoint was dialysis on or before day 21 after start of treatment. Secondary endpoints were the combined event dialysis or death on or before day 21 after start of treatment and creatinine clearance on day 1, 2 and 3. The study groups did not differ in intraoperative data, need for mechanical ventilation, renal function, central hemodynamics or treatment with diuretics, inotropes or IABP. The mean durations of ANP or placebo infusion were 5.3 ± 0.8 and 4.3 ± 0.7 days, respectively. Treatment with ANP improved creatinine clearance in contrast to placebo (**Fig. 2**). The Kaplan-Meier estimates of the probability of dialysis and dialysis-free survival are shown in Figures 3 and 4. Six (21 %) patients in the ANP group compared with 13 (47 %) in the placebo group needed dialysis before or at day 21 (hazard ratio 0.28 [95 % CI 0.10 – 0.73]; $p = 0.009$). Eight (28 %) patients in the ANP group compared with 17 (53 %) in the placebo group suffered from the combined endpoint dialysis or death before or at day 21 (hazard ratio 0.35 [95 % CI 0.14 – 0.82]; $p = 0.017$). Administration of ANP was not stopped prematurely in any of the patients and there were no differences between groups with respect to the incidence of hypotension during the first 24 hours after start of treatment or the number of hypotensive episodes. Creatinine clearance was approximately 30 ml/min at patient enrollment in this study [34] and renal dysfunction was, therefore, much less severe when compared to the studies by Allgren et al. [31] and Lewis et al. [32], suggesting that the beneficial effects of ANP on renal function and outcome are seen in patients with moderately depressed early renal dysfunction.

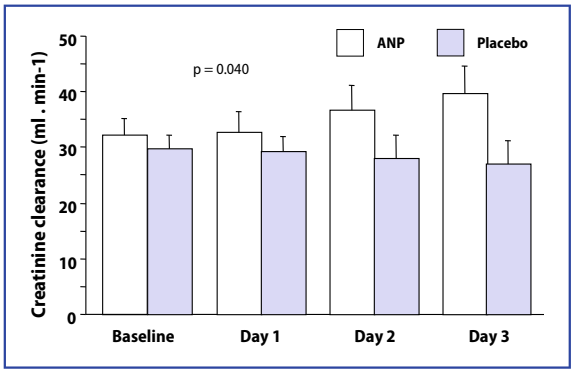

Fig. 2. Effects of atrial natriuretic peptide (ANP, 50 ng/kg/min) vs placebo on creatinine clearance 3 days after start of treatment. From [34] with permission.

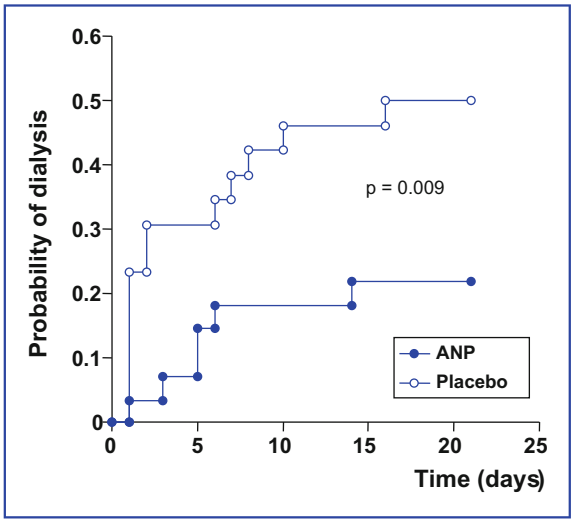

Fig. 3. Effects of atrial natriuretic peptide (ANP, 50 ng/kg/min) vs placebo on probability of dialysis in patients with early ischemic acute renal failure after complicated cardiac surgery. From [34] with permission.

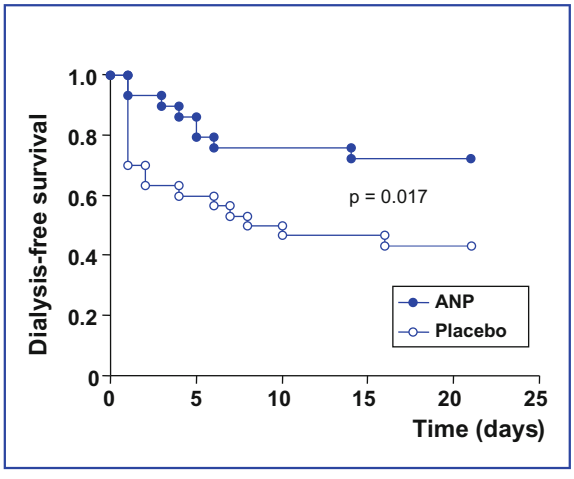

Fig. 4. Effects of atrial natriuretic peptide (ANP, 50 ng/kg/min) vs placebo on dialysis-free survival in patients with early ischemic acute renal failure after complicated cardiac surgery. From [34] with permission.

Effects of ANP in Other Forms of Clinical Acute Renal Failure

Cyclosporine-induced Acute Renal failure

Immunosuppression with cyclosporine after transplantation is complicated by nephrotoxicity. Cyclosporine induces renal vasoconstriction with a fall in renal blood flow and GFR, suggesting a preferential vasoconstriction of the renal afferent arterioles [35]. Valsson et al. [19] studied the effects of ANP (50 – 100 ng/kg/min) in heart transplant recipients with early, cyclosporine-induced acute renal failure. In these patients, ANP infusion produced a marked increase in renal blood flow (53 %) and GFR (69 %) and a decrease in renal vascular resistance (-45 %) with no change in the filtration fraction [19]. This partial or complete reversal of cyclosporine-induced renal vasoconstriction may thus be explained by the opposite effects of ANP and cyclosporine on preglomerular resistance vessels.

Liver Transplantation

Acute renal failure occurring immediately after liver transplantation is a major problem resulting in a poor prognosis. Akamatsu et al. [36] studied the efficacy of ANP in preventing acute renal failure after liver transplantation. Thirty-seven patients who underwent living donor liver transplantation were prospectively randomized into two groups: Patients who received ANP (n = 19, 50 – 100 ng/kg/min) for five days and those who received conventional diuretics (n = 18). The peri- and post-operative changes in hemodynamic status and renal function were compared between the two groups. There were no statistical differences in the changes in hemodynamic status between groups. The incidence of hemodialysis was 11 % in the ANP group and 39 % in the diuretic group ($p = 0.04$). Postoperative creatinine clearance was significantly higher in the ANP group.

Radiocontrast-induced Nephropathy

In a multicenter, prospective, randomized, controlled trial, Kurnik et al. [37] evaluate the efficacy of an intravenous ANP-analog (anaritide, ANP 4 – 28) to prevent radiocontrast-induced nephropathy. Patients with stable chronic renal failure were assigned to receive either placebo or one of three doses of anaritide (10, 50 or 100 ng/kg/min) for 30 minutes before and continuing for 30 minutes after radiocontrast administration. This short-term administration of intravenous anaritide before and during a radiocontrast study did not reduce the incidence of radiocontrast-induced nephropathy in patients with preexisting chronic renal failure. However, in a more recent randomized controlled trial, Morikawa et al. [38] showed that ANP at a dose of 0.042 μg/kg/min was effective in preventing radiocontrast-induced nephropathy in patients with chronic renal failure. ANP treatment in this study was initiated 4 – 6 hours before angiography and continued for 48 hours. Once again, this supports the concept that in addition to the dose, the duration of infusion is an important determinant in the efficacy of ANP as a renoprotective agent.

Meta-Analysis of ANP in the Management of Acute Renal Dysfunction

In a recent meta-analysis on the role of ANP in acute renal failure after cardiovascular surgery, ANP administration at a low dose was associated with a reduction in the

incidence of acute renal failure requiring dialysis (odds ratio = 0.32 [0.15 – 0.66], p = 0.002) and a statistically non-significant trend to reduced 30-day or hospital mortality [39]. Other beneficial effects of ANP included a reduction in postsurgery peak serum creatinine, an increase in urinary output, a reduction in postoperative aldosterone levels, and reductions in mechanical ventilation duration and ICU length of stay.

Conclusion

In patients with early postoperative acute renal failure or cyclosporine-induced acute renal failure, ANP improves GFR and renal blood flow by renal vasodilation of the afferent arterioles. The renal vasodilatory effects of ANP in postoperative ischemic acute renal failure are maintained during long-term infusion (> 48 h). Renal tolerance to ANP does not appear to occur. A two-center study suggested that low dose ANP infusion reduces the probability of dialysis and improves dialysis-free survival in early ischemic acute renal failure after cardiac surgery complicated by circulatory shock. A similar study showed that ANP may decrease the need for dialysis after liver transplantation.

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Renal Dysfunction in Chronic Liver Disease

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Introduction

Acute kidney injury (AKI), chronic kidney disease, and the evaluation of numerous exogenous and endogenous measures of kidney function and injury continue to be the focus of much research in different patient populations. The key reason behind this effort is the well described independent association that small changes in kidney function are strongly linked with increased mortality, extending to those with chronic liver disease.

The accurate assessment of kidney function and injury is currently affected by the reliance on the measured concentration of serum creatinine, which is significantly affected by the degree of cirrhosis, hyperbilirubinemia, and the nutritional state of the patient. Improved understanding of the pathophysiology of kidney injury and development of more accurate measures of kidney function and injury are necessary to evoke a positive shift in kidney injury diagnosis, treatment, and outcomes. Furthermore, the number of patients with chronic liver disease and chronic kidney disease continues to rise, due to the large numbers of individuals worldwide affected by viral hepatitides, obesity, hypertension, and diabetes. Consequently, preventative health care messages must be louder and further reaching in order to reverse this trend.

Co-existing Liver and Kidney Disease

Chronic liver disease and primary liver cancer account for 1 in 40 (2.5 %) deaths worldwide, with hepatitis B the commonest cause in the developing world, followed by alcoholic liver disease and hepatitis C in the Western world [1]. Non-alcoholic steato-hepatitis and non-alcoholic fatty liver disease are increasing causes of chronic liver disease in the general population of Western countries with prevalence rates of 1 – 5 % and 10 – 24 %, respectively [2]. This observation is related to the increasing incidence of obesity in the Western population and the associated metabolic syndrome, consisting of atherosclerotic coronary vascular disease, hypertension, hyperlipidemia, diabetes, and chronic kidney disease. Metabolic syndrome and non-alcoholic steato-hepatitis/non-alcoholic fatty liver disease are linked by the key feature of insulin resistance. Although initially considered to be a benign disease, non-alcoholic fatty liver disease seems to represent a spectrum of disease with benign hepatic steatosis at one end and steatotic hepatitis at the other. Approximately 30 – 50 % of individuals with steato-hepatitis will develop fibrosis, 15 % cirrhosis, and 3 % liver failure [2]. Importantly, non-alcoholic fatty liver disease probably accounts for a

large proportion of patients diagnosed with cryptogenic cirrhosis and at least 13 % of cases of hepatocellular carcinoma [3, 4].

Obesity and metabolic syndrome are also strongly associated with the development of hypertension and diabetes, which affect 70 % of the patient population with end-stage renal disease in the USA [5]. There is increasing evidence that obesity itself is an independent risk factor, albeit small, for the progression of chronic kidney disease. Some work has highlighted the association of low-birth weight and reduced nephron mass with an increased risk of obesity and the phenomenon of chronic kidney disease later in life [6]. A small proportion of obese patients will develop obesity-related glomerulosclerosis, a focal segmental glomerulonephropathy associated with proteinuria and progression to end-stage renal disease. Despite numerous obesity-related factors, the overall individual risk for the development of chronic kidney disease in the absence of diabetes and hypertension is low; nevertheless, obesity is likely to contribute increasingly to the burden of chronic disease and end-stage renal disease in the future.

Hepatitis C has long been associated with several glomerulopathies, most notably cryoglobulin- and non-cryoglobulin-associated membranoproliferative glomerulonephritis. The prevalence of cryoglobulinemia is around 50 % [7], although extrarenal manifestations are often absent in the majority of these patients. Viral RNA, proteins and particles have been inconsistently isolated from kidney biopsy specimens, making it difficult to establish whether hepatitis C is causative in other forms of glomerulopathy [7]. In seropositive hepatitis C populations, hepatitis C infection has been reported to be associated with focal segmental glomerulosclerosis, membranous nephropathy with or without nephrotic range proteinuria, IgA nephropathy, and proliferative glomerulonephritidies [7].

Hepatitis C has also been associated with an increased risk of albuminuria, progression of diabetic nephropathy, and progression of chronic kidney disease to end-stage renal disease [7]. The worldwide prevalence of hepatitis C among patients on hemodialysis is high, ranging from 4 – 60 % [8]. This rate is on the decline, due to stricter adherence to universal infection control measures, with or without isolation, which have been implemented to a greater extent in the USA and in European countries. Risk factors for infection include the length of time of hemodialysis, the number of blood transfusions for renal anemia, and nosocomial transmission [8]. These patients often develop significant chronic liver disease, which adds an additional mortality burden while on hemodialysis. The presence of hepatitis C infection also has a negative effect on patient and renal survival following kidney transplantation [9].

Hepatitis B virus (HBV) is also associated with renal disease, but it is mostly encountered in children from endemic areas. The incidence of HBV-associated renal disease in Europe is low due to the lower prevalence of chronic HBV infection. HBV is associated with a number of renal diseases, including polyarteritis nodosa, membranous and membranoproliferative glomerulonephritis. Most patients have a history of active HBV but are asymptomatic with positive surface antigen and core antibody; in those with membranous nephropathy, e antigen is positive. The pathogenic role of HBV has been demonstrated by the presence of antigen-antibody complexes in kidney biopsy specimens and in particular deposition of HBV e antigen in membranous glomerulonephritis [9, 10].

Autosomal-dominant polycystic kidney disease is associated with polycystic liver disease in up to 75 – 90 % of cases [11]. There are a number of risk factors for liver involvement, including female gender, age, and degree of renal dysfunction [11]. A

distinct form of autosomal dominant isolated liver cystic disease was recognized in the mid-1980s. Most patients are asymptomatic, but when symptoms do occur, they are often related to cyst size and number. Symptoms include abdominal pain, nausea, early satiety, breathlessness, ascites, and biliary obstruction; all can precipitate to result in a significantly malnourished state related to gastric compression. The medical complications seen with autosomal-dominant polycystic kidney disease including intracranial aneurysms, and valvular heart lesion are also encountered in those with cystic liver disease. Therapies involve cyst rupture or sclerosis and liver transplantation if symptoms persist [11].

Familial amyloidosis polyneuropathy is an autosomal dominant disease caused by a point mutation in the gene coding for transthyretin, also called pre-albumin. The amino acid, valine, is replaced by methionine. The mutated protein produced by the liver forms a beta-pleated sheet structure, which accumulates in tissues, particularly nerves and the kidney, resulting in amyloid deposition. Familial amyloidosis polyneuropathy appears in the second decade of life leading to death within 8 – 13 years. Orthotopic liver transplantation (OLT) represents the best form of treatment, when performed early in the course of the disease, by halting the progression of the peripheral neuropathy and chronic kidney disease. The kidneys are frequently affected and this is recognized by proteinuria and declining kidney function. OLT reduces serum pre-albumin levels but the amount deposited in the kidney remains the same post transplantation. OLT should not be contemplated for patients with severe proteinuria or advanced chronic kidney disease [12].

Serum Creatinine Concentration for the Assessment of Kidney Function in Chronic Liver Disease

Kidney function is evaluated by assessing the glomerular filtration rate (GFR), which can be determined by measuring the volume of plasma that can be completely cleared of a given substance over a defined unit of time. The ideal marker for GFR determination is often quoted as having the following characteristics: Appears constantly in the plasma, can be freely filtered at the glomerulus, and does not undergo tubular reabsorption, secretion or extra renal elimination [13]. For many years now, the assessment of GFR has relied on the measurement of the concentration of serum creatinine, which is associated with many problems. Creatinine is a product of the metabolism of creatine, which is produced in the liver from three amino acids, methionine, arginine, and glycine, and stored in muscle to be used as a source of energy once phosporylated. Creatinine does not appear in the plasma at a constant rate; it is secreted in the tubule and can undergo extrarenal elimination, thought to involve creatinase in the gut. Serum creatinine concentration displays an exponential relationship with GFR, rendering it specific, but not a sensitive measure of GFR. The creatinine pool is affected by gender, age, ethnicity, nutritional state, protein intake and importantly liver disease [14].

In chronic liver disease, the reduction in the serum creatinine pool is due to a 50 % decrease in hepatic production of creatine; increases in the volume of distribution due to the accumulation of extracellular fluid, edema, and ascites; malnutrition and loss of muscle mass, which is related to repeated episodes of sepsis and large volume ascites affecting satiety [15]. Ultimately, patients with chronic liver disease have a significantly lower baseline serum creatinine concentration than the general population (35 – 75 umol/l).

Analytical methods for measuring the serum creatinine concentration have been associated with problems, particularly related to interference from chromatogens, like unconjugated and conjugated bilirubin. The degree of error can be up to 57 % [16], but modern auto-analyzers using the endpoint Jaffe method have overcome such interference. Nevertheless, interpreting serum creatinine results in the context of hyperbilirubinemia still requires a degree of caution despite these adjustments. In particular, patients with chronic liver disease display smaller and delayed (up to 48 – 72 hours) changes in serum creatinine for a given change in GFR, thus impairing the recognition and underestimating the degree of change in GFR [17, 18].

Acute Kidney Injury Network Criteria for staging Acute Kidney Injury

In 2005 the Acute Kidney Injury Network (AKIN) was formed, comprising a group of experts in nephrology and critical care who sought to revise the Acute Dialysis Quality Initiative (ADQI) group's original work from the previous year, which resulted in the development of the RIFLE (Risk, Injury, Failure, Loss, End-stage renal disease) criteria. A unifying term for acute renal failure, acute kidney injury (AKI), which encompassed all causes of acute renal failure, was established along with specific defining criteria and a classification based on severity of disease (**Table 1**) [19]. Patients are assigned to the worse category within the RIFLE criteria, defined by changes in serum creatinine concentration or GFR from baseline or urine output per unit body weight per hour over a defined period of time. The AKIN refined the RIFLE criteria to reflect data demonstrating the finding that small changes in serum creatinine had a significant impact on patient mortality [19]. The 'Risk' category for AKI was broadened to include changes in serum creatinine up to 26.4 umol/l within a 48 hour time frame.

The stages of AKI in this revised classification were numbered 1, 2, and 3 rather than being named 'Risk', 'Injury' and 'Failure'. The category of 'Failure' becomes Stage 3 AKI and incorporates anyone commenced on renal replacement therapy regardless of serum creatinine or rate of urine output (**Table 1**). More subtle changes include the exclusion of urinary tract obstruction and easily reversible causes of transient change in serum creatinine or urine output, such as volume depletion. Importantly, the inappropriate use of estimated GFR in the acute setting was addressed by removing the GFR criteria altogether.

Despite these revisions, there remain problems with both staging systems and these have been the focus of much discussion in the literature. Direct comparison of the two staging systems has been performed and, as expected, AKI is more sensitive

Table 1. Acute Kidney Injury Network (AKIN) acute kidney injury staging criteria [19]

	Serum creatinine (μmol/l)	Urine output (ml/kg/h)
Stage 1	> 26.4 μmol/l > 150 – 200 % change from baseline	< 0.5 for > 6 hours
Stage 2	> 200 – 300 % change from baseline	< 0.5 for > 12 hours
Stage 3	> 300 % change from baseline OR > 44 μmol/l change from 354 μmol/l	< 0.3 for 24 hours or anuria for 12 hour

than RIFLE, but this difference only affects around 1 % of patients [20]. The choice of baseline creatinine for studies has been highlighted to be of critical importance, markedly affecting the incidence of AKI. Several retrospective studies have calculated the baseline serum creatinine by manipulating the Modification of Diet in Renal Disease (MDRD) equation for estimating GFR assuming that patients had an estimated GFR of 75 – 100 ml/min/1.73 m^2 [21].

It is also evident that slow but persistent changes in serum creatinine over a longer time course than 48 hours can be missed and sometimes impossible to classify. Urine output too is associated with a number of confounding factors, in particular diuretic use, which affects interpretation. Extracorporeal therapies like continuous veno-venous hemofiltration (CVVH), a form of renal replacement therapy used in the critically ill, are often initiated for non-renal reasons, for example, hyperlactatemia or hyperammonemia which are frequently encountered in acute liver failure. More prospective studies with more attention to detail are required to improve the AKI criteria, in particular ensuring that baseline creatinine is measured and not estimated, and providing greater description of the indications for and timing of renal replacement therapy [21].

Despite these limitations, AKI staging does address the phenomenon of the lower baseline serum creatinine seen in patients with chronic liver disease. The broadening of stage 1 is beneficial in the setting of chronic liver disease, because we know that changes in serum creatinine will be smaller and delayed. Urine output, although riddled with numerous confounders, not least diuretic therapy and the difficulties of the un-catheterized patient, can still yield important information if measured accurately on the ward in conjunction with daily weight assessment to provide an assessment of overall fluid balance. Diuretic therapy response varies in patients with decompensated chronic liver disease and has a significant impact on survival outcomes; those that are less responsive tend to experience complications of hyponatremia and AKI with greater frequency [22].

Acute Kidney Injury Pathogenesis

AKI is more than just an isolated ischemic injury. The ischemic insult stimulates an inflammatory response with increased expression of adhesion molecules attracting leukocytes. Intra-luminal debris from tubular cells damaged by ischemia impairs reabsorption of sodium, which polymerizes Tamm-Horsfall proteins forming a gel-like substance that occludes the tubule causing increased backpressure and leaking. Endothelial injury affects tonicity of the afferent arteriole, activates the clotting cascade and releases endothelin which causes further vasoconstriction thus compromising the microcirculation. An injurious reperfusion period can then follow, due to the depletion of ATP, which releases proteases with oxidative substances that further damage the cytoskeleton of the tubules. This pathogenesis perhaps explains the unresponsive nature of this condition when identified late in its clinical course [23].

Patients with Chronic Liver Disease are more Susceptible to Acute Kidney Injury

Advanced chronic liver disease is responsible for a significant number of physiological changes that affect the circulation and kidney perfusion. Cirrhosis results in the

accumulation of vasodilatory mediators, in particular nitric oxide (NO), which specifically vasodilates the splanchnic circulation reducing the effective circulating blood volume and mean arterial pressure. Hypoperfusion of the kidneys leads to a reduction in the sodium concentration of tubular fluid reaching the distal tubule stimulating the macular densa, to release renin, thus activating the renin-angiotensin-aldosterone (RAA) axis. Glomerular filtration pressure is dependent on afferent and efferent vascular tone. Chronic disease states often seen in association with chronic liver disease, such as atherosclerotic vascular disease, hypertension and chronic kidney disease, affect the responsiveness of the afferent arteriole, thus shifting the auto regulation curve to the right. Consequently, adjustments in vascular tone of the afferent arteriole are smaller, reducing the ability to increase glomerular perfusion during episodes of hypotension. This, coupled with increased levels of angiotensin II, a product of RAA activation, causes vasoconstriction of blood vessels, in particular the afferent and efferent arteriolar renal vessels. Aldosterone acts on the distal tubule increasing the retention of salt and water. Consequently, there is decreased renal perfusion coupled with avid retention of fluid which increases abdominal ascites accumulation causing abdominal distension and elevation of the intra-abdominal pressure, which further compromises renal perfusion and propagates the vicious cycle.

Furthermore, in advanced chronic liver disease, an intrinsic defect in cardiac performance during exercise has been demonstrated and termed cirrhotic cardiomyopathy [24]. This syndrome encompasses a number of myocardial and electrophysiological changes that occur in cirrhosis and lead to attenuated cardiac function, particularly when exposed to stressful events like sepsis. The features of this condition include: A hyperdynamic myocardium with an increase in baseline cardiac output; attenuated systolic contraction and diastolic relaxation; electrophysiological abnormalities; and unresponsiveness to beta-adrenergic stimulation. Portal hypertension leads to shunting of blood away from the liver, thus reducing portal venous blood flow in the liver. This is thought to affect sodium and water excretion by the kidney via the postulated hepatorenal reflex mechanism whereby the release of adenosine is believed to act as a neurotransmitter stimulating sympathetic nerves supplying the renal vasculature causing vasoconstriction and oliguria. These mechanisms, attempting to maintain the effective circulating blood volume coupled with cirrhotic cardiomyopathy and reduced venous return from raised intra-abdominal pressure, render the circulation helpless in the pursuit of renal perfusion preservation.

Stress events like sepsis, gastrointestinal bleeding, and the use of diuretics, vasodilators or nephrotoxic drugs, which cause renal vasoconstriction, like non-steroidal anti-inflammatory drugs and radiographic contrast agents, can tip this fine balance between circulatory performance and adequacy of renal perfusion resulting in renal ischemia and its associated multi-faceted sequelae. Subsequently, AKI ensues, unless timely interventions targeted at reversing these physiological changes are initiated.

Hepatorenal Syndrome

Hepatorenal syndrome was first described in 1939 in patients undergoing biliary surgery [25] and today it remains a clinical entity assigned specific defining criteria. It is divided into two types based on specific clinical and time course features: Hepatorenal syndrome type 1 is a form of AKI, similar to that encountered in sepsis, which necessitates the exclusion of reversible factors, treatment of hypovolemia,

nephrotoxic medications, and a period of resuscitation to assess response to diuretic withdrawal and volume expansion; hepatorenal syndrome type 2 is a form of chronic kidney disease related to diuretic resistant ascites and its management, which typically evolves over months, perhaps displaying features in common with the ischemic nephropathy encountered in severe cardiac failure.

The classifying criteria for defining hepatorenal syndrome are under constant review and scrutiny, in a similar fashion to the AKI and chronic kidney disease classifications. Problems persist with all three classifications largely due to the reliance on serum creatinine concentration. As already discussed, serum creatinine performs poorly as a marker of kidney function in many different cross-sectional patient populations, not least those with chronic liver disease. The subgroup classification of types 1 and 2 hepatorenal syndrome have surprisingly not yet embraced the AKI and chronic kidney disease staging criteria, respectively. The definition of hepatorenal syndrome is centered on the use of an arbitrary level for serum creatinine concentration of 130 μmol/l, which does not account for gender, ethnicity, age or for the lower baseline serum creatinine concentrations seen in patients with chronic liver disease. Consequently, patients with chronic liver disease will lose more than 50 % of residual renal function before a diagnosis of hepatorenal syndrome can be entertained. Despite the flaws associated with the AKI classification, which are explained below, it seems to have some clear advantages, with at least the recognition that individual baseline creatinine concentration is a much better starting reference point.

Acute Kidney Injury and Chronic Liver Disease

The incidence of AKI in hospitalized patients with chronic liver disease is around 20 % [26]. There are three main causes of AKI in chronic liver disease: Volume-responsive pre-renal failure, volume unresponsive pre-renal failure with tubular dysfunction and acute tubular necrosis (ATN), and hepatorenal syndrome type 1, with prevalence rates of 68 %, 33 %, and 25 % respectively [27]. Of note, these three clinical scenarios should only be considered once acute kidney parenchymal disease and obstructive uropathy have been excluded. This exclusion can be achieved by performing an ultrasound of the kidneys, dipstick urine analysis assessing the presence of hematuria and proteinuria, and appropriate same day serological testing for antibodies against the glomerular basement membrane and for vasculitis if other clinical features suggest such diagnoses are possible. Additionally, the thorough evaluation and pursuit of occult sepsis is crucial with the early introduction of appropriate broad spectrum antibiotics often proving to be vital. Approximately 20 % of patients with decompensated chronic liver disease will have spontaneous bacterial peritonitis [28]. The diagnostic ascitic tap is an invaluable test to rule out this condition, which can be a precipitant of AKI in about 30 % of cases. Hypotension in patients with chronic liver disease should prompt meticulous assessment for gastrointestinal bleeding, with variceal hemorrhage an easily treatable cause. Again a detailed search for sepsis and thorough interrogation of the drug chart to stop medications that compromise blood pressure or could in anyway be nephrotoxic is always warranted. Established beneficial treatments include fluid resuscitation, vasopressor analog use, albumin infusions, and the omission of nephrotoxic drugs [29, 30].

Biomarkers of AKI

Traditional blood markers of kidney injury, such as serum creatinine, urea and urine markers, fractional excretion of sodium, and casts on microscopy, are insensitive and non-specific for the diagnosis of AKI. Novel kidney injury biomarkers in both serum and urine have been discovered using genomic and proteomic technology and they are demonstrating superiority in detecting kidney injury before changes in serum creatinine occur. These markers have been assessed primarily after a known specific insult in both adult and pediatric populations, such as cardiopulmonary bypass for cardiac surgery, kidney transplantation, contrast administration, or sepsis and other pathologies encountered in intensive care populations. Subsequently, numerous systematic reviews have been undertaken to assess the validity of these studies. Currently the literature supports the concept of a panel of biomarkers for detecting AKI, including two serum and three urine biomarkers: Serum neutrophil gelatinase lipocalin (sNGAL) and cystatin C, and urinary kidney injury molecule 1 (KIM-1), interleukin-18 (IL-18) and NGAL (uNGAL) [31].

Table 2 illustrates the major studies for each of these biomarkers in the setting of AKI with as many as 31 studies demonstrating broadly similar outcomes [32–35]. However, it is difficult to translate these studies to the wider patient population or indeed specifically to those with chronic liver disease. Many of the 31 studies excluded patients with chronic kidney disease, which affects 30 % of patients admitted to intensive care and these patient have an increased risk of AKI [36]. Two large multicenter studies are underway evaluating these biomarkers and our research group at King's College Hospital is evaluating the use of these biomarkers in patients with chronic liver disease. Some work has already demonstrated the usefulness of NGAL post-orthotopic liver transplantation to predict AKI [37]. Whether this will translate to improved kidney injury outcomes remains to be demonstrated, but it is intuitive to believe that an earlier diagnosis would be associated with improved outcomes, much like troponin in patients with acute coronary syndromes.

XI

Kidney Disease Outcome Quality Initiative Criteria for Staging Chronic Kidney Disease

The definition and classification of chronic kidney disease was established in 2002 by the Kidney Disease Outcome Quality Initiative (KDOQI) group in the USA [38]. There were numerous factors prompting the group to establish clarity for the definition of chronic renal failure, which was already an extensive health care burden. With up to 100,000 new patient cases per year reaching end-stage renal disease, something had to done to try and detect kidney disease earlier.

The Cockcroft-Gault equation [39] has been widely used to detect renal dysfunction, adjust drug dosing for drugs excreted by the kidneys, and assess the effectiveness of treatments for progressive kidney disease. It has also been used to evaluate patient's health insurance claims and assign them points, which would prioritize them on the waiting list for a kidney transplant, similar to the way in which the model for end-stage liver disease (MELD) is now used for liver transplantation. However, there is established evidence that the degree of chronic kidney disease and not just end-stage renal disease is an important risk factor for cardiovascular disease and AKI [40]. Moreover, new treatments, in particular angiotensin converting enzyme (ACE) inhibitors, have been shown to slow the progression of chronic kid-

Table 2. Summary of studies evaluating the role of novel blood and urine kidney injury biomarkers

Study N [Ref]	Biomarker	Biomarker profile	Precipitants and Confounders	Clinical setting	Cut-off	AKI definition	Sensitivity	Specificity	AUC
Mishra et al N = 71 [32]	Serum NGAL	25 kDa protein bound to gelatinase from neutrophils. Expressed in low levels in normal tissues, kidney, lung and colon. Increased level with damage to epithelial cells.	Sepsis Ischemia Nephrotoxins CKD UTI and systemic sepsis	Cardiac surgery Children 2 h post cardiac surgery	50 µg/l	> 50 % rise from baseline serum creatinine	0.7	0.94	NR
Herget-Rosenthal et al N = 85 [33]	Serum cystatin C	13 KDa protein from cysteine protease inhibitor family produced by all nucleated cells. Measure of GFR as freely filtered at proximal tubule Unaffected by gender, age, ethnicity or muscle mass	Changes in GFR Hyperthyroidism Corticosteroids	ICU patients 1 day prior to clinical AKI	> 50 % rise from baseline serum creatinine	> 50 % rise	0.82	0.95	0.97
Mishra et al N = 71 [32]	Urine NGAL	25 KDa protein bound to gelatinase from neutrophils	Ischemia Nephrotoxins UTI CKD Systemic sepsis	Cardiac surgery Children 2 h post-surgery	50 µg/l	> 50 % rise	1.0	0.98	0.99
Parikh et al N = 71 [34]	Urine IL-18	Pro-inflammatory cytokine regulation of T-helper cells. Induced and cleaved in proximal tubule after AKI	Ischemia (Not raised in CKD, UTI or pre-renal AKI)	Cardiac surgery 12 h post-surgery	50 pg/ml	> 50 % rise	0.5	0.94	0.73
Han et al N = 40 [35]	Urine KIM-1	Type 1 transmembrane protein not detected in normal kidney. Highly expressed in proximal tubule after AKI	Ischemia Nephrotoxins (Not raised in CKD, UTI or pre-renal AKI)	Cardiac surgery 12 h post-surgery	7 ng/mg/ serum creatinine	> 50 % rise	0.74	0.9	0.83

CKD: chronic kidney disease; AKI; acute kidney injury; UTI: urinary tract infection; NGAL: neutrophil gelatinase lipocalin; IL: interleukin; KIM: kidney injury molecule; GFR: glomerular filtration rate; ICU: intensive care unit; AUC: area under the curve; NR: not reported

ney disease by reducing the damaging effects of the proteinuria and raised intra-glomerular pressure encountered with hypertension [41].

It was recognized that the Cockcroft-Gault equation relied on the serum creatinine concentration, which is notably affected by age, gender, and ethnicity. The MDRD study in 1999 [42] was undertaken to assess patients with established chronic kidney disease and the effect that dietary protein restriction and strict blood pressure control had on preventing the progression of chronic kidney disease. In this study, a baseline period was used to collect demographic data, and to perform timed urine creatinine clearance and I-Iothalamate radionucleotide GFR measurement on the enrolled patients. The investigators formulated seven equations using a number of combinations including demographic, serum, and urine variables, and incorporating gender, age, ethnicity and serum creatinine. In version 7 of the equation, the additional serum variables of albumin and urea were used in place of the urine variable. This equation provided a validated estimated measure of GFR in patients with chronic kidney disease and from this the staging classification was developed. Importance was leveled at establishing a staging system, because adverse outcomes in chronic kidney disease are linked to the degree of chronic kidney disease and future loss of kidney function. Additionally, chronic kidney disease was understood to be a progressive disease and consequently the staging classification could be adapted to give emphasis to treatment goals to slow progression. The term 'chronic renal failure' was redefined in a similar fashion to 'acute renal failure' and newly termed 'chronic kidney disease'. It was then possible to classify chronic kidney disease into five stages for patients with renal disease and the old classification of mild, moderate, or severe chronic renal failure was abandoned [42].

These five stages have been under review given the epidemiological data demonstrating a significant difference in patient numbers in chronic kidney disease stages 3 and 4 [43]. This difference has been attributed to the significant increase in cardiovascular associated mortality in late chronic kidney disease stage 3 (estimated GFR 30–45 ml/min/1.73 m^2). Consequently chronic kidney disease stage 3 is now subdivided into 3A (estimated GFR 59–45 ml/min/1.73 $m^{2)}$ and 3B (estimated GFR 44–30 ml/min/1.73 m^2) (**Table 3**).

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Stage	Estimated GFR (ml/min/1.73 m^2)
1	> 90
2	89–60
3A	59–45
3B	44–30
4	29–15
5	< 15

Table 3. Kidney Disease Outcome Quality Initiative (KDOQI) staging criteria for chronic kidney disease [38]

There are problems with this staging system, which relate to the original study population and its application to the wider community. An MDRD equation calculation for an estimated GFR above 60 ml/min/1.73 m^2 has been shown to be inaccurate, underestimating GFR in patients with normal kidney function [43]. The original study population had a mean GFR of 40 ml/min/1.73 m^2 and included only a few Asian, elderly, and diabetic patients. There are debates about the critical level of estimated GFR for chronic kidney disease in terms of cardiovascular risk, currently deemed to be around 60 ml/min/1.73 m^2, and the relation of this level to the age and

ethnicity of the patient, and the chronicity of the condition. All have a bearing on the implications of labeling patients as having chronic kidney disease and the treatments, if necessary, to address cardiovascular risk and disease progression [26, 44].

Assessment of Chronic Kidney Disease in Patients with Chronic Liver Disease

The reliance on serum creatinine concentration is pivotal to the problems with estimated GFR and the gulf between the original MDRD study population and patients with chronic liver disease. This has been highlighted by a meta-analysis that reviewed creatinine clearance and estimated GFR and demonstrated a mean overestimation of 18.7 ml/min/1.73 m^2 [45]. Timed urine creatinine clearance also performs poorly, significantly overestimating GFR in patients with chronic liver disease, particularly at the lower range of GFR measurements [46]. So why use estimated GFR if it performs so poorly? Despite its drawbacks, it is the most cost-effective method of assessing kidney function in the chronic setting and provides greater clarity on the extent of disease if one considers the overestimation and uses the extended version, which incorporates albumin and urea. Serial measures tend to provide greater information than measures in isolation.

Future Directions

Patients with chronic liver disease and chronic kidney disease warrant better evaluation of residual kidney function than is currently offered. Cystatin C has been shown to be a better marker of GFR in patients with chronic liver disease both before and in the immediate period after transplantation [47, 48]. Equations have been developed to give better accuracy to the estimation of GFR using measured cystatin C concentration [48]. However, these equations have been evaluated in small study populations using different gold standard measures of GFR compared to the creatinine based equations. Cystatin C equations have, though, been shown to perform better, with greater accuracy in predicting GFR, in cirrhotic and post-transplant patients using either the Hoek or Larsson equations [47, 48].

uNGAL has also been shown to be significantly elevated in proteinuric patients with membranous nephropathy or membranoproliferative glomerulonephritis with chronic kidney disease when compared to a control group with normal kidney function and no proteinuria [30]. sNGAL has been shown to be significantly elevated in patients with chronic kidney disease or kidney transplant compared to controls [37]. It also appears to increase with chronic kidney disease stage and severity suggesting a role in tracking progression of chronic kidney disease [49]. However, increased sNGAL in the setting of chronic kidney disease is poorly understood; the suggested hypothesis links proteinuria and the apoptotic effect this has on proximal tubular cells. Further evaluation is required, but these biomarkers have shown promise as markers of chronic kidney disease progression.

Ultimately, patients with chronic liver disease and chronic kidney disease need residual kidney function to be evaluated using gold standard measures of GFR, probably at 3–6 monthly intervals. The evaluation of cystatin C and serum NGAL in the interim period to monitor progression and perhaps detect acute changes could lead to improved outcomes for this group of patients.

Orthotopic Liver Transplantation

OLT offers the best long-term outcome for patients with advanced liver disease. The method for allocating liver grafts to patients with advanced liver disease relies on scoring systems, like MELD, which helps to predict survival without transplantation. The MELD score incorporates serum creatinine and this carries a high integer weighting which may have a significant impact on the composite score. Consequently, there are two significant problems associated with MELD. First, the prognostication of chronic liver disease itself is somewhat blurred by the emphasis apportioned to kidney dysfunction. Second, the reliance on serum creatinine potentially underestimates prognosis with respect to renal outcomes and overestimates true prognosis with respect to liver outcomes. To address this imbalance, MELD should perhaps incorporate a measure of GFR, either by using a gold standard measure of GFR or cystatin C, to more accurately represent residual kidney function. In recognition of these problems, MELD has been adapted to form the UKELD score, which incorporates the serum sodium concentration, with downward adjustment of the integer weighting for serum creatinine [51]. Consequently, in the UK population, UKELD is a better predictor of survival following listing for liver transplantation [50].

The incidence of chronic kidney disease among liver recipients is high, around 27 %, and up to 10 % reach end-stage, requiring renal replacement therapy within 10 years [51]. There are a number of independent risk factors in the pre-transplant period that are associated with chronic kidney disease post-transplantation. These include chronic kidney disease stage, age, gender, ethnicity, and the presence of hypertension, diabetes and hepatitis C prior to transplantation [52]. Importantly, chronic kidney disease post-liver transplantation is associated with a four-fold increase in mortality [53]. Strategies have focused on tailoring immunosuppression regimens to improve long-term renal outcome, in particular, reducing the nephrotoxic calcineurin inhibitor burden, which is often possible due to the immunotolerant properties of the liver. The ReSpECT study compared standard tacrolimus dosing and steroids; low-dose tacrolimus plus steroids; and delayed introduction and low-dose tacrolimus plus steroids plus mycophenolate moefitil. The authors demonstrated reduced nephrotoxicity in the delayed, low dose tacrolimus group [54]. Daclizumab, a monoclonal antibody, was used to provide immunosuppressive cover during the delayed period before the introduction of tacrolimus. The study had a few limitations, however, namely the use of estimated GFR calculated with the Cockcroft-Gault formula, and the fact that a significant number of patients were withdrawn from the high dose group. However, it importantly demonstrated that the tailoring of an immunosuppressive regimen can have a significant impact on nephrotoxicity without detrimental effects on graft function or patient survival [54].

There has also been an increasing trend toward combined liver-kidney transplant if patients have AKI or chronic kidney disease prior to transplantation. However, appropriate allocation of these organs to patients that are most suitable for either OLT alone or combined liver-kidney transplant has created a major dilemma as no single reliable factor has been shown to be predictive of renal recovery or progression of chronic kidney disease after successful OLT.

Pre-emptive kidney transplantation for patients with isolated kidney disease is considered if dialysis is predicted to start within 6 months, which is typically associated with a GFR less than 15 ml/min. Combined liver-kidney transplant is currently indicated for those with combined kidney and liver disease on hemodialysis with

viral, polycystic, or primary oxaluria as etiologies. In this scenario, there is a drive to transplant these patients earlier when their liver disease is not so advanced, e.g., Child Pugh score A or B, because of worse outcomes associated with Child Pugh C cirrhosis. Extensive polycystic liver and kidney disease where the mass of cysts exceeds 20 kg causing malnutrition and cachexia is seen as an indication for transplantation, even though liver synthetic function is often well preserved. Primary oxaluria type 1 is an enzymatic defect resulting in renal calculi and extensive extrarenal oxalate deposits. Combined liver-kidney transplant is recommended early in the course of this disease to prevent extra renal manifestations, in a similar way to familial amyloidosis polyneuropathy [55].

End-stage liver and kidney disease is a recognized indication for combined liver-kidney transplant and was first performed in 1983. Retrospective studies have, however, evaluated factors that may help predict the reversibility of kidney dysfunction in patients with end-stage liver disease. There is some evidence that chronic kidney disease (defined as renal dysfunction for more than 12 weeks), pre-transplant serum creatinine > 160 umol/l, and diabetes, are predictors of poor post-transplant kidney function with estimated GFR of less than 20 ml/min/1.73 m^2 [52]. There is a paucity of research in this field. The implementation and use of improved measures of residual kidney function and the incorporation of these into MELD would help to more precisely prioritize patients and ensure organ allocation is appropriate for liver, kidney, and combined transplant procedures.

Conclusion

Chronic liver disease is associated with primary and secondary kidney disease and impacts markedly on survival. The evaluation of kidney function and injury relies on the measurement of the concentration of serum creatinine, which is affected by the degree of liver disease and the analytical method employed. The integral role of creatinine concentration in the different classifications of AKI, chronic kidney disease and the survival predictive score, MELD, for chronic liver disease, confers large inaccuracies across this population, but currently offers the most cost-effective measure available. Hepatologists should perhaps use exogenous measures of kidney function and biomarkers, like cystatin C and the cystatin C-based equation for estimated GFR, more frequently, as these have been shown to be superior to creatinine. Improved assessment of the degree of residual kidney function may assist clinical decisions regarding risk of AKI, drug therapy in chronic liver disease, the tailoring of post-liver transplant immunosuppression regimens, and the allocation of organs for combined liver and kidney transplantation. Kidney injury biomarkers need further evaluation in the chronic liver disease population, but they seem likely to continue to perform well. Earlier diagnosis and implementation of currently established beneficial therapies seems to be pivotal in potentially reducing the severity of kidney injury and increasing survival outcomes; whether this will be realized remains to be seen.

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Hemofiltration and Hybrid Therapies in 2010

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Introduction

Despite major recent therapeutic improvements, septic shock remains a leading cause of mortality in intensive care patients [1]. In addition, it is important to realize that the mortality rate of patients with septic acute kidney injury (AKI) is much higher than that of patients with non-septic AKI [2]. For more than a decade, it has been suggested that reducing blood cytokine levels in such patients could, at least theoretically, lead to reduced mortality [3, 4]; however, in view of the complexity of the pharmacodynamics and pharmacokinetics of cytokines, this concept is not so simple to apply. Indeed, recent studies have attempted to demonstrate that high volume hemofiltration (HVHF) with enhanced adsorption can modulate and ameliorate sepsis- induced hemodynamic instability [5]. This recently published paper [5] suggested that membranes with enhanced adsorption are the key and that increased extraction from the central circulation is sufficient to obtain a beneficial clinical effect. 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. Therefore, HVHF and enhanced adsorption should work synergistically in this model. In order to consolidate this hypothesis, it seems fruitful to discuss the three separate theories that have been put forward in recent years as possible explanations for the clinical findings observed in septic patients who underwent a number of different blood purification techniques. The HVHF and hybrid techniques that are currently available to the clinician are diverse and deserve a brief description.

Until recently, AKI in intensive care was, on the whole, considered a condition of hemodynamic origin and consequently efforts were largely concentrated on increasing renal flow by increasing cardiac flow and perfusion pressure [6]. AKI was thought to be a consequence of low renal blood flow, whether induced by cardiogenic shock or distributive (septic) shock. Early in this decade, Bellomo's group presented data shedding new light on the animal model of septic AKI. Because renal blood flow, both medullar and cortical, was maintained and even increased in severe septic shock [7], earlier concepts were undermined and it became clear that septic AKI was a totally different physiological phenomenon to non-septic AKI. Furthermore, it was demonstrated that there was an important role for apoptosis in sepsis and septic shock rather than purely necrosis [8]. Despite these findings, and although animal models have provided substantial advances in elucidating the etiology of lesions, such as tubular apoptosis [9], whether apoptosis really plays a key role in mechanisms of organ dysfunction in humans remains a matter of debate [10].

Mechanisms of Removal and Transport by Synergistic Action of HVHF and Enhanced Adsorption

A potential synergistic action of HVHF and enhanced adsorption can be further defended by reviewing three previous theories regarding mediator removal during plasma separation techniques. In the peak concentration hypothesis [11–13] of Ronco and Bellomo, efforts concentrate on removing mediators and cytokines from the blood compartment in the pro-inflammatory phase of sepsis. It is hoped that by reducing the amount of free cytokines, remote organ (associated) damage can be limited, thereby improving patient survival. In this theory, changes in mediators and cytokines at interstitial and tissue levels are not taken into account, although it seems logical that they are of clinical importance. In this setting, techniques that facilitate rapid and substantial removal of mediators are preferred.

After an extensive literature review, a second model was developed coupling mediator removal from the blood compartment to changes in the interstitial and blood compartments. This model, the threshold immunomodulation hypothesis, sometimes referred to as the Honoré concept [14, 15], takes a more dynamic view of the system. Pro-mediators and 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. At this level, the cascades are interrupted and no further harm can be done to the tissues. However, when applying plasma separation techniques in clinical practice, determination of this threshold point is difficult as there may still be significant changes taking place at the interstitial and tissue level, while no changes in the blood compartment can be observed. A number of observational studies using HVHF (and derived plasma separation techniques) demonstrated improved hemodynamics and survival in some patients without a significant drop in mediator blood levels [16–18]. One could, therefore, postulate that substantial biological effects can be obtained with HVHF without any dramatic decrease in plasma cytokine levels, although harmful tissue levels still decrease. It remains unclear in this model how HVHF promotes mediator and cytokine flow from the tissue and interstitium to the blood compartment.

In the mediator delivery hypothesis [19], otherwise known as the Alexander concept, the beneficial use of HVHF and especially of high replacement volumes (3 to 5 l/hour) has been emphasized. With this technique a 20 to 40-fold increase in lymphatic flow has been demonstrated in several papers [20–22], which could 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 could be of great importance, not only for extraction but also to stimulate lymphatic transport between the interstitium and tissue compartments and the blood compartment. It, therefore, seems plausible that HVHF enhances transfer of mediators to the blood stream and that enhanced adsorption plays a role in the efficient removal of those mediators from the blood circulation, the two components thus acting synergistically.

Synergistic action of HVHF and Enhanced Adsorption: Clinical Feasibility and Effects beyond Hemodynamics

Undoubtedly, the strength of the concomitant use of HVHF and enhanced adsorption lies in the fact that they can substantially increase mediator removal when used

together. However, some drawbacks of this combined technique should be noted. In focusing on effective adsorption, changing the membranes is frequently essential and herein lies a potential hurdle for implementation in daily medical practice, because of increasing costs and the nursing workload during the hemofiltration sessions [23]. To counter this, clinicians and investigators instigated frequent membrane changes only in the very early phase of septic shock, when modulation of serum endotoxin and cytokine levels seems most critical. Furthermore, the phenomenon of adsorption may be transient because of the saturation of the membrane but also due to the de-adsorption process which takes place after only a few hours [24]. Last but not least, it would be desirable to have data showing that improved hemodynamics as a result of a plasma separation technique correlated with improved outcome as this is most relevant to the clinician [25]. No study has yet been able to demonstrate this correlation although some recent studies have come very close [26]. Therefore, it remains unproven whether there is a link between improved hemodynamics and eventual improvement in mortality [27].

In recent years, some studies have demonstrated that improved hemodynamics were associated with improved mortality but this was achieved via mechanisms beyond hemodynamic improvement. For example, Yekebas et al. [28] demonstrated that the early application of HVHF in a pig model of pancreatogenic sepsis reduced the secondary infection of ascites and blood and was associated with lower mortality. This was the first time that early application of HVHF was associated with a reversal of the 'immunoparalysis' induced by sepsis. In other words, HVHF restored late immuno-homeostasis and downregulated back to normal the (over)-compensatory anti-inflammatory response syndrome [29]. Kellum et al. provided some additional evidence of this concept [30]. Sepsis was induced in a rat model and the animals were randomly assigned to a plasma separation technique to assess the effect

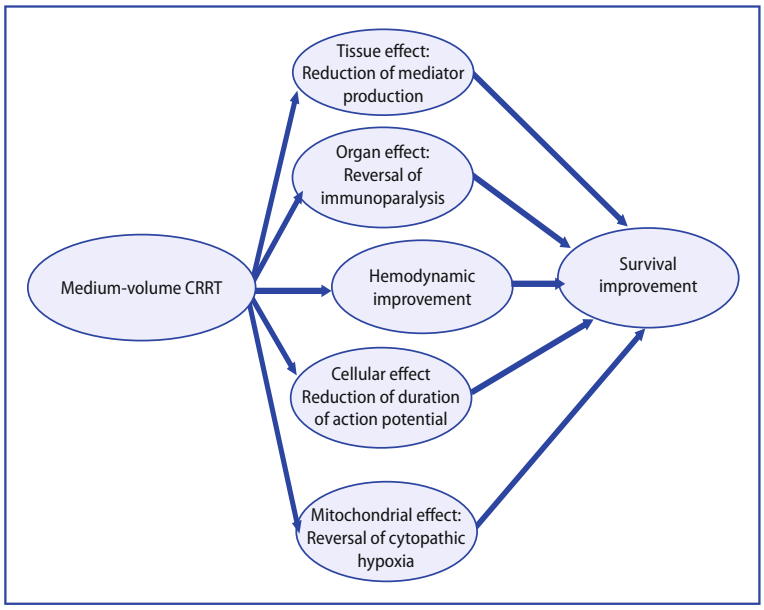

Fig. 1. Hemodynamics and beyond: Have we found the missing link?

of the technique on the liver production of mediators via nuclear factor-kappa B (NF-κB) production. Application of a plasma separation technique not only improved hemodynamics but also survival [30]. These experiments also demonstrated for the first time that a plasma separation technique was able not only to reduce mediator blood levels but also mediator production in the liver. The exact mechanism of this upstream downregulation remains to be elucidated. Finally, Li et al. [31] investigated the role of HVHF directly in a pig model of sepsis. In some of the animals, the activity of the mitochondrial respiratory chain was measured in the myocardium. These investigators demonstrated that sepsis induced a dramatic reduction of this activity which was, however, fully restored by HVHF. Altogether, these three series of experiments demonstrate the link between improved hemodynamics and improved survival by mechanisms beyond hemodynamics [32, 33] (**Fig. 1**).

New Pathophysiological Insight regarding Septic Acute Kidney Injury

Most scientists were, until very recently, convinced that septic AKI was not an apoptotic process but could lead (at some stage) to necrosis. From a theoretical point of view, necrosis results from the additive effect of a number of independent biochemical events that are activated by severe depletion of cell energy stores. In contrast, apoptosis occurs via a coordinated, predictable and pre-determined pathway. These biochemical differences between apoptosis and necrosis have important therapeutic implications. Once a cell has been severely injured, necrosis is difficult to prevent. In contrast, the apoptotic pathway can potentially be modulated to maintain cell viability [34]. The components of the apoptotic pathway that are potentially amenable to therapeutic modulation are numerous, at least in theory [35]. In this new therapeutic avenue for septic AKI or apoptotic-inflammatory AKI, the administration of caspase inhibitors seems to be taking on a role of increasing importance. Indeed, caspase inhibitors ameliorate ischemia-reperfusion injury in multiple organs including the kidney. However, the extent to which this protective effect of caspase inhibition is caused by reduced (intra-renal) inflammation, or by amelioration of renal tubular cell loss due to apoptosis, remains uncertain [36]. In addition to caspase inhibition, the apoptotic pathway offers many potential targets for therapeutic interventions to prevent renal tubular cell apoptosis. All inhibitors likely reduce renal function impairment. In a model of glycerol-induced AKI in rats [37], results demonstrated that caspases participate in various pathogenic mechanisms in glycerol-induced AKI, inclduing inflammation, apoptosis, vasoconstriction, and tubular necrosis. The early inhibition of caspases attenuated these mechanisms and reduced the renal function impairment in glycerol-induced AKI [37]. It has also been demonstrated that apoptosis occurs in the kidney during lipopolysaccharide (LPS)-induced AKI. However, the relative importance of apoptosis in LPS-induced AKI remains unproven. As the caspase enzyme cascade plays a key role in the development of apoptosis, Guo and co-workers [38] hypothesized that treatment with a caspase inhibitor would protect mice from LPS-induced AKI. A study format was chosen whereby mice received an injection of LPS and were treated with either a broad-spectrum caspase inhibitor or remained untreated. It was concluded that caspase inhibition may protect against LPS-induced AKI, not only by preventing apoptotic cell death but also by inhibiting inflammation [38]. These authors further hypothesized that apoptotic kidney cells may even be a source of local inflammation

leading to subsequent non-apoptotic renal injury [38]. Another recent study showed that plasma from septic burn patients with AKI could initiate pro-apoptotic effects and functional alterations in renal tubular cells and podocytes *in vitro*, effects that correlated with the degree of proteinuria and renal dysfunction [39]. In this model, sepsis and burn had additive or even synergistic effects [39]. This study certainly encourages further research of therapeutic interventions in several areas such as the binding and elimination of the source of endotoxin by extracting the source of sepsis, the blocking of various apoptotic pathways, or even the extracorporeal removal of circulating toxic mediators using high flow hemofiltration, high permeability hemofiltration, or coupled plasma filtration with absorption [40]. In this very recent study [39], extracorporeal therapy with polymyxin-B membranes (PMX-B) reduced the pro-apoptotic activity of the plasma of septic patients on cultured renal cells. These data provide further confirmation of the role of apoptosis in the development of sepsis-related AKI [39]. It seems likely that plasma separation techniques can prove benefit in renal injury through the removal of pro-apoptotic factors and cytokines.

Update on Very Recent Trials in Critically ill Patients with AKI

While all the studies discussed earlier have been promising, larger studies and randomized controlled clinical trials are now needed, especially to evaluate the effects of dosing and timing of renal replacement therapy (RRT). The results from one such study, the so-called Veterans Affairs/National Institutes of Health (VA/NIH) acute renal failure study, were published in 2008 [41]. This was a very large and well conducted randomized study comparing two different doses of continuous RRT (CRRT, 20 versus 35 ml/kg/h) and two different intensities of intermittent RRT depending on the hemodynamic status of the patient. This study could not demonstrate 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 [42, 43], notably on the supposed 35 ml/kg dose of CVVH in the intensive treated group. Treatment in this group was divided 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, 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 had 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 the intensive care unit (ICU) [44]. In the same vein, a recent review highlighted that in the recently published VA/NIH trial [41], the delay in timing was most probably responsible for the high rate of dialysis dependency [45]. Finally, in the light of the data, associated with important pitfalls identified in the VA/NIH trial [42, 43], an expert panel from the Société de Réanimation de Langue Française (SRLF) in France [45] (not necessarily the strongest advocates of the 35 ml/kg/h dose) felt obliged to publish a recommendation addressed to the intensivist community in France, stating the continued importance of the 35 ml/kg/h dose in AKI in

ICU patients. In addition, and in spite of the recently published Australian and New Zealand Intensive Care Society (ANZICS) clinical trials group RENAL study [46], which compared augmented (40 ml/kg) with normal RRT (25 ml/kg) in ICU patients with severe AKI and showed no differences between groups (in terms of mortality), ICU physicians remain prudent to avoid underdosing of therapy especially in septic AKI as indeed the RENAL study was not designed to specifically assess septic AKI. While most of the large randomized trials investigating hemofiltration doses in AKI patients are now completed, one remaining study is comparing HVHF with standard CVVH in septic AKI. The so-called IVOIRE (hIgh VOlume in Intensive Care) study [47] will try to expand on the findings of the initial study by Ronco and colleagues [48] in septic patients. This large randomized study will include patients with septic shock plus AKI, and compare patients receiving HVHF at 35 or 70 ml/kg/h. The first interim analysis will be performed when 150 patients have been included, at the end of 2009.

Conclusion

In recent years, a number of different RRT techniques have been developed and studied in septic patients. Manipulation of ultrafiltrate dose, membrane porosity, mode of clearance, and combinations of techniques have yielded promising findings. However, at present, conclusive evidence based on well-designed, randomized controlled trials remains scarce, limiting the practical implementation of many techniques in daily practice outside the context of a study. From the few well-designed and published studies that we have so far, it is safe to say that optimization of delivered dose in RRT with an ultrafiltration rate between 35 and 45 ml/kg/h, with adjustment for predilution and down time as recommended by the The DOse REsponse Multicentre International collaborative initiative (DO-RE-MI) study [49], can be recommended for the septic patient with AKI until other data become available [45]. If continuous hemofiltration is not available, daily dialysis is recommended in septic AKI [50]. The results of further dose outcome studies with higher ultrafiltration rates will likely be the stepping stone to further improvements in daily clinical practice. Hybrid techniques (like combined HVHF and enhanced adsorption) will also likely have a role in the expanding field of RRT in the septic patient in the near future. In terms of septic AKI *per se*, revision of outdated concepts, with subsequent regime changes seems inevitable in the light of recent histological findings from biopsies in patients with septic AKI (demonstrating the increasing role of apoptosis in septic AKI). Intervention in inflammatory pathways, both directly and by optimization of plasma separation techniques, promises to be rewarding. Changes in fluid regimes and vasopressor use during resuscitation merit further investigation in septic AKI. Early detection of renal dysfunction using new biomarkers will have a direct effect on intervention and change clinical practice.

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Timing of Renal Replacement Therapy

W. De Corte, I. De laet, and E.A.J. Hoste

Introduction

Acute kidney injury (AKI) defined by the sensitive Risk, Injury, Failure, Loss, and End-stage kidney disease (RIFLE) or AKI criteria occurs in 10 to 60 % of intensive care unit (ICU) patients, and is associated with increased mortality [1, 2]. Despite advances in ICU care, the mortality of patients with AKI has remained more or less stable over recent years [3]. A possible explanation for this unchanged mortality in AKI includes the plethora of definitions used to define AKI, but also differences in case mix, including more older and more seriously ill patients.

Although renal replacement therapy (RRT) has been in use for more than half a century, many aspects of this therapy remain controversial. The timing of initiation of RRT is one of the issues on which there is no consensus. In analogy with findings in early sepsis, it seems plausible that early initiation of RRT may positively impact on outcomes in ICU patients with AKI. So, why is there this general reluctance for early initiation of RRT in ICU patients with AKI? We should also take into account that there is a historic tendency to avoid RRT as long as possible. This is logical from a nephrological and chronic kidney disease based point of view. You spare your patients as long as possible the dreaded routine of 4 hours of dialysis, 3 times a week, with its important impact on social life. Further, the concept of 'Primum non nocere' – do no harm – may overrule the obvious benefits of RRT when the evidence for early initiation is so limited. Possible adverse effects of RRT include hypotension, arrhythmia, hemorrhage, and complications of vascular access placement. There is also a notion that, especially in intermittent RRT, procedure-related hypotension causes renal ischemia, and further deterioration of AKI. This may slow the recovery of renal function and lead to the development of end-stage renal failure [4, 5].

In this chapter we will describe the evidence related to the timing of initiation of RRT in ICU patients with AKI. Building on this evidence we highlight the emerging – but underemphasized – paradigm shift concerning timing of initiation of RRT in this patient group.

AKI: An Historical Overview

A Problem of Uremia

Willem Johan Kolff fabricated the world's first successful artificial kidney in 1942. In those days, AKI was considered a problem of uremia. This vision, beautifully demonstrated by the title of Kolff's publication in 1947, "New ways of treating uremia",

stood for several decades [6]. Dialysis was in these early days reserved as a treatment for uremic symptoms in patients with AKI.

The Concept of Prophylactic Dialysis

Several years later, in 1953, Teschan introduced the concept of 'prophylactic' dialysis, postulating that "... dialysis, applied before uremic symptoms appeared, should prevent both the uremic syndrome and many of it's commonly lethal sequellae" [7]. When the concept of 'prophylactic dialysis' was introduced, it seemed logical to keep serum urea as the most important parameter for guiding initiation of RRT and change only the level of serum urea required. Again this vision remained in place for several decades and is illustrated by several studies published since the 1960s (**Table 1**). Until recently, the discussion was about which serum urea threshold should be used to optimize outcome after AKI. A whole series of mostly retrospective studies suggested that initiation of RRT at lower serum urea concentrations or earlier in the course of AKI was associated with improved outcome. A prospective randomized study by Conger supported this concept [8]. However, two other prospective randomized studies using different serum urea cut-offs were unable to demonstrate that early initiation of RRT based on lower serum urea was associated with better outcomes [9, 10]. The Acute Kidney Injury Network (AKIN) working group on timing of initiation of RRT summarized, during the Vancouver meeting in 2006, the classical indications for initiation of RRT in AKI patients [11] (**Table 2**). A blood urea nitrogen concentration (BUN) greater than 76 mg/dl (after Liu et al. [12]) was considered a relative indication, and a BUN greater than 100 mg/dl (after Kleinknecht et al. [13], Conger et al. [8], and Gillum et al. [9]) an absolute indication.

Table 1. Studies that evaluated timing of initiation of renal replacement therapy based on low or high serum urea concentration.

Year	Author	Study design	Number of patients	Serum urea cut-off, mg/dl		Mortality, %	
				Early	**Late**	**Early**	**Late**
1961	Parsons [29]	R	33	336	448	25	88
1966	Fischer [30]	R	162	341	518	57	74
1972	Kleinknecht [13]	R	500	200	350	29	42
1975	Conger [8]	P	18	112	269	20	64
1986	Gillum [9]	P	34	185	224	59	47
1999	Gettings [31]	R	100	135	135	61	80
2002	Bouman [10]	P	106	240	240	29	25
2006	Liu [12]	P	243	170	170	35	41

R: retrospective; P: prospective

From Acute Renal Failure to AKI, and from Renal Replacement Therapy to Renal Support: A Paradigm Shift

In recent years, perhaps due to better understanding of the intricate interplay between different organ systems and the importance of seemingly small changes, the concept of the disease previously known as 'acute renal failure', or complete failure of the kidneys, has evolved into a more complex and textured view on the problem

Table 2. The indications for renal replacement therapy (RRT) in patients with acute kidney injury (AKI). The RIFLE classification has been extensively validated, whereas the AKIN stages still need further confirmation. The data indicate that the indications for and timing of RRT must be viewed within the context of the patient's entire clinical condition, with most indications being relative and a small number of absolute indications. It must also be clearly stated that the traditional indications for timing of RRT in relatively stable patients with isolated acute oliguric renal failure as a single-organ system failure do not apply to critically ill patients with AKI as a component of multiorgan failure. In addition, there is a growing body of evidence that fluid overload as a result of AKI contributes significantly to mortality and morbidity and that control of volume status with CRRT can improve outcomes, especially in pediatric AKI and following cardiac surgery [32–36]. A pH cut off of 7.15 was chosen in parallel to the Surviving Sepsis Campaign guidelines [37]. Bicarbonate intervention studies did not show benefit when administered in patients with pH > 7.15. From [11] with permission

Indications	Characteristics	Absolute/Relative
Metabolic abnormality	BUN > 76 mg/dl (27 mmol/l)	Relative
	BUN > 100 mg/dl (35.7 mmol/l)	Absolute
	Hyperkalemia > 6 mEq/l	Relative
	Hyperkalemia > 6 mEq/l with EKG abnormalities	Absolute
	Dysnatremia	Relative
	Hypermagnesemia > 8 mEq/l (4 mmol/l)	Relative
	Hypermagnesemia > 8 mEq/l (4 mmol/l) with anuria and absent deep tendon reflexes	Absolute
Acidosis	pH > 7.15	Relative
	pH < 7.15	Absolute
	Lactic acidosis related to metformin use	Absolute
Anuria/oliguria	RIFLE class R	Relative
	RIFLE class I	Relative
	RIFLE class F	Relative
Fluid overload	Diuretic sensitive	Relative
	Diuretic resistant	Absolute

BUN: blood, urea, nitrogen

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in which moderate kidney dysfunction or AKI is also considered. AKI may have numerous and, most of the time, multiple causes and can be observed in a wide range of clinical settings. Moreover, AKI causes a new myriad of problems related to solute and toxin clearance, fluid and electrolyte balance.

Septic shock and major surgery account, respectively, for one third to one half of the episodes of AKI observed in ICUs [14]. However, the etiology of AKI is often multifactorial and results from combined insults such as hypotension, sepsis and toxic exposure. Approximately 70–80 % of patients with severe AKI have associated respiratory and circulatory failure, or multiple organ dysfunction syndrome. Moreover, therapeutic and diagnostic interventions, e.g., volume resuscitation related to severe sepsis or medical imaging, requiring administration of nephrotoxic radio contrast media, may contribute to worsening of AKI. In addition, the knowledge that removal of waste products, such as urea, is only one aspect of kidney function and other functions may also be important to the complex picture of multiple organ dysfunction syndrome led to the realization that guidance of RRT initiation by serum urea concentration alone was very unlikely to deliver the best treatment. Perhaps, the introduction of the idea of 'renal support', first mentioned by Mehta [4], reflects a more plausible approach. In this concept of 'renal support', RRT is used as a bridge to maintain meta-

bolic, fluid and acid-base parameters in optimal state, so as to allow for recovery of all organ functions, including kidney function [4]. Within this new concept, indications and, therefore, timing of initiation of RRT have yet to be defined.

Definition of Timing of Initiation of RRT in ICU Patients

The clinical outcomes related to timing of initiation of RRT are influenced by how timing is defined. At present there is no widely accepted definition of 'timing of initiation' of RRT. As stated by the AKIN consensus group, 'timing' can be described by qualitative criteria e.g., time from hospital admission to RRT, or by a more quantitative characterization based on severity of illness, e.g., change in serum urea or serum creatinine concentrations, or number and severity of comorbidities.

What does the Evidence tell Us?

Urea

Historically, timing of initiation of RRT was based on serum urea. The patient cohorts described in these landmark studies, dating back over a 50-year period, are not at all comparable to the AKI patients we are currently treating in our ICUs. Prospective studies on this topic were performed 10 to 38 years ago. In other words, studies that used serum urea as a marker for timing of initiation of RRT probably currently have limited validity. In addition, the individual studies were underpowered, and included patients from very specific cohorts, elements that also limit their validity. Recent studies have not demonstrated that serum urea can differentiate between outcomes [15, 16].

Finally, the biological rationale that urea is a good biomarker for severity and duration of AKI is weak. Serum urea is determined by many other variables that have no relation to kidney function, such as catabolism, administration of corticosteroids (as for instance in sepsis or acute respiratory distress syndrome [ARDS]), gastrointestinal bleeds, etc [17]. In summary, serum urea is no longer a good variable for assessment of timing of initiation of RRT.

Volume overload

Another indication for RRT may be volume overload. A sub-analysis of the Sepsis Occurrence in Acutely ill Patients (SOAP) database showed that after correction for other covariates a positive fluid balance was associated with an increased 60-day mortality (OR = 1.21, 95 % CI = 1.19, 1.28) [18]. Others have confirmed that volume overload is associated with mortality [19]. Volume overload may therefore be an important parameter for timing of initiation of RRT.

Early initiation in the course of AKI

Circumstantial evidence suggests that early initiation is better. In Australia, early initiation of RRT is common practice. In addition, Australian intensivists almost completely rely on continuous RRT (CRRT). Silvester et al., in their prospective epidemiologic study of Australian adult ICUs, reported an in-hospital mortality rate for patients with acute renal failure requiring RRT of 46.8 % and an ICU mortality of 39.5 % [20], which is less than the 60 % mortality reported in the Beginning and Ending Supportive Therapy for the Kidney (BEST Kidney) study, a multicenter study conducted in 23 countries [14], and in a multicenter study in Austria [21]. Early ini-

tiation may not only improve survival but also kidney recovery. Silvester et al. [20] also reported a lower rate of patients with non-renal recovery or dialysis dependency at hospital discharge compared to that reported by the BEST Kidney investigators (8.3 % vs 13.8 %) [14].

In the BEST Kidney study [14], initiation of RRT after 5 days or more of ICU stay was associated with a 2.2 odds ratio (OR) (95 % CI = 1.44 – 3.37) for mortality. Similar findings were reported by Payen et al., who found that mortality of patients in whom RRT was initiated after 2 days of ICU stay was 20 % higher compared to patients with early initiation of RRT [18]. Finally, Mehta et al. found that early consultation by a nephrologist, i.e., early initiation of RRT, was associated with a 25 % lower mortality in dialyzed patients [22]. Serum urea concentration did not differentiate between survivors and non-survivors in the BEST Kidney study [14].

A meta-analysis of 23 comparative studies, suggested that early initiation was associated with better outcome [23]. The studies included in this meta-analysis were heterogeneous concerning the definition of timing of RRT, and were mostly retrospective in design. These findings should, therefore, be considered as hypothesis generating rather than as high level evidence.

It is difficult to draw a definitive conclusion on the definition of 'timing' from these scarce and retrospective data. From a pathophysiological viewpoint, however, it seems logical that timing should be defined on quantitative data defining severity of AKI and associated organ failure, rather than on a temporal definition.

Future Directions: Early Goal-directed Therapy to Improve Renal Outcome

Although the evidence is limited, it seems plausible that RRT should be initiated early in the course of AKI, in analogy to the approach of 'early goal-directed therapy' in the treatment of patients with severe sepsis or after major surgery [24, 25]. Intuitively, a similar 'early goal-directed' approach may be beneficial in managing (severe) AKI in ICU patients. Unfortunately, there are as yet no data to support this interesting theory. In an effort inspired by this 'early' philosophy, a recent paper introduced the concept of "door-to-dialysis" time [26]. This approach seems attractive, but again, there are too few data to consider adopting this concept in general ICU practice. It seems clear that additional research to define the optimal timing of initiation of RRT is needed. We suggest a well designed prospective randomized trial on the timing of initiation of RRT. The design of such a trial needs careful consideration. We propose that patients in such a study are stratified according to severity of illness. Based on the above, we believe that serum urea can be discarded as a biomarker for this study. RIFLE or AKI criteria have been proposed as alternatives, and are probably more accurate in differentiating less severe from more severe AKI. Volume status, and hemodynamic status are determinants that should also be considered. Finally, endpoints should focus on long term (3 months to 1 year) 'renal outcome' and survival, because mortality and development of end-stage renal disease is markedly increased up to 1-year after AKI [27, 28]. Given the high cost of chronic RRT and the scarcity of organs for renal transplantation, renal outcome emerges as a very important and relevant endpoint.

Conclusion

The timing of initiation of RRT in ICU patients with AKI is a complex problem. As a consequence, this has been difficult to study and varies among different clinicians

and institutions [20]. At present there is no widely accepted definition of what 'timing of initiation' of RRT means. Whether timing of RRT should be measured from ICU admission, from the diagnosis of severe AKI, or using arbitrary thresholds of traditional or new biomarkers remains controversial. Recent data suggest a benefit of early RRT. These data also emphasize the need for a consensus definition, given the fact that clinical outcomes related to the timing of initiation of RRT are influenced by how timing is defined. Initiation of RRT based on serum urea should be abandoned since evidence is limited and based on studies that have little applicability to modern intensive care. In addition, serum urea is determined by many other variables that have no relation to kidney function. The RIFLE classification for AKI has been proposed as a more accurate alternative. We suggest that a prospective randomized trial is needed on the timing of initiation of RRT in ICU patients with AKI, stratifying patients according to the RIFLE classification, volume status, and hemodynamic status. We suggest the use of renal outcome and long-term outcome as endpoints for this study.

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XII Neurological Aspects

Multimodal Monitoring: A Critical Tool in the Neuro-ICU

K. Shukri and F.S. Ali

Introduction

Cerebrovascular accidents and severe traumatic brain injury are a significant cause of morbidity and mortality worldwide. Approximately 90 % of patients with secondary brain insults after head injury require intensive care unit (ICU) admission [1]. The etiology of these insults can by systemic, e.g., hypoxemia, hypotension, anemia, acid-base disturbance, uncontrolled glucose levels, or cerebral, e.g., intracranial hypertension, cerebral edema, seizures, regional blood flow disturbance, free radical induced damage, mitochondrial dysfunction, metabolic and ionic derangement [2].

Monitoring in ICU patients with acute brain injury is classified into clinical examination, systemic and cerebral monitoring of variables, and imaging modalities (**Table 1**). The clinical neurological examination is unreliable and absent [3]; imaging modalities are non-continuous and cannot be obtained at the bedside; and general systemic monitoring reflects global physiology [4]. New methods of cerebral multimodal monitoring have emerged in the last decade, including invasive and non-invasive cerebral oxygenation, cerebral microdialysis, transcranial Doppler, and continuous electroencephalogram (EEG) monitoring which can detect brain metabolism, blood flow and function, and assess prognosis. These developments have led to a trend towards development of new strategies for the management of acute brain injury to optimize the physiological environment in the brain so as to minimize primary and secondary insults and improve neurological outcome. Indeed, there is growing evidence that a substantial component of the cell death of primary injury occurs hours after the injury and that its time-course overlaps with secondary injury [5].

Table 1. Monitoring techniques in acute brain injury

Neurological examination	Pupils, reflexes, muscle tone, new focal deficits
General systemic monitoring	Arterial blood pressure, heart rate, respiratory rate, body temperature, arterial blood gases, laboratory tests
Imaging monitoring modalities	Computed tomography (CT)-scan, magnetic resonance imaging (MRI), positron emission tomography (PET) scan, cerebral angiography
Mulitimodal cerebral monitoring	Intracranial pressure (ICP)/cerebral perfusion pressure (CPP), brain tissue oxygen pressure ($PbtO_2$), jugular venous oxygen saturation ($SjvO_2$), oxygen extraction, electroencephalogram (EEG) Evoked potentials, transcranial Doppler flow Microdialysis (lactate/pyruvate/glutamate levels) Near-infrared spectroscopy

To date, no randomized controlled trials have been conducted to demonstrate superiority of one monitoring modality over another in terms of improved outcomes. The goal of monitoring in the injured brain is to enable detection of harmful physiological events before they cause irreversible brain damage. Recently, data have suggested that interventions previously thought to improve tissue oxygenation by improving intracranial pressure (ICP) and cerebral perfusion pressure (CPP) may increase therapy intensity without improving outcomes [6].

ICP monitoring is present in the guidelines of the European Brain Injury Consortium and the Brain Trauma Foundation [7, 8], but its efficacy remains under debate. A recent study in patients with severe head injury who had survived and remained comatose for > 24 hrs reported that ICP-targeted management was not associated with improved outcomes compared to management based on clinical observations and computed tomography (CT)-findings [9]. However, patients with severe head injury in the absence of a mass lesion may benefit from ICP/CPP-targeted therapy [10].

In this chapter we will discuss some potential applications of multimodal monitoring, using three illustrative case scenarios.

Multimodal Monitoring in Hypoxic-Ischemic Encephalopathy

> Case scenario: A 40-year old man underwent therapeutic hypothermia post-cardiac arrest. After completing the rewarming phase, the patient started to have frequent uncontrollable seizures. What ideal neuromonitoring modalities can be used in patients undergoing therapeutic hypothermia? Should every patient with anoxic-ischemic encephalopathy who is treated with therapeutic hypothermia have continuous EEG monitoring?

About 40 % of patients with cardiac arrest can be resuscitated with restoration of spontaneous circulation and respiration. The one-year survival rate of initially unconscious survivors is between 10 – 25 % [11]. Hypoxic-ischemic encephalopathy is the cause of mortality in 30 – 40 % of patients following cardiac arrest [12]. The use of mild therapeutic hypothermia after cardiac arrest has improved neurological outcomes and survival for patients with ventricular tachycardia and ventricular fibrillation [13 – 16].

The role of neuromonitoring in cardiac arrest survivors undergoing mild therapeutic hypothermia is in the detection of complications related to anoxic-ischemic encephalopathy, assessment of seizure activity, and prognostication. The incidence of non-convulsive status epilepticus in comatose survivors with brain injury is 19 to 34 % [17, 18]. Occult seizures can be masked by the use of neuromuscular blocking agents and heavy sedation. Use of continuous EEG throughout the hypothermia and rewarming phase or a baseline EEG and post-cooling EEG has been shown to be beneficial [18, 19].

Survivors of cardiac arrest have a high risk of elevated ICP and low CPP during the rewarming phase. CT findings of brain edema support the need for invasive cerebral monitoring, including ICP, CPP, brain tissue oxygen pressure ($PbtO_2$) and possible microdialysis, in order to preserve cerebral metabolic homeostasis and minimize morbidity. Lemiale et al. demonstrated that the cerebral oxygen extraction ratio was a strong neuroprognosticator by day 3 after cardiac arrest [20]. Cerebral oxygen extraction is the difference between the oxygen hemoglobin saturation of cerebral arterial and mixed venous (i.e., internal jugular) blood, and can be measured by jugular venous oximetry monitoring which is a minimally invasive tech-

Table 2. Recommended multimodal monitoring for hypoxic–ischemic encephalopathy

Neurological condition	Multimodal monitoring modality	Parameter	Rationale	Limitations
Hypoxic-ischemic encephalopathy	1. EEG	Epileptic activity	To detect persistent seizures	Non-continuous Taken in isolation
	2. cEEG	Activity changes suggesting ischemia Continuous seizures	Detect non-convulsive seizures	Invasive if in-depth cEEG used
	3. $SjvO_2$	Cerebral oxygen extraction	Detect global cerebral oxygenation Prognostication	Invasive but safe Does not detect regional changes
	4. Somatosensory-evoked potentials	Cortical N20 response to median nerve stimulation	Ideal prognostic test	Test is sensitive to poor outcome in 50 %
	5. Train of four		Assess the depth of neuromuscular blockade	

EEG: electroencephalogram; cEEG: continuous electroencephalogram; $SjvO_2$: jugular venous oxygen saturation

nique and provides an indirect assessment of cerebral oxygen utilization. Blood from the venous sinuses of the brain drains via the internal jugular veins into the right atrium. A fiber-optic catheter or central line catheter is inserted retrogradely into the internal jugular vein; its correct position is confirmed when the catheter tip is level with the mastoid air cells on a lateral neck radiograph (level with the bodies of C1/C2). Aspiration of blood from the jugular bulb represents the mixed cerebral blood flow. The normal jugular venous oxygen saturation ($SjvO_2$) is 60 – 70 %. A low $SjvO_2$ (high oxygen extraction) may indicate a low cerebral blood flow in relation to cerebral metabolic rate of oxygen consumption ($CMRO_2$) [21].

We, therefore, suggest that, in patients undergoing therapeutic hypothermia for post-cardiac arrest, continuous EEG and $SjvO_2$ monitoring are of value but should be used in selected groups of patients based on the duration of anoxia, duration of cardiopulmonary resuscitation (CPR), and the use of neuromuscular blocking agents. There is no evidence to support the use of ICP/CPP monitoring, $PbtO_2$ or microdialysis in all patients with anoxic-ischemic encephalopathy (**Table 2**).

Multimodal Monitoring in Traumatic Brain Injury

> Case Scenario: A 25 year-old woman with severe traumatic brain injury (TBI) has a sudden increase in ICP to 30 mmHg and a reduction in CPP to less than 50 mmHg with dilated pupils and seizures. Aggressive pharmacological treatment is unsuccessful and the patient dies. Two questions are posed related to the monitoring in such a case: Is ICP/CPP monitoring adequate in patients with TBI, and are there other parameters that could have been monitored which could influence treatments to improve outcomes?

Severe TBI is clinically defined as any head injury that results in a post-resuscitation Glasgow Coma Scale (GCS) of 8 or less on admission or during the ensuing 48 hours

[22]. The overall mortality of patients with severe TBI who survive to reach the hospital is up to 65 % [23]. Despite encouraging animal studies, human trials assessing the use of pharmacological agents in patients with TBI have all failed to show efficacy. ICP monitoring has become an integral part in the management of TBI, but is still not practiced universally as there is no class 1 evidence to support its use or to suggest that it is associated with improved outcomes.

Monitoring $SjvO_2$ is a simple and safe technique which estimates global cerebral oxygen delivery and utilization, but lacks sensitivity for regional changes. Reduction of $SjvO_2$ to < 55 % indicates that cerebral oxygen delivery is inadequate to meet demand and this is related to reduced cerebral blood flow secondary to decreased CPP. Reduction of $SjvO_2$ to < 50 % in TBI is associated with poor outcome [24]. A study using positron emission tomography (PET) revealed that $SjvO_2$ did not decrease to less than 50 % until 13 % of the brain became ischemic [25]. Barbiturate-induced pharmacological cerebral metabolic suppression in patients with head injury can be guided by $SjvO_2$ monitoring. This was demonstrated by Cruz et al. who evaluated $SjvO_2$ before and after intravenous administration of phenobarbital for management of refractory intracranial hypertension in comatose patients with traumatic brain swelling. Outcomes were better in patients with $SjvO_2 > 45$ % [26]. Limitations of $SjvO_2$ monitoring include its inability to detect focal regions of ischemia, the fact that good quality data are obtained in only 50 % of placements, and its variation with $PbtO_2$ [27]. Moreover, there are no randomized prospective trial data that convincingly demonstrate poor outcomes in patients with low $SjvO_2$ values. Nevertheless, despite the limitations, $SjvO_2$ monitoring has the potential to impact on patient care in the neuro-ICU.

A new monitoring modality consists of invasive probes to monitor focal $PbtO_2$. One currently used system is the Licox System, which measures interstitial brain tissue oxygenation in mmHg and brain temperature via a polarographic Clark Type electrode, and is used in conjunction with ICP/CPP monitoring methods. This probe is inserted approximately 35 mm below the dura into the white matter of the brain either on the injured side or the non-injured side but should not be placed directly into the lesion. The Licox System is usually placed within 24–48 hours of injury as the sooner cerebral hypoxia is detected the sooner treatment can be initiated to try and limit secondary injury. A normal $PbtO_2$ value is 25–35 mmHg. $PbtO_2$ can provide notification of hypoxic periods and is considered independent predictor of unfavorable outcome and death. The advantage of this device is that recalibration is not necessary and, once inserted, it allows valid and stable measurement for hours or even days.

$PbtO_2$ has been strongly correlated with outcome. Bardt et al. [28] monitored $PbtO_2$ in 35 patients with TBI and noted that outcome measures were different when the $PbtO_2$ was < 10 mmHg for more than 30 minutes. Moreover, treatments to maintain $PbtO_2$ are associated with more favorable patient outcomes [29]. Implementation of protocols using $PbtO_2$ monitoring is associated with improved resource utilization, improved patient care, reduced duration of mechanical ventilation, and reduced ICU and hospital lengths of stay [30–32]. We have developed a color-coded protocol matrix for management intervention in severe acute brain injury using measurement of $PbtO_2$, ICP, and cerebral oxygenation extraction ratio as a guide to integrate and link data for decision making (**Table 3**).

Table 3. Protocol matrix for intervention in severe acute brain injury according to measurement of cerebral oxygen extraction ratio (O_2ER), intracranial pressure (ICP), and brain tissue oxygen pressure ($PbtO_2$)

Normal $PbtO_2$: 20–35 mmHg • Risk of death increases – < 15 mmHg for 30 minutes – < 10 mmHg for 10 minutes • $PbtO_2$ < 5 mmHg – high mortality • $PbtO_2$ < 2mmHg – neuronal death	$PbtO_2$ oxygen accuracy: • $PbtO_2$ 0–20 mmHg accuracy is ± 2 mmHg • $PbtO_2$ 21–50 mmHg accuracy is ± 10 % • $PbtO_2$ 51–150 mmHg accuracy is ± 13 % Temperature Accuracy: ± 0.2 °C		cerebral oxygen extraction ratio	
$PbtO_2$ < 20 mmHg	**$PbtO_2$ > 20 mmHg**		**Cerebral O_2ER < 40 %**	**Cerebral O_2ER > 40 %**
		ICP < 20 mmHg		
		ICP > 20 mmHg		
head elevation and position airway and ventilation control sedation and analgesia control of fever control of hypertension prevention of seizures CSF drainage urgent CT hyperosmolar therapy hyperventilation barbiturate coma hypothermia surgical mass evacuation ± decompressive craniotomy for uncontrollable and sustained ICP	continue monitoring head elevation and position airway and ventilation control sedation and analgesia control of fever control of hypertension prevention of seizures	cautious interpretation of data is critical check head position, ventilation, oxygenation, temperature, blood pressure, seizures and correlate neuromonitoring data with clinical judgment or probe may be displaced or malfunctioning No study has shown that ICP increases when $PbtO_2$ is normal	head elevation and position airway and ventilation control sedation and analgesia control of fever control of hypertension prevention of seizures urgent CT hyperosmolar therapy hyperventilation barbiturate coma hypothermia surgical mass evacuation	

CSF: cerebrospinal fluid; CT: computed tomography

Multi-modal Monitoring in Cerebrovascular Disease

Case scenario: A 55 year-old man was admitted to the ICU following a subarachnoid hemorrhage (SAH). On day 6, the patient developed new focal neurological deficits and his condition deteriorated rapidly with a CT scan showing extensive cerebral ischemia. The use of which neuromonitoring measures could have prevented this catastrophe?

Massive hemispheric infarctions secondary to middle cerebral artery (MCA) or internal carotid artery (ICA) hemorrhage are an important cause of mortality and morbidity in the neuro-ICU. Early identification of patients at risk is necessary to decide on appropriate management. The effectiveness of ICP monitoring is limited, but microdialysis and $PbtO_2$ monitoring may have a role [33]. Microdialysis allows continuous on line monitoring of changes in brain tissue chemistry by inserting a 0.62 mm diameter catheter lined with a polyamide dialysis membrane into the brain parenchyma which is perfused with physiological solution at ultra flow rates using a precision pump.

Steifel and colleagues [34] studied the effect of multimodal monitoring on medical anti-edema treatment. ICP, CPP and $PbtO_2$ were continuously measured within the white matter of frontal lobe unilaterally or bilaterally; 27 measurements were made in 21 patients with a total of 297 anti-edema drug administrations analyzed in 11 patients. Mannitol was often associated with an increase in CPP and $PbtO_2$ whereas the use of thiopental and tromethamine had negative or contrary effects. The cornerstones in the management of massive cerebral edema are osmotherapy and hyperventilation but the most important factor is to be able to predict early which patients may experience rapid deterioration from tissue shifts and edema expansion.

SAH is a common and fatal type of hemorrhagic stroke secondary to rupture of an intracranial aneurysm with a mortality of 45 % [35]; 15 % of patients die before reaching the hospital and a significant percentage are left with some disability [36]. Complications of SAH include rebleeding, hydrocephalus, seizures, and delayed ischemic neurologic deficit. The majority of patients with SAH, regardless of clinical and radiographic grade, should be monitored for delayed ischemic neurologic deficit; clinical neurological signs vary and a concomitant rise in blood pressure may be the first warning sign. In patients who are comatose, delayed ischemic neurologic deficit may not manifest clinically [37].

Critically ill unstable patients with SAH are unlikely to have catheter-based cerebral angiopathy which is the gold standard for detection of cerebral vasospasm. Therefore, using optimal neuromonitoring techniques can help detect changes that may tailor the management earlier and improve outcomes. Continuous EEG has a role in detecting occult seizures, non-convulsive seizures, sedation status, prognosis, and cerebral ischemia. Ischemia causes characteristic changes in brain electrical activity, therefore continuous EEG provides excellent information on regional and global function of the brain. Continuous EEG detected ischemic changes due to vasospasm 3 days before changes in clinical examination and transcranial Doppler scans [38]. The sensitivity and specificity of continuous EEG for detection of ischemia and the optimal recording parameters have yet to be established.

Ramakrishna and colleagues examined the relationship between $PbtO_2$ and death after SAH [39]. Forty-six patients with a GCS of 8 or less, median age of 58 years, underwent $PbtO_2$ monitoring. The relationship between the $PbtO_2$ and the 1-month survival was examined. The result showed that survivors had a higher mean daily $PbtO_2$ and shorter episodes of compromised $PbtO_2$ than the non-survivors [39]. A recent study showed that in 18 of 26 patients who had unilateral decompression hemicraniectomy for extensive cerebral edema after aneurysmal SAH or severe TBI, pathological changes in monitoring parameters always preceded clinical deterioration. In 9 of 20 patients with SAH, decreases in $PbtO_2$ occurred several hours before neurological deterioration or ICP increase; however, this was not always the case in patients with TBI [40]. Belli et al. [41] showed that an abnormal lactate/pyruvate

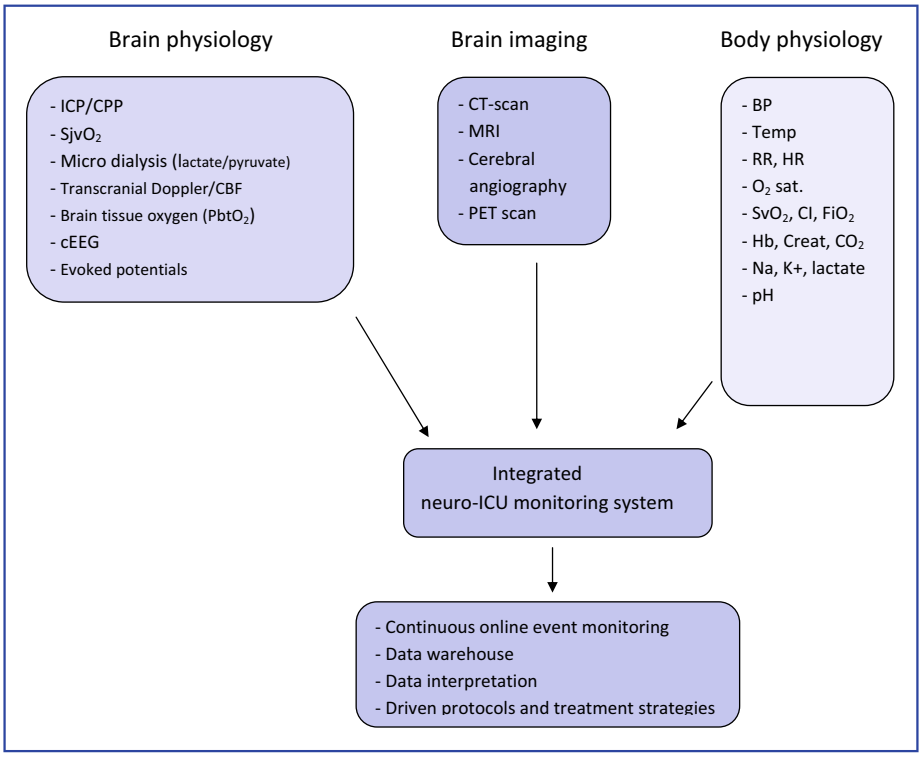

Fig. 1. Integrated neuro-ICU multimodality system of the future. ICP: intracranial presure; CPP: cerebral perfusion pressure; CBF: cerebral blood flow; cEEG: continuous electroencephalogram; CT: computed tomography; PET: positron emission tomography; SvO_2: mixed venous oxygen saturation; MRI: magnetic resonance imaging; RR: respiratory rate; HR: heart rate; $SjvO_2$: jugular venous oxygen saturation; $PbtO_2$: brain tissue oxygen pressure; creat: creatinine; CI: cardiac index

ratio (> 25) could predict an ICP increase in 89 % of cases. Changes in biochemical parameters can occur before intracranial hypertension develops. A 20 % increase in lactate/pyruvate ratio and glycerol concentration preceded the onset of delayed ischemic neurological deficit in 17 of 18 SAH patients by a mean interval of 11 hours [42].

The role of transcranial Doppler and $SjvO_2$ monitoring is limited in SAH but the two monitoring modalities can be used jointly to distinguish hyperemia and vasospasm as high flow velocity indicates hyperemia with a high $SjvO_2$ whereas a low or normal $SjvO_2$ is more likely to indicate vasospasm.

Conclusion

Successful intensive care management of neuro-critically ill patients requires a thorough understanding of the disease processes and their complications. Knowledge of the advantages and limitations of multimodal neuromonitoring techniques is crucial and has allowed a movement away from rigid physiological targets towards an individually tailored, patient specific approach. The role of brain tissue oxygenation,

metabolic markers from microdialysis, and continuous EEG is vital in detecting changes in the injured brain which can help improve outcomes of patients with brain injury by enabling interventions to be started before permanent damage occurs. The future is promising for neuro-ICUs to develop protocolized management guidelines linked to data provided from multimodal monitoring techniques, but the challenge is to develop integrated computerized systems (**Fig. 1**) that can gather systemic and cerebral monitoring data with imaging data and present it in a simple format that highlights trends and identifies patients at risk of deterioration at an early stage.

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Hemodynamic Management of Acute Spinal Cord Injury

O. Solaiman and D. Zygun

Introduction

Acute traumatic spinal cord injury primarily afflicts young people and significantly reduces independence, bestows life-long disability, and consumes huge societal resources. The estimated incidence of acute traumatic spinal cord injury in North America varies from 27–81 cases per million inhabitants per year [1]. The prevalences of spinal cord injury were estimated to be 280 and 681 individuals per million inhabitants in Finland and Australia, respectively. Despite recent efforts at prevention, including laws mandating seat belt use, the incidence of spinal cord injury has not changed significantly and may actually be increasing in certain parts of the population [2, 3]. In addition, the estimated (2006) treatment cost of spinal cord injury is $9.7 billion per year [1]. A number of pharmacological agents (methylprednisolone sodium succinate, and the related compound, tirilazad mesylate; GM-1 ganglioside; thyrotropin-releasing hormone; gacyclidine; naloxone; and nimodipine) have been investigated in large, prospective, randomized, controlled clinical trials, but all have failed to demonstrate convincing neurological benefit. Spinal cord injury is frequently associated with systemic hypotension attributable to hypovolemia, direct spinal cord trauma, or both [4].

Hypotension has been shown to be associated with worse outcomes after traumatic injury [4] and is amenable to therapy. However, there is insufficient evidence to support treatment standards for the hemodynamic management of patients with acute spinal cord injury. The aim of this chapter is to: 1) review the incidence and pathophysiology of acute traumatic spinal cord injury-induced cardiovascular dysfunction; 2) review the existing evidence supporting blood pressure augmentation in patients with acute traumatic spinal cord injury; 3) introduce the concepts of spinal cord perfusion pressure and intrathecal pressure, and their treatment; and 4) discuss the potential risks of these treatments.

Overview of the Incidence and Pathophysiology of Acute Traumatic Spinal Cord Injury-induced Cardiovascular Dysfunction

We lack a full understanding of the pathophysiology of abnormal cardiovascular control in patients with acute spinal cord injury. Furlan and Fehlings describe five potentially contributing factors: 1) Disruption of the descending cardiovascular (or vasomotor) pathways; 2) morphological changes in the cardiac and vasomotor sympathetic preganglionic neurons; 3) sprouting and the potential formation of inappropriate synapses with spinal interneurons; 4) abnormal spinal efferents; and 5)

development of altered sympathetic neurovascular transmission and smooth muscle responsiveness [5]. These authors propose that disruption of the descending cardiovascular (or vasomotor) pathways is the most evident contributing factor during the acute stage after severe spinal cord injury at T6 or a more cranial level.

The autonomic nervous system is an essential communication link between the brain and the cardiovascular system. In an immunohistochemical examination of postmortem spinal cord tissue, individuals who developed severe hypotension, bradycardia, or autonomic dysreflexia during the acute stage after cervical spinal cord injury showed significantly fewer preserved axons within the dorsal aspects of the lateral funiculi of spinal cord sections a few segments caudal to the injury site, in comparison with individuals who presented no significant signs and symptoms of abnormal cardiovascular control [6]. Clinically, the location and severity of the spinal cord injury determines the incidence and degree of cardiovascular dysfunction [6–8]. Cervical or high-thoracic spinal cord injury (T6 or above) inhibits supraspinal sympathetic control of cardiovascular functions leaving unopposed parasympathetic cardiac regulation via the vagus nerve. This can result in hypotension, bradycardia and other cardiac arrhythmias. Neurogenic shock, defined as systolic blood pressure < 100 mmHg and a heart rate < 80 beats per minute, was identified at presentation in 19.3 % (95 % CI 14.8–23.7 %) of patients with cervical injuries compared to 7 % (3–11.1 %) and 3 % (0–8.85 %) of patients with thoracic and lumbar cord injuries, respectively [8]. Tuli and colleagues found that the presence of neurogenic shock (systolic blood pressure < 90 mmHg) was associated with a delay in the timing of surgical intervention in patients with cervical motor complete spinal cord injury [9]. Spinal cord injury can provoke cardiac electrophysiological abnormalities, including sinus bradycardia, repolarization changes, atrioventricular block, supraventricular tachycardia, ventricular tachycardia, and primary cardiac arrest. Similar to neurogenic shock, the incidence of cardiac arrhythmias is related to the location and severity of the injury [10, 11]. The frequency of bradyarrhythmias peaked on day 4 after injury and gradually declined thereafter with resolution of abnormalities within 6 weeks [10].

Blood Pressure Augmentation in Patients with Acute Traumatic Spinal Cord Injury

Despite a paucity of level 1 evidence, current clinical practice guidelines support the correction of hypotension in patients with acute spinal cord injury [4, 12]. However, the appropriate resuscitation endpoints and optimal mean arterial blood pressure (MAP) for maintenance of spinal cord perfusion are not known [12]. Vale and colleagues prospectively applied resuscitation principles in a non-randomized study of volume expansion and blood pressure maintenance in 77 patients who presented with acute neurological deficits as a result of spinal cord injuries occurring from C1 through T12 [13]. All patients were managed in the intensive care unit (ICU) using Swan-Ganz and arterial blood pressure catheters and were treated with intravenous fluids, colloid, and vasopressors to maintain MAP above 85 mmHg for 7 days after injury. The study was uncontrolled but the authors suggested the neurological outcomes described were better than in the published literature at the time. The authors stated that there were no recognized complications of volume resuscitation or blood pressure augmentation, but only described a lack of hemorrhagic stroke, stroke, myocardial dysfunction or death. Levi et al. performed an uncontrolled retrospec-

tive cohort study to analyze the demographic, neurologic, and hemodynamic data of 50 consecutive patients during their first week post spinal cord injury [14]. Their protocol included invasive hemodynamic monitoring (with arterial line and Swan-Ganz catheter) and support with fluids and dopamine and/or dobutamine, titrated to maintain a hemodynamic profile with adequate cardiac output (to be determined by oxygen consumption and delivery) and a MAP of > 90 mmHg. The hemodynamic parameters did not differentiate between patients with complete or incomplete injury. None of the 10 patients with "severe hemodynamic deficit" (as defined by low peripheral vascular resistance index [PVRI], low systemic vascular resistance index [SVRI], or PVRI/SVRI ratio of < 0.08) improved functionally, as opposed to 13 of the 29 with the same neurological deficit but without these criteria. Wolf et al. reported results from 52 patients with acute traumatic bilateral locked facets who were treated at one trauma center during a 3 1/2-year period [15]. The standardized protocol included intensive and invasive monitoring of vital signs, and hemodynamic manipulation to keep MAP > 85 mmHg during the first 5 days post-injury. Despite lack of a control group, the authors felt the protocol of aggressive medical and surgical therapy resulted in significant neurological improvement. Tator and colleagues described their experience with 144 patients with acute spinal cord injury who were treated between 1974 and 1979 [16]. In one of the few controlled studies

Table 1. Summary of studies on blood pressure management after spinal cord injury

Studies	Description of study	Target MAP	Conclusions
Vale et al., 1997 [13]	Prospective pilot study of 77 acute SCI patients treated in the ICU with aggressive hemodynamic support	> 85 mmHg for 7 days after injury	Improved outcome with aggressive medical care at 1 year follow up
Levi et al., 1993 [14]	50 patients with acute SCI treated in ICU with aggressive hemodynamic support	> 90 mmHg for 7 days after injury	Improved outcome with aggressive hemodynamic support at 6 weeks post injury
Levi et al., 1991 [27]	103 acute SCI patients, 50 incomplete Group A), 53 complete (Group B) treated in ICU with aggressive hemodynamic support	> 85 mmHg for 7 days	Improved outcomes, no significant difference between early and late surgery in either group
Wolf et al., 1991 [15]	52 patients with locked facets reduced within 4 h, treated in ICU with aggressive medical care, 49 patients operated in day 1 and 26 delayed	> 85 mmHg for 5 days	Improved neurological outcomes with hemodynamic therapy
Tator et al., 1984 [16]	144 acute SCI patients managed in the ICU, strict attention to the treatment of hypotension and respiratory failure with fluid resuscitation and ventilatory support	Not stated	Improved neurological outcome, less mortality with early transfer to ICU
Zach et al., 1976 [17]	Prospective assessment of 117 acute SCI patients at Swiss center, ICU setting. Aggressive medical therapy and blood pressure support (Rheomacrodex × 7 d; dexamethasone × 10 d). No comparison or control group	Not stated	Improved neurological outcomes with aggressive medical treatment and blood pressure management.

MAP: mean arterial pressure; SCI: spinal cord injury; ICU: intensive care unit

in the literature, the authors compared their results with a historical cohort of 358 patients with spinal cord injury. The patients managed from 1974 to 1979 were treated with vigorous crystalloid infusions and transfusion of whole blood or plasma for volume expansion. The authors reported reduced mortality and morbidity, shorter length of stay, and lower cost of treatment with aggressive management compared with their historical cohort. Zach et al. aggressively treated 117 consecutive patients with spinal cord injury with volume expansion for blood pressure maintenance [17]. These authors observed a correlation between earlier admission time and neurological outcome, concluding that early institution of medical management including blood pressure maintenance improved outcome after spinal cord injury. These studies (**Table 1**) have been cited as support for the role of blood pressure augmentation. However, the retrospective, non-randomized, and uncontrolled methodology of the studies presented prevents definitive conclusions.

Spinal Cord Perfusion Pressure, Intrathecal Pressure, and Treatment

In acute severe traumatic brain injury (TBI), a mainstay of management currently includes maintenance of cerebral perfusion pressure (CPP) [18]. CPP has been used as an index of the input pressure determining cerebral blood flow and therefore perfusion. There is a substantial body of evidence that systemic hypotension independently increases the morbidity and mortality from TBI [18]. In severe TBI, 49–87 % of patients demonstrate an absence of or impairment in pressure autoregulation [19]. In the setting of dys-autoregulation, a fall in CPP leads to a reduction in blood flow and subsequently to ischemia. Appling the same principle to acute spinal cord injury, spinal cord perfusion pressure, as determined by the difference between the MAP and the cerebrospinal fluid (CSF) pressure in the intrathecal space (intrathecal pressure), and its management have recently garnered interest in an attempt to minimize secondary injury after spinal cord injury. A decrease in spinal cord perfusion pressure, resulting in spinal cord ischemia, can occur with either a decrease in arterial blood pressure or an increase in intrathecal pressure, or both. Insertion of a lumbar subarachniod catheter in the setting of acute spinal cord injury offers the ability to lower intrathecal pressure by draining CSF, and measurements of spinal CSF pressures could allow targeted hypertensive therapy to maintain spinal cord perfusion pressure. Indeed, CSF drainage is supported by its use to prevent paraplegia during thoracoabdominal aortic aneurysm repair. In animal experiments, when CSF pressure is equal to or exceeds distal aortic pressure, paraplegia uniformly occurs [20]. Coselli et al. performed a randomized clinical trial in 145 patients to evaluate the impact of CSF drainage on the incidence of spinal cord injury after extensive thoracoabdominal aortic aneurysm repair [21]. CSF drainage was initiated during the operation and continued for 48 hours after surgery with a target CSF pressure of 10 mmHg or less. Nine patients (13.0 %) in the control group had paraplegia or paraparesis while only two patients in the CSF drainage group (2.6 %) developed deficits ($p = 0.03$). Cina et al. undertook a quantitative systematic review of randomized controlled trials and observational studies to determine the effectiveness of CSF drainage to prevent paraplegia in thoracic aneurysm and thoracoabdominal aortic aneurysm surgery [22]. These authors concluded that evidence from randomized and non-randomized trials and from cohort studies supported the use of CSF drainage as an adjunct to prevent paraplegia in the management of thoracoabdominal aortic aneurysm surgery.

To our knowledge there is only one randomized clinical trial of CSF drainage in acute traumatic spinal cord injury. Kwon et al. [23] randomized 22 patients within 48 hours of acute spinal cord injury to drainage or no-drainage treatment groups. Lumbar drains were maintained for 72 hours. The authors evaluated changes in intrathecal pressure before and after surgical decompression, pressure waveforms, safety of draining CSF to lower intrathecal pressure, and neurological recovery in relation to the drainage of CSF. The mean intrathecal pressure on insertion of the catheter was 13.8 ± 1.3 mmHg, and it increased to a mean peak of 21.7 ± 1.5 mmHg intraoperatively. The peak intrathecal pressure in the postoperative period was significantly higher than the peak intraoperative value in the no drainage group but not in the drainage group, 30.6 ± 2.3 mmHg and 28.1 ± 2.8 mmHg respectively. The Pearson correlation coefficient between MAP and intrathecal pressure was, in most cases, negative. This indicates that increases in intrathecal pressure were not associated with increases in MAP, and the negative coefficients indicate that the intrathecal pressure increases were more commonly associated with decreases in MAP. The insertion of lumber subarachnoid catheters and CSF drainage were not associated with significant adverse events. The study was inadequately powered to determine whether CSF drainage was associated with neurological recovery. Further studies are needed to assess the use of spinal cord perfusion pressure management and CSF drainage in acute traumatic spinal cord injury.

Potential Risks of Blood Pressure Augmentation in Acute Spinal Cord Injury

In spinal cord injury, few studies have been diligent in the systematic reporting of adverse events related to blood pressure augmentation therapy. In TBI, recent guidelines have reduced perfusion pressure targets and suggested aggressive attempts to maintain CPP above 70 mmHg with fluids and pressors should be avoided because of the risk of acute respiratory distress syndrome (ARDS) [18]. In a study comparing two management strategies in patients with severe TBI, a fivefold increase in the incidence of ARDS was observed in the cerebral blood flow-targeted group [24]. Further, delivery of blood pressure augmentation or performance of CSF drainage may be associated with the risks of central line insertion (infection, thrombosis, pneumothorax, arrhythmia), fluid and inotrope use, lumbar catheter insertion [25], and increased ICU length of stay. Further, if spinal cord pressure autoregulation is impaired after injury, induced hypertension may potentially increase hemorrhage and edema [26].

Conclusion

Cardiovascular dysfunction following acute traumatic spinal cord injury may be associated with the development of secondary ischemic injury to the spinal cord. Poor grade evidence suggests a role for blood pressure augmentation in patients with acute spinal cord injury. In addition, although spinal cord perfusion pressure management, including CSF drainage, may prevent such ischemic injury in thoracoabdominal aorta aneurysm repair, there is currently insufficient evidence to recommend this approach in acute traumatic spinal cord injury. The paucity of data mandates urgent prospective investigations to determine the optimal hemodynamic management of acute spinal cord injury.

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Quantitative CT Scan and CT-Estimated Brain Specific Gravity in TBI

V. Degos, T. Lescot, and L. Puybasset

Introduction

An uncontrolled increase in intracranial pressure (ICP), often due to cerebral edema, is the most common cause of death in patients with traumatic brain injury (TBI). Different types of edema coexist in TBI patients: Vasogenic edema and cytotoxic edema. Vasogenic edema occurs with the extravasation of fluid into the extracellular space following blood brain barrier (BBB) disruption. Cytotoxic edema results from a shift of water from the extracellular compartment into the intracellular compartment due, in part, to alterations in normal ionic gradients. Description of the localization and knowledge of the chronology, determinants, and kinetics of the BBB disruption are necessary to adapt therapeutic strategy.

Although nuclear magnetic resonance is not advisable at the acute phase in human TBI, especially in unstable TBI patients, this examination is one of the most accurate for the study of brain edema. Diffusion-weighted imaging provides a useful and non-invasive method for visualizing and quantifying diffusion of water in the brain associated with edema. Apparent diffusion coefficients can be calculated and used to assess the magnitude of water diffusion in tissues. For example, high apparent diffusion coefficient values indicate more freely diffusible water, which is considered as a marker of vasogenic edema. On the other hand, cytotoxic edema restricts water movement and results in decreased signal intensities in the apparent diffusion coefficient map. In a rat model of diffuse TBI, early increase in apparent diffusion coefficient values during the first 60 minutes was observed, followed by a decrease in apparent diffusion coefficient values reaching a minimum at one week [1]. This result suggests a biphasic edema formation following diffuse TBI without contusion, with a rapid and short disruption of the BBB during the first hour post injury, leading to an early formation of vasogenic edema. Contrary to the non-contused areas, there are numerous arguments in favor of a profound and prolonged alteration of the BBB in traumatic areas of contusion appearing on computed tomograpy (CT) scans [2–4], in part, secondary to regional ischemia [5–7]. Several methods have been used to study edema formation and the BBB changes following animal and human TBI, but the underlying mechanisms are still not well understood. For these reasons, it might be interesting to find a new and more accessible technique to study the edema formation in the acute phase of human TBI, and especially to compare non-contused and contused areas and to follow changes in the BBB in these areas over time.

CT imaging, the iconographic goal standard to describe acute brain lesions, is widespread and accessible. CT image acquisitions are prompt and reproducible with high quality. With specific software, the volume, weight and an estimation of specific gravity can be quantified from CT Digital Imaging and Communications in Medi-

cine (DICOM) images and these are useful to study different anatomic areas at different periods after injury. The goal of this chapter is to describe the use of quantitative CT scan results in non-contused and contused areas in patients with TBI, focusing on the observed differences between contused and non contused areas.

Quantitative Computed Tomography

Since its development in the 1970s, CT scan has become a radiological examination of choice in the acute assessment of patients with acute brain lesions and especially TBI. CT maps the way by which different tissues attenuate or absorb the beam of X-ray. A crucial point is that the radiological attenuation is linearly correlated with the physical density in the range of human tissue densities [8, 9]. For example, blood-clots have relatively little water and absorb X-rays more than the normal brain; they are displayed as hyperdense areas. On the other hand, ischemia and liquid collections are displayed as dark areas because there is an increase in water content.

BrainView, a recent software package developed for Windows workstations, provides semi-automatic tools for brain analysis and quantification from DICOM images obtained from cerebral CT scans. For each examination, BrainView inputs a series of continuous axial scans of the brain. It then automatically excludes the extracranial compartments on each section (**Fig. 1**). Interactive slice-by-slice segmentation allows different anatomical territories indexed throughout the whole sequence to be selected. The software is the upgrade of Lungview, developed earlier by the same institution (Institut National des Télécommunications) and used for lung and heart weight, volume and density analysis by our group [10–12]. For each compartment of a known number of voxels, the volume, the weight and the estimated specific gravity are computed using the following equations:

(1) Volume of the voxel = surface × section thickness.
(2) Weight of the voxel = (1 + CT / 1000) × volume of the voxel where CT is the CT attenuation coefficient (expressed in Hounsfield Units).
(3) Volume of the compartment = number of voxels × volume of the voxel.
(4) Weight of the compartment = summation of the weight of each individual voxel included in the compartment.
(5) estimated specific gravity of the compartment = Weight of the compartment/volume of the compartment. The estimated specific gravity is expressed as a physical density in g/ml.

The BrainView technology was first validated *ex vivo*. We measured the specific gravity of different solutes by determining the weight of one liter of these solutes (**Fig. 2**). The estimated specific gravity of the same solutes was also computed using BrainView. The two values were linearly correlated especially in the range of densities in human brain tissue [13]. Using the correlation between the specific density and the radiological attenuation, BrainView allowed us to assess the weight, volume, and estimated specific gravity of different anatomical parts of the brain (the two hemispheres, the cerebellum, the brainstem and the intraventricular and subarachnoid cerebrospinal fluid (CSF), the white and gray matters, contused and non-contused hemispheric areas). The technology also allows us to compare different populations (TBI patients, subarachnoid hemorrhage (SAH) patients, controls) or the same population at different periods (first hours after injury, CT controls at 1 week, before or after a therapeutic intervention, etc....).

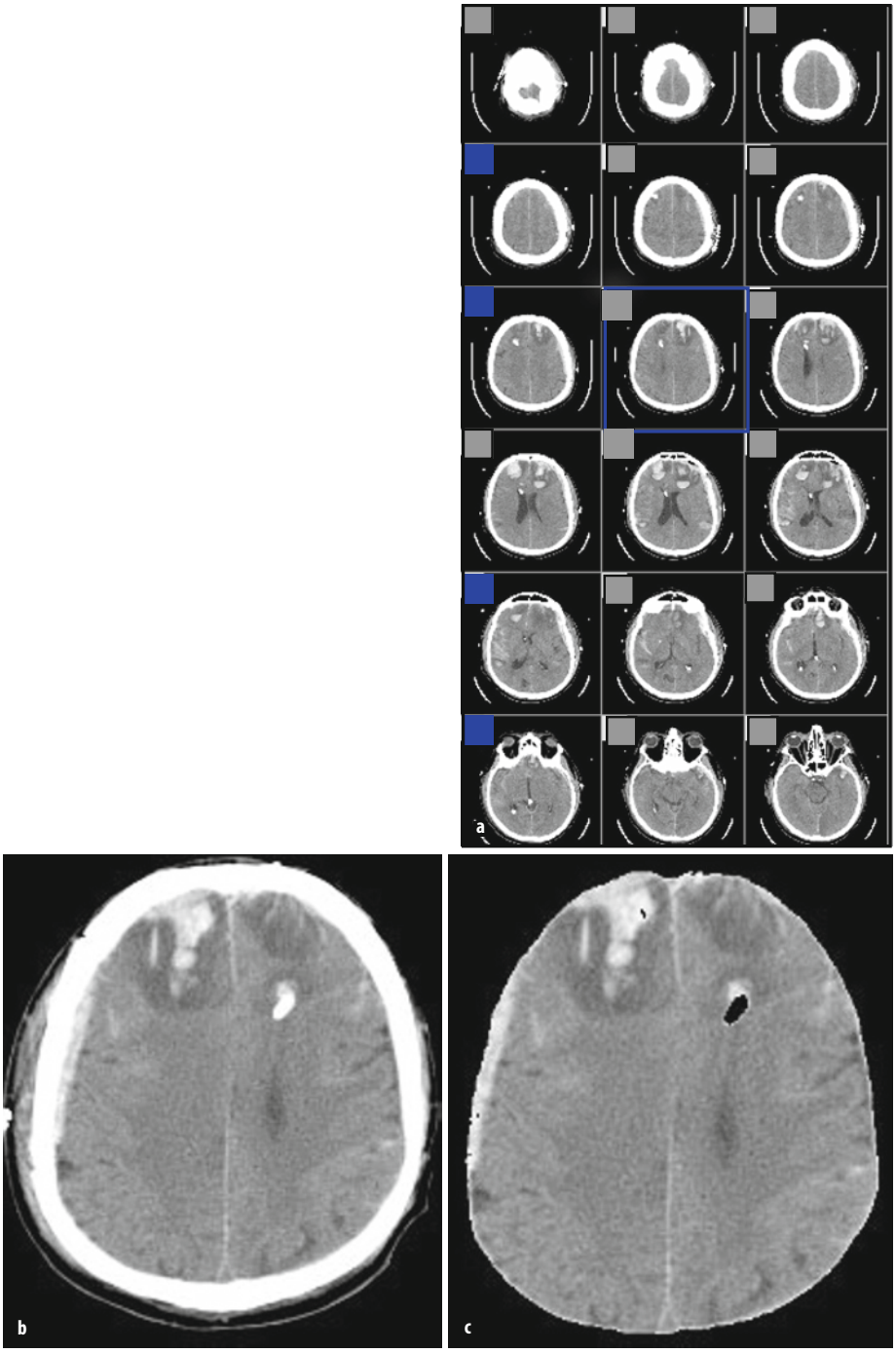

Fig. 1. BrainView software working window. CT DICOM image imports (**a**, **b**); automatic exclusion of extracranial compartments (**c**).

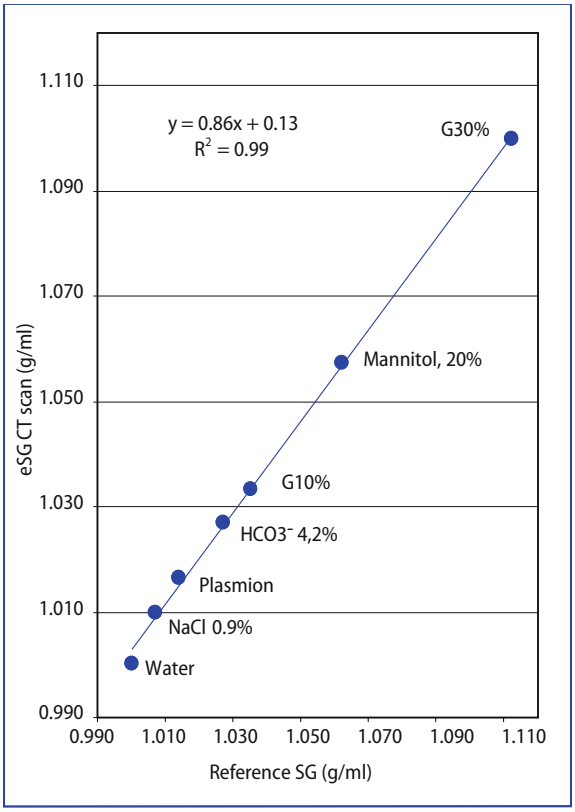

Fig. 2. Comparison between the specific gravity (SG) of the different solutes measured by the electronic scale method (weight/volume) and the estimated specific gravity (eSG) with quantitative CT scan. From [13] with permission

In theory, measurement of estimated specific gravity is a good reflection of density variations. When studying the consequence of BBB disruption in TBI, a complete disruption of the BBB with leakage of water, electrolytes, proteins, and cells would increases the brain estimated specific gravity since the added volume (exudate) has a density greater than the brain. However, partial disruption of the BBB with leakage of water and electrolytes would decrease the density since the added volume (transudate) has a density less than the brain (**Fig. 3**).

XII

Quantative CT Study of Non-contused Hemispheric Areas

Using the BrainView methodology, the weight, the volume and the estimated specific gravity were measured in 15 patients with TBI 3 ± 2 days after the trauma and in 15 controls. For similar age and overall intracranial volume, patients with TBI had a brain weight 82 g heavier and hemisphere weight 91 g heavier than controls [13]. The volume of intraventricular and subarachnoid CSF was reduced in patients with TBI. In this first series of measurements in 15 patients with TBI, the estimated specific gravity of the hemispheres, brainstem and cerebellum was significantly higher in patients with TBI compared to controls (all $p < 0.0001$). The increase in estimated specific gravity was statistically similar in these three anatomical compartments,

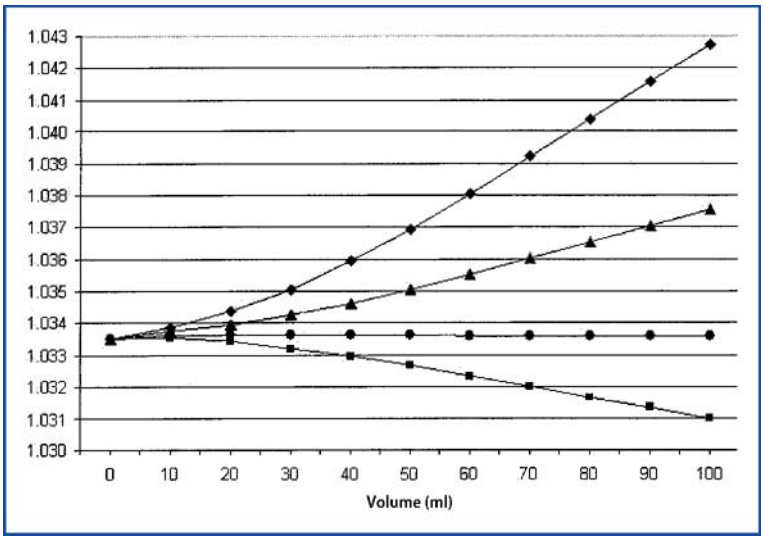

Fig. 3. Computation of the resulting specific gravity after adding a given volume (x axis) of a solute with a density of 1.026 g/ml (square), 1.0335 (round), 1.045 (triangle) and 1.060 (diamond) in hemispheres with a volume of 1041 ml, a weight of 1076 g and a specific gravity of 1.0335 g/ml (mean values of controls). The density of plasma is 1.026 g/ml, the density of blood is 1.060 g/ml, and 1.045 g/ml is the density of a solute explaining an increase in the hemispheric volume of 85 ml combined with an increase in specific gravity from 1.0335 up to 1.0367 g/ml (mean value of controls and TBI patients). From [13] with permission

and in white and gray matter. Furthermore, there was no correlation between the hemispheric estimated specific gravity and age, natremia at time of CT, presence of a traumatic SAH, or presence of intraparenchymal blood [13].

To confirm these results, a second study was performed in a larger cohort of 120 patients with severe TBI. The measurement of estimated specific gravity from the initial CT scan performed in the first 5 hours after trauma was also increased. The increase in estimated specific gravity was present in the overall intracranial content and in the non-contused hemispheric areas [14]. The follow up changes in estimated specific gravity of the total intracranial content showed that it took more than ten days to retrieve a normal value of estimated specific gravity (**Fig. 4**).

The same cohort was divided into two groups according to the initial estimated specific gravity of the non-contused hemispheric areas. The normal specific gravity group was defined as patients having an estimated specific gravity less than 1.96 SD above controls. In the increased specific gravity group, patients had an estimated specific gravity higher than 1.96 SD. Patients with the highest estimated specific gravity had a lower Glasgow Coma Scale (GCS) score and more often had a mydriasis at the scene of the accident, more frequently received osmotherapy at the initial phase, more frequently had an extra ventricular drain implanted for ICP monitoring and CSF drainage, more frequently received barbiturates as a second line therapy and more frequently had a CT scan classified in the third category of the Marshall score. In this cohort, the initial GCS, the simplified acute physiology score (SAPS) II, the velocity, the occurrence of mydriasis at the scene and the use of osmotherapy were predictors of outcome at ICU discharge and at one year. Only the SAPS II and

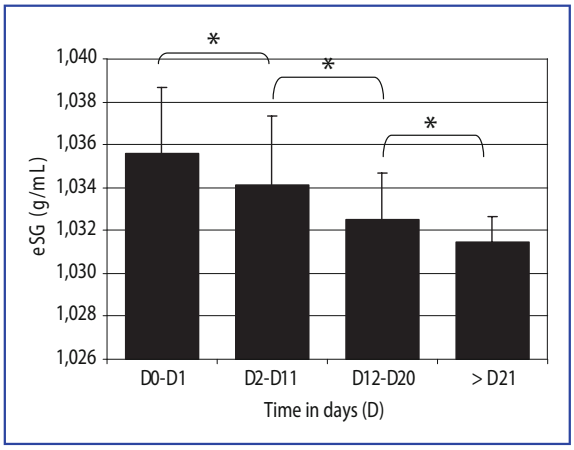

Fig. 4. Follow-up changes in estimated specific gravity (eSG) of the overall intracranial content (n = 15). * $p < 0.05$. From [14] with permission

Table 1. Factors related to outcome at intensive care unit (ICU) discharge and 1 year later in patients with severe TBI. From [14] with permission

	ICU discharge		1 yr	
	GOS 1–3 (n = 46)	GOS 4–5 (n = 74)	GOS 1–3 (n = 37)	GOS 4–5 (n = 83)
Age (yr)	37 ± 15	33 ± 14	39 ± 15	33 ± 14
Initial GCS	6 ± 3	8 ± 3†	6 ± 3	8 ± 3†
SAPS 2	50 ± 11	40 ± 9†	51 ± 12	41 ± 10†
Mechanisms				
Assault	6 (13)	5 (7)	6 (16)	5 (6)
Fall	13 (28)	20 (27)	10 (27)	23 (28)
MVA	22 (48)	38 (51)	16 (43)	44 (53)
Pedestrian	5 (11)	11 (15)	5 (14)	11 (13)
Velocity				
Low	15 (32)	7 (10)*	14 (38)	8 (10)†
Mydriasis on scene				
Yes	21 (46)	17 (23)*	17 (46)	21 (25)*
Use of osmotherapy on scene				
Yes	24 (52)	17 (23)*	19 (51)	24 (29)*
eSG overall intracranial content	1.0352 ± 0.0034	1.0338 ± 0.0026*	1.0348 ± 0.0032	1.0341 ± 0.0029
eSG noncontused areas	1.0353 ± 0.0033	1.0340 ± 0.0027*	1.0351 ± 0.0032	1.0343 ± 0.0029

GCS: Glasgow comas scale; GOS: Glasgow outcome scale; SAPS: simplified acute physiological score; eSG: estimated specific gravity; MVA: motor vehicle accident; * $p < 0.01$; † $p < 0.001$.

the use of osmotherapy remained significant predictors in multivariate analysis. The estimated specific gravities of the overall intracranial content or of the non-contused areas were also predictors of outcome, but only at ICU discharge and in the monovariate analysis (**Table 1**). This indicates that the estimated specific gravity was strongly correlated with the intensity of therapeutics to maintain ICP below 20 mmHg; but long-term outcome may be independent of the intensity of the initial brain edema, providing that the increased ICP is well treated. To understand the

relationship between estimated specific gravity and brain swelling, we compared the estimated specific gravity values of patients with TBI and patients with high grade SAH with a similar severity of brain swelling. The increase in estimated specific gravity was only present in the TBI group [15], and not observed in the high grade SAH group. In a fourth study, we compared the estimated specific gravity in the non-contused hemispheric areas before and after a hypertonic saline bolus administration, and we observed an increase in estimated specific gravity associated with a decrease in the volume, corresponding to a correct permeability of the BBB in these areas [16].

Quantitative CT Study of Contused Hemispheric Areas

In TBI, osmotherapy, e.g., with hypertonic saline, has been shown to decrease ICP; it is thus used in emergency to control ICP augmentation. From a theoretical point of view, it can be expected that hypertonic saline is effective only in the areas of the brain where the BBB is still functional after trauma. As the BBB seems to present alterations in contused areas, the patient population that is most likely to respond to hypertonic saline needs to be further defined. A prospective study was designed to evaluate, with a quantitative CT scan, the regional effects of hypertonic saline on contused and non-contused brain tissue after TBI [16].

Global and regional brain volumes, weights and estimated specific gravities were compared with BrainView, before and after hypertonic saline bolus administration in a prospective series of 14 patients 3 ± 2 days after severe TBI. Hypertonic saline had opposite effects on non-contused and contused hemispheric areas (**Fig. 5**). Hypertonic

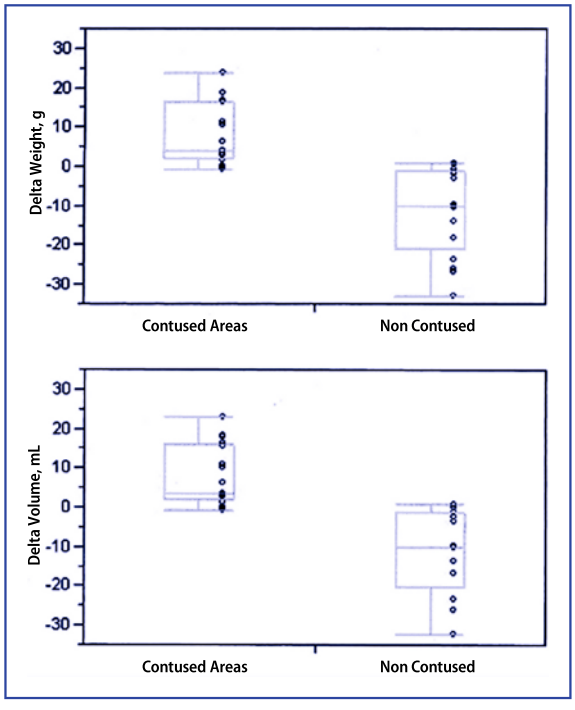

Fig. 5. Mean effect of hypertonic saline on the weight and volume of contused and non- contused areas. The box plots summarize the distribution of points at each factor level, with the ends of the boxes being the 25th and 75th quartiles. The line across the middle of the box identifies the median sample value. The whiskers extend from the ends of the box to the outermost data point that falls within the distances computed. From [16] with permission

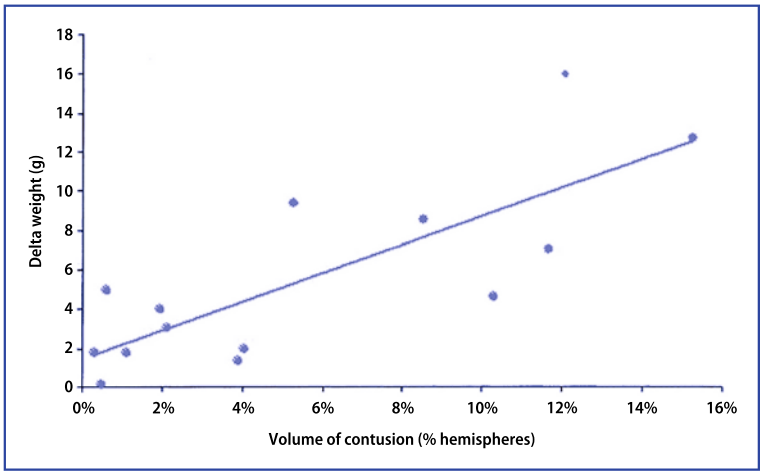

Fig. 6. Change in the weight of contusion according to its initial volume assessed as a percentage of the hemispheres. From [16] with permission

saline decreased the volume of the non-contused hemispheric tissue by 14 ± 9 ml while increasing the specific gravity by 0.029 ± 0.027 %. The volume of the contused tissue ranged from 3 ml to 157 ml (50 ± 55 ml). Hypertonic saline increased the volume of contused hemispheric tissue by 6 ± 4 ml without any concomitant change in density. The increase in the contusion volume with hypertonic saline injection was significantly related to the baseline contusion volume expressed in percentage ($r^2 = 0.62$, $p = 0.01$, **Fig. 6**). Hypertonic saline consistently decreased the weight of the non-contused areas while increasing the estimated specific gravity, indicating a decrease in water content and consequently a functional BBB. On the other hand, hypertonic saline always increased the weight of the contusion. Using quantitative CT scan, this study was able to describe the BBB permeability selectively in contused and non-contused areas in human TBI. The BBB was still permeable in contused areas 3 days after TBI, and thus hypertonic saline should be given with caution in TBI with large contusions after the immediate resuscitation period while the patient is in the ICU.

Interpretation of Estimated Specific Gravity Variation

As the quantitative brain CT studies showed, contused and non-contused hemispheric areas have opposite behaviors in terms of estimated specific gravity variation. In the non-contused areas, a large percentage of the TBI patients presented an early increase in estimated specific gravity (5 hours after trauma). This increased estimated specific gravity in TBI was diffuse, present in the white and gray matter, and required more than 10 days to become normal. The estimated specific gravity was also correlated with the therapeutic intensity level in the ICU and the outcome at ICU discharge. Contrary to the contused hemispheric areas, the BBB of the non-contused areas was sufficiently semipermeable to lead to a decreased water content after osmotherapy.

The observation of an increased estimated specific gravity in patients with TBI is in opposition with some of the experimental literature. Studies performed in murine

models of head trauma report a decrease in estimated specific gravity with a rise in the cerebral water content [17, 18]. However, and similar to our three studies [14–16], Bullock et al. observed an increased specific gravity with severe TBI [19]. Specific gravity determined on small pieces of subcortical tissue using a graduated specific-gravity column was also increased in another human TBI study [20].

In our studies, the increase in estimated specific gravity was concomitant to a gain in weight. One may argue that the increased estimated specific gravity could be due exclusively to hyperemia caused by vascular dilation. However, there are some strong experimental [21] and human data against this hypothesis. Recently, Marmarou et al. demonstrated using MRI that brain edema is the major fluid component contributing to traumatic brain swelling following TBI in humans [22]. These authors observed a reduction in cerebral blood volume in proportion to cerebral blood flow following severe brain injury. As shown on the abacus presented on **Figure 3**, since blood has an estimated specific gravity of 1.060 g/ml [23], an increase in cerebral blood volume of 45 ml would be theoretically necessary to increase hemispheric estimated specific gravity from the mean value of controls to the mean value of TBI patients. Considering that normal cerebral blood volume is about 5 % of the overall intracranial volume, this would mean a 65 % increase in cerebral blood volume. Together, the mean change in hemispheric volume that we observed was 85 ml, a value much higher than could be explained by the change in cerebral blood volume alone.

Another hypothesis to explain the increase in estimated specific gravity could be the presence of traumatic macro-hemorrhagic lesions. We first reported that the estimated specific gravity value was increased in the white matter, excluding the subarachnoid space and thus SAH [13]. Also, the estimated specific gravity values of the total intracranial content and of the non-contused hemispheric areas were similarly elevated [14], a finding that argues against a major role for visible macro-hemorrhagic lesions in estimated specific gravity elevation.

The last hypothesis to explain the increase in estimated specific gravity is the very early BBB disruption already described in different experimental models of TBI [24, 25]. There are many experimental arguments showing that BBB disruption is early and brief. Time window studies indicate that the barrier seals within a few hours following severe head injury [26]. In the experimental model of Barzo et al, permeability of the BBB returned to control values as soon as 30 min after the head trauma [1]. Tanno et al. also observed a pronounced abnormal permeability to IgG and horseradish peroxidase occurring within the first hour after injury that was widespread throughout both hemispheres after a lateral, fluid percussive brain injury in the rat [27]; maximal permeability occurred at 1 h after injury. This was confirmed by Baldwin et al. [2]. In humans, this early, transient and diffuse opening of the BBB may increase the brain's specific gravity since the edematous fluid could have a specific gravity higher than the brain parenchyma. Theoretically, a leak of plasma decreases the overall hemispheric estimated specific gravity since the specific gravity of plasma (between 1.0245 and 1.0285 g/ml) is less than that of the brain. According to **Figure 3**, the volume added in hemispheres of TBI patients should have a density of 1.045 g/ml to explain the increase in estimated specific gravity (considering the mean values). This value is not explainable by plasma leakage alone, but must also involve cells. Thus, it can be hypothesized that BBB opening occurs immediately after TBI in some patients, leading to extravasation of cells and proteins into the extracellular space. Extravasation of blood cells may exacerbate the edema and lead to prolonged ICP elevation and to a higher treatment intensity. Therefore, the value

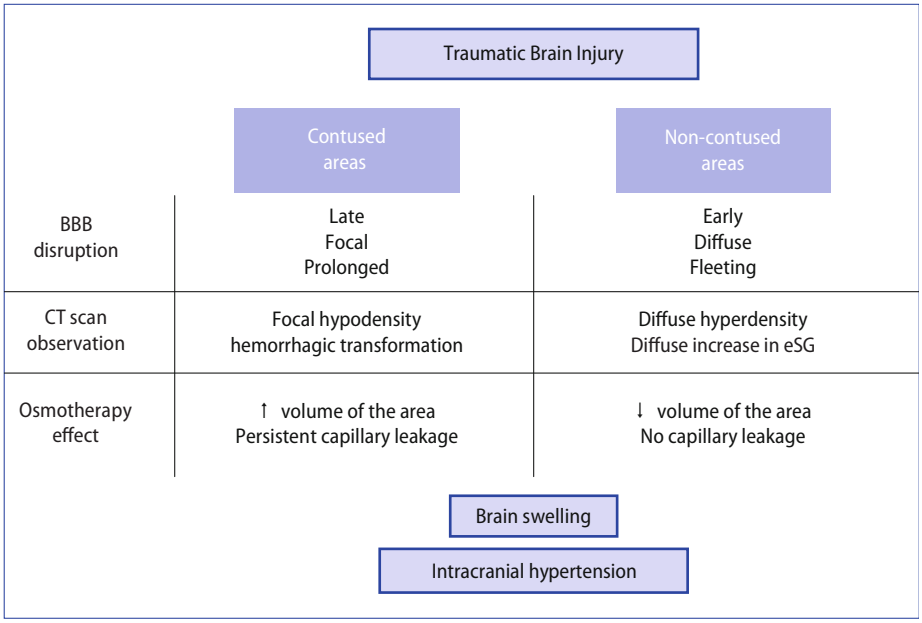

Fig. 7. Illustration of blood brain barrier modification after traumatic brain injury in contused and non-contused areas. eSG: estimated specific gravity

of the estimated specific gravity of the non-contused areas may reflect the specific initial and transient BBB dysfunction associated with TBI and indicate the future workload in regard to ICP treatment.

Regarding the contused areas, experimental data suggest that the BBB remains open for a prolonged period of time after trauma [2, 3]. Our quantitative CT scan study of contused areas suggested that this is true in human TBI, since hypertonic saline consistently increased the weight and volume of contused areas. In the experiment by Tanno et al., at 24 h after injury abnormal permeability was restricted to the impact site and this area remained permeable up to 72 h after trauma [27]. Experimentally, Beaumont et al. demonstrated using an intravenous bolus of Gd-DTPA with serial T1 magnetic resonance images that BBB permeability was greatest at the site of contusion [28]. Gd-DTPA accumulation was greatly enhanced by secondary insults, such as hypoxia and hypotension. **Figure 7** shows an illustration of regional and chronological modifications in the BBB and in CT scans after TBI in contused and non-contused areas.

Conclusion

Quantitative CT scan is validated for the brain and may help to better characterize the regional differences (contused and non-contused areas) in TBI and the time-course of BBB disruption. These studies argue for a distinction between the contused and non-contused areas and also for a consideration of the chronological changes in the lesions. The clinical usefulness of the automatic determination of estimated specific gravity in human TBI to characterize the BBB state or to establish outcome information will have to be addressed in a large prospective study.

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Cerebral Perfusion in Sepsis

C.S. Burkhart, M. Siegemund, and L.A. Steiner

Introduction

Sepsis, the host's reaction to infection, characteristically includes multi-organ dysfunction. Brain dysfunction is often one of the first clinical symptoms in sepsis and may manifest as sepsis-associated delirium in up to 70 % of patients [1, 2], less often as focal deficits or seizures [3]. As severely reduced global perfusion leading to hypotension, maldistribution of regional blood flow, and tissue hypoperfusion is a key feature of severe sepsis and septic shock, the question whether there is a link between cerebral perfusion and brain dysfunction in sepsis is obvious. However, clinical and experimental data on cerebral perfusion in sepsis are often inconsistent and most reports only include small numbers of animals or patients. We summarize the current literature on the effects of the inflammatory response on cerebral perfusion and review the effects of altered cerebral perfusion on brain function in sepsis.

Sepsis and the Brain

In sepsis, the brain may be affected by many systemic disturbances, such as hypotension, hypoxemia, hyperglycemia, hypoglycemia, and organ dysfunction (e.g., increased levels of ammonia in liver dysfunction or urea in acute kidney injury). Direct brain pathologies, such as ischemic brain lesions, cerebral micro- and macrohemorrhage, microthrombi, microabscesses, and multifocal necrotizing leukencephalopathy, have also been described in histopathologic examinations [4, 5]. However, in addition to these metabolic and 'mechanical' effects on the brain, inflammation by itself causes profound alterations in cerebral homeostasis in sepsis.

Inflammation and the Brain

Sepsis at the outset causes a hyperinflammatory reaction, followed by a counteractive anti-inflammatory reaction. Pro- and anti-inflammatory cytokines are initially upregulated. Despite its anatomical sequestration from the immune system by the blood-brain barrier, the lack of a lymphatic system, and a low expression of histocompatibility complex antigens, the brain is not isolated from the inflammatory processes occurring elsewhere in the body. The circumventricular organs lack a blood-brain barrier, and through these specific brain regions blood-borne cytokines enter the brain [5, 6]. The circumventricular organs are composed of specialized tissue and are located in the midline ventricular system. They consist of the organum vas-

culosum, the pineal body, the subcommissural organ, and the subfornical organ. They also express components of the immune system (Toll-like receptors [TLR]), and receptors for cytokines such as interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α).

A further mechanism by which the brain can detect systemic inflammation is through afferent vagal fibers ending in the nucleus tractus solitarius, which senses visceral inflammation through its axonal cytokine receptors. In response to the detection of systemic inflammation, behavioral, neuroendocrine, and autonomic responses are generated including expression of immune receptors and cytokines, inducible nitric oxide synthase (iNOS), and prostaglandins leading to oxidative stress, mitochondrial dysfunction, and apoptosis [5, 7, 8].

Effects of Sepsis on the Blood-brain Barrier and the Vascular Endothelium

The blood-brain barrier, established by the tight junctions of the endothelial cells in interaction with astrocytic foot processes and pericytes, is responsible for a tightly regulated microenvironment in the brain. It prevents circulating noxious substances from entering into the brain and regulates brain capillary blood flow [1]. In sepsis, cerebral endothelial cells are activated by lipopolysaccharide (LPS) and pro-inflammatory cytokines, including bradykinin, IL-1β, and TNF-α; TNF-α also activates iNOS [9]. These changes in the cerebral microcirculation are associated with the upregulation of mRNA for local production of IL-1β, TNF-α, IL-6, and NO by induction of iNOS. Furthermore, leukocytes stick to the wall of blood vessels and enter the brain, mediated by adhesion molecules. The expression of one such adhesion molecule, the intercellular adhesion molecule (ICAM), is increased in septic rats [10]. These local factors can promote endothelial dysfunction and result in blood-brain barrier breakdown leading to an increased permeability of the blood-brain barrier and to perivascular edema, as has been demonstrated in several animal models of sepsis [11–13]. The former facilitates the passage of neurotoxic factors, while the latter impairs the passage of oxygen, nutrients, and metabolites. The increased diapedesis of leukocytes and the perivascular edema decrease microcirculatory blood flow in the brain capillaries. Further evidence for an alteration in the blood-brain barrier comes from work by Alexander and colleagues [14]. In an animal model, these authors demonstrated that endotoxemia-triggered inflammation in the brain led to an alteration in the blood-brain barrier, including an upregulation of aquaporin 4 and associated brain edema. This sequence of events appeared to be mediated by TNF-α signaling through the TNF receptor 1 [14].

In a recent magnetic resonance imaging (MRI) study in nine humans with septic shock and brain dysfunction, sepsis-induced lesions could be documented in the white matter suggesting blood-brain barrier breakdown [15]. However, in a pathologic study no evidence of cerebral edema was reported in 23 patients who died of septic shock [4].

NO is produced by the endothelium and plays an important role in the regulation of vascular tone; its increased release may be responsible for the vasodilatation and hypotension in sepsis [16]. iNOS is activated by endotoxins and cytokines leading to local and general vasodilatation [8, 17, 18]. NO is also considered a potent cerebral vasodilator [19]. Thus, NO may play an important role, not only in mediating systemic vascular resistance, hypotension, and cardiac depression, but also in cerebral

vasodilatation during sepsis. However, in an ovine model of hypotensive-hyperdynamic sepsis, Booke and colleagues [20] demonstrated that inhibition of NOS did not alter cerebral blood flow (CBF) and postulated that CBF is regulated by mechanisms other than NO during sepsis. Nonetheless, in situations of ischemia and reperfusion the presence of great amounts of NO can cause an increased production of reactive oxygen species (ROS), like peroxynitrite, responsible for the destruction of membranes in cells and mitochondria.

Finally, another mechanism by which the brain is affected in sepsis is the generation of ROS by activated leukocytes. Exposed to these radicals, erythrocyte cell membranes become less deformable and may be unable to enter the brain microcirculation, thus aggravating the cerebral hypoperfusion seen in sepsis [21, 22]. The brain itself with its high oxygen consumption and low antioxidant defense is susceptible to damage by ROS. Generation of ROS may alter oxidative phosphorylation and cytochrome activity in the mitochondria and impair cerebral energy production.

Cerebral Perfusion

Cerebral Perfusion Pressure

Mean arterial pressure (MAP) is notoriously low in severe sepsis and septic shock. Accordingly, cerebral perfusion pressure (CPP) is low. Moreover, in view of the possible presence of brain edema, the influence of intracranial pressure (ICP) on CPP must be considered. Pfister at al. [23] measured ICP non-invasively in 16 patients with sepsis and reported moderate elevations of ICP > 15 mmHg in 47 % of patients; an increase > 20 mmHg was not observed. CPP < 50 mmHg was found in 20 % of their patients. Assuming that cerebrovascular pressure autoregulation is intact and the plateau of the autoregulatory curve is not shifted, their results suggest that CPP in the majority of the patients they investigated was likely to remain in the lower range of the autoregulatory plateau. However, this interpretation is partially in contrast to measurements of CBF in patients with sepsis. Bowton et al. [21] demonstrated that CBF was reduced in patients with sepsis independent from changes in blood pressure or cardiac output. These authors used the ^{133}Xe clearance technique to measure CBF in nine septic patients. Similarly, Maekawa et al. [22] found significantly lower CBF in six patients with sepsis-associated delirium than in awake controls. In an experimental model of human endotoxemia, Moller and colleagues [24] repotrted a reduction in CBF after an intravenous bolus of endotoxin in healthy volunteers. However, the authors assumed that CO_2 reactivity was intact in their subjects and explained this CBF reduction to hypocapnia occurring because of general symptoms of malaise, although they did not measure CO_2 reactivity in their subjects.

Regulation of Cerebral Perfusion

CO_2-reactivity

Using transcranial Doppler (TCD) and arterial partial pressure of CO_2 ($PaCO_2$) levels between 3.0 and 7.0 kPa, Matta and Stow [25] found relative CO_2-reactivity to be within normal limits in ten patients with sepsis. Their patients were in the early stages of sepsis (< 24 h after admission to ICU), were all mechanically ventilated, and received infusions of midazolam and fentanyl. Absolute CO_2-reactivity was lower than had been reported in subjects who were awake but consistent with values

obtained during sedation and anesthesia. Similarly, Thees and colleagues [26] reported a normal response to a decrease in $PaCO_2$ in ten patients with sepsis using TCD and cardiac output measurement by thermal dilution. Their patients were all mechanically ventilated, and sepsis had been established for > 48 h. Bowton and colleagues [21] also reported normal specific reactivity of the cerebral vasculature to changes in CO_2 in nine septic patients. However, Terborg and colleagues [27] reported impaired CO_2-reactivity in septic patients, independent of changes in MAP. They used TCD and near-infrared spectroscopy (NIRS) to assess CO_2-induced vasomotor reactivity by inducing hypercapnia through reductions in the ventilatory minute volume in eight mechanically ventilated septic patients. It is important to note that all their patients suffered from a neurological or neurosurgical illness, which may have affected the results. Similarly, Bowie and colleagues [28] observed significantly impaired cerebral CO_2-reactivity in septic patients in a study of 12 sedated and ventilated patients who had sepsis for > 24 h using TCD at normocapnia, hypocapnia, and hypercapnia. The small sample sizes, differences in timing of the measurements of CO_2-reactivity and in the severity of illness between groups, which is reflected by the significant differences in mortality as well as in some of the drugs used in the management of these patients, may be responsible for the conflicting findings.

Cerebrovascular pressure autoregulation

Only a few studies have addressed the effects of sepsis on cerebral autoregulation. Matta and Stow [25] reported intact pressure autoregulation in ten mechanically ventilated patients with sepsis (not in septic shock) using a phenylephrine infusion to increase MAP by 20 mmHg and calculated an index of autoregulation by dividing the percentage change in estimated cerebral vascular resistance by the percentage change in MAP. Conversely, Smith and colleagues [29] reported loss of cerebrovascular autoregulation in 15 patients with septic shock as they were able to demonstrate a correlation between cardiac index and CBF using TCD and cardiac output measured by thermodilution. In a recent study, Pfister and colleagues [30, 31] found disturbed cerebral autoregulation in patients with sepsis-associated delirium – but not in patients with 'plain' sepsis – using TCD and NIRS. This suggests that cerebral autoregulation is possibly intact in patients with sepsis but disturbed with more severe disease or complications manifesting as septic shock or sepsis-associated delirium.

Perfusion and Brain Dysfunction

Cerebral ischemia

Cerebral ischemia is a reality in sepsis: In a post-mortem analysis of the brain of patients who died from sepsis, multiple small ischemic lesions could be identified in different areas of the brain [4]. Possible explanations are the hypotension seen in sepsis, especially when concurrent with preexisting cerebrovascular disease or autoregulatory failure. Thrombotic mechanisms due to a high hematocrit and increased viscosity of blood in sepsis may lead to watershed infarction as has been described in a septic patient with prolonged hypotension [3].

Cerebral perfusion and sepsis-associated delirium

Sepsis-associated delirium is a common organ dysfunction in sepsis and may actually occur before failure of other organs. It can be found in up to 70 % of patients

with the sepsis syndrome and is correlated with the severity of sepsis [32–34]. Depending on the criteria used for diagnosis, it may be detected in almost all patients with sepsis [32, 35]. Sepsis-associated delirium has been reported as an independent predictor of death [36]; however it may only reflect the severity of illness and may not be the cause of death itself. Sepsis-associated delirium presents as an alteration of the mental state and may range from lethargy or mild disorientation to obtundation and coma. The pathophysiology of sepsis-associated delirium is incompletely understood and is probably multifactorial. Mechanisms postulated to cause sepsis-associated delirium include brain activation by inflammatory mediators via the vagus nerve and the circumventricular organs, which interfere with the liberation of neurotransmitters and neurohormones. Oxidative stress and formation of ROS compromising cell function and endothelial activation resulting in disruption of the blood-brain-barrier are other mechanisms proposed to play a role in development of sepsis-associated delirium [5]. However, cerebrovascular autoregulation may also play a role in sepsis-associated delirium [25, 27, 29, 30, 36]. Pfister and colleagues [30] reported less efficient autoregulation in patients with sepsis-associated delirium compared to patients without sepsis-associated delirium. However, in the same patients, cerebral oxygenation measured by NIRS did not differ between patients with and without sepsis-associated delirium. Thus, reduced cerebral blood flow and disturbed cerebrovascular autoregulation may – among others – be important precipitating factors for sepsis-associated delirium [2, 30]. Alternatively, it could also be argued that disturbed autoregulation is merely a reflection of a more severe inflammatory stimulus that is associated with a more profound dysfunction of the blood-brain barrier and hence endothelial/autoregulatory dysfunction.

Effects of catecholamines on cerebral perfusion in patients with sepsis

Data on the cerebrovascular effects of catecholamines in sepsis are scarce. The blood-brain barrier prevents catecholamines from entering the brain as long as it is intact. Cerebral hemodynamics are not directly affected by norepinephrine and phenylephrine in anesthetized patients without cerebral pathology [37]. After head injury however, dopamine, norepinephrine and phenylephrine all seem to increase CBF with the effect of norepinephrine being more predictable than that of dopamine [38]. This is possibly due to the fact that in head injury there is also a disruption of the blood-brain barrier that allows, e.g., norepinephrine to access intracerebral β receptors leading to an increase in cerebral metabolism and, hence, CBF [39]. Accordingly, it could be speculated that in sepsis also the cerebral effects of vasopressors may be unpredictable depending on the degree of blood-brain barrier dysfunction.

A representation of documented and hypothetical factors influencing cerebral perfusion in sepsis is shown in **Figure 1**.

Conclusion

The inflammatory response observed in sepsis triggers profound changes in the brain. Blood-brain barrier permeability is increased, and substantial changes in regulation of CBF and cerebral perfusion may occur. Hypoperfusion due to severe hemodynamic instability will obviously lead to ischemic brain injury. Furthermore, the changes in pressure autoregulation may result in an increased vulnerability of the brain to hypoperfusion. However, this does not explain the full range of brain

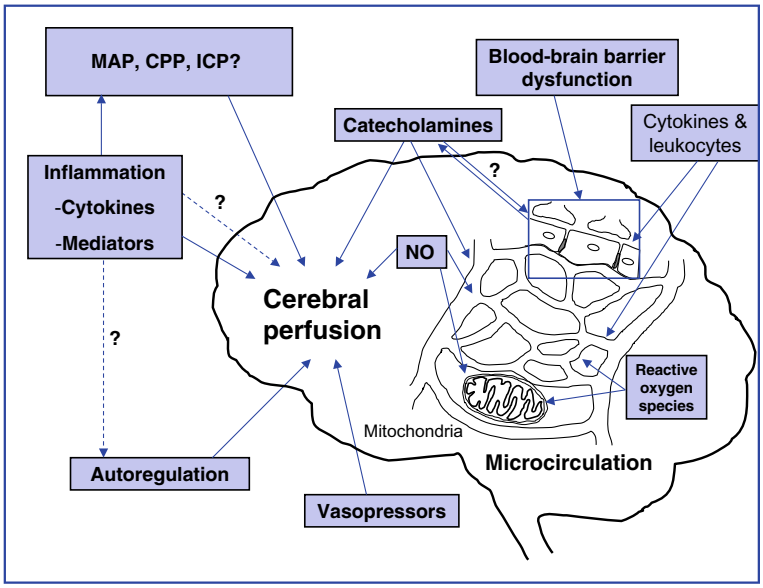

Figure 1. Synopsis of documented and hypothetical factors influencing cerebral perfusion in sepsis. Some of the factors (e.g., nitric oxide [NO]) influence cerebral perfusion at different levels of the brain circulation. It could be speculated that the effect of vasopressors may be unpredictable depending on the degree of blood-brain barrier dysfunction. MAP: mean arterial pressure; CPP: cerebral perfusion pressure; ICP: intracranial pressure

dysfunction found in septic patients. So far it has not been possible to establish a clear link between cerebral perfusion and sepsis-associated delirium. It is conceivable that the effects of the inflammatory response on the brain *per se* are the key events leading to sepsis-associated delirium, and that the observed changes in CBF regulation are rather a consequence of inflammation than a cause of sepsis-associated delirium.

XII

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Systemic Complications after Subarachnoid Hemorrhage

A. Caricato, R. Maviglia, and M. Antonelli

Introduction

Aneurysmal subarachnoid hemorrhage (SAH) is a neurologic emergency that affects an estimated 10 individuals in a population of 100,000 annually, and is associated with high mortality rates and significant morbidity among survivors [1, 2]. The most important independent determinants of outcome include neurological status on admission [3–8], age [3, 5, 7–9], large aneurysm size (> 10 mm) [6], and aneurysm rebleeding [10–12].

Medical complications may also have a considerable impact on neurological outcomes and survival (**Table 1**). These complications are very common and, in recent large prospective cohorts, the proportion of death directly attributable to extracerebral organ injuries was estimated to be between 23 and 42 % [13–16]. Medical complications are potentially modifiable derangements that can exacerbate brain injury after SAH, and consist mainly of respiratory, cardiac, electrolyte, and metabolic abnormalities. Recently, fever, anemia and hyperglycemia were found to be significantly associated with mortality and poor functional outcome after SAH [17]; furthermore at 24 hours after admission, hypoxemia, metabolic acidosis, hyperglycemia, and cardiovascular instability were the physiological abnormalities that independently predicted poor outcome [15].

The pathophysiological mechanisms surrounding the development of medical complications after SAH are not completely understood. They are probably multifac-

Table 1. Medical complications of subarachnoid hemorrhage

Cardiac	Electrolytes
Arrhythmias	Hyponatremia
Enzyme release	Hypernatremia
Regional wall motion abnormalities	Hypomagnesemia
Apex sparing	Hypokalemia
Basal sparing ('takotsubo cardiomyopathy')	Diabetes insipidus
Systolic failure	Syndrome of inappropriate antidiuretic hormone
Diastolic failure	Cerebral salt wasting syndrome
Pulmonary	Hyperglycemia
Early onset pneumonia	Fever
Late onset pneumonia	Anemia
Cardiogenic pulmonary edema	Thrombocytopenia
ALI/ARDS	Leukocytosis
Pulmonary embolism	
(Neurogenic pulmonary edema)	

torial, involving a massive catecholamine release at the time of the hemorrhage and activation of a remarkable inflammatory and immunological response, both within the brain and systemically.

Cardiac Abnormalities

After SAH, several transient cardiac abnormalities have been described in patients with normal coronary arteries. These cardiac abnormalities consist mainly of electrocardiographic (EKG) alterations and a mild increase in cardiac enzymes, while severe cardiac failure or potentially lethal arrhythmias were found in only a minority of cases. Solenski et al. in a case series of 457 patients noted cardiac arrhythmia in 35 % of cases, and in 5 % these were considered life-threatening [13]. In a recent meta-analysis including 2124 patients from 32 studies, ST segment or T wave changes were observed in 46 % and QT prolongation in 30 % of subjects [18]. The prognostic value of an abnormal EKG in this setting has been questioned and is not clearly defined.

Troponin I increases after SAH in proportion to the severity of the initial bleeding, but values greater than 3 ng/ml are not common. In 253 patients with clinical or EKG findings of cardiac injury after SAH, troponin I increased in 68 % of the cases, and in 32 % its value was greater than 2 ng/ml [19]. In a retrospective study, Bulsara et al. demonstrated that values of troponin I less than 2.8 ng/ml in patients with severe impairment of global contractility (ejection fraction < 40 %) could be used to differentiate acute myocardial infarction from reversible cardiac abnormalities associated with SAH [20]. According to several authors, the peak value of troponin I may have prognostic significance, particularly with regard to the risk of death, delayed cerebral ischemia, and cardiovascular complications [19–22].

Recently, prospective echocardiographic examination performed on consecutively enrolled SAH patients, showed that systolic and diastolic left ventricular failure occurred much more frequently than previously believed. Banki et al. found regional wall motion abnormalities in 28 % of the patients, and a reduction in global contractility in 15 % of the patients [23]. This pattern was generally rapidly reversible and did not correlate with coronary artery distributions. Kopelnik and colleagues found an even higher incidence of diastolic dysfunction, which was observed in 71 % of the patients [24]. In these cases, an increase in markers of cardiac failure, such as brain natriuretic peptide (BNP), was frequently seen. Based on these observations, routine ecocardiographic evaluation has been proposed in SAH, and when significant abnormalities are observed, extensive use of hemodynamic monitoring could be useful to manage fluid administration and catecholamine infusion rates.

Massive release of catecholamines from sympathetic nerves is thought to be the main mechanism of cardiac damage, probably triggered by ischemic lesions in the hypothalamus, the insular cortex, or in other sites of the autonomic nervous system, induced by the bleeding [25]. Histological examination of the heart of patients who died after SAH is consistent with this hypothesis, since lesions are similar to those seen during experimental catecholamine infusion or in pheochromocytoma, and do not follow a vascular ischemic pattern. Recently, a report described an echocardiographic pattern of severe left ventricular systolic dysfunction in SAH patients, with basal wall motion sparing [26]. These features were similar to those observed in a syndrome of profound myocardial stunning precipitated by acute emotional stress, the so-called ‘takotsubo cardiomyopathy’, named for the fishing pot with a narrow

neck and wide base that is used to trap octopus [27]. Similar pathophysiological mechanisms are probably involved in these two different cardiomyopathies.

Lung Abnormalities

Pulmonary complications are among the most common medical sources of morbidity after SAH, with a prevalence of 14–29 % [13–14, 16, 28]. In a large retrospective study based on 305 patients, pulmonary complications were observed in 22 % of the patients; pneumonia accounted for more than 50 % of the cases, cardiogenic pulmonary edema was observed in 30 %, and neurogenic pulmonary edema in 6 % [28].

Few data are available on pneumonia in SAH. Early onset pneumonia is frequent and represents around 50 % of the pulmonary infections. The incidence could probably be reduced by prophylactic administration of antibiotics at the time of intubation [29, 30], but their prognostic role seems to be less significant compared to late onset pneumonia, mainly caused by nosocomial microorganisms [31].

In SAH patients, the term 'neurogenic pulmonary edema' has been used to describe a syndrome of hypoxemic respiratory failure and pulmonary edema in the absence of any other mechanism of lung injury (pneumonia, trauma, sepsis, heart disease). Its pathogenesis is not clearly understood. According to the "blast theory", proposed by Theodore and Robin in 1975 [32], a severe transient increase in pulmonary capillary pressure increases pulmonary vascular permeability leading to interstitial and alveolar pulmonary edema. Neurogenic pulmonary edema may, however, also occur independently from hemodynamic mechanisms; in fact, several studies have postulated that an inflammatory state is common after SAH and may increase endothelial permeability in the pulmonary microvessels. Moreover, the permeability of the alveolo-capillar membrane may be modulated directly by adrenergic receptors after the massive catecholamine release at the time of the bleeding.

Furthermore, some authors observed that cardiac abnormalities were found in several patients with neurogenic pulmonary edema. Muroi et al. measured cardiac index and observed values below 3 l/min/m^2 in 33 % of their patients; in addition in 37 out of 39 patients continuous infusion of catecholamines was needed during the acute stage [33].

It is likely that the term 'neurogenic pulmonary edema' includes physiologically heterogeneous conditions. Of note, these studies did not use the standardized American–European Consensus Conference definition of acute lung injury/acute respiratory distress syndrome (ALI/ARDS) based on criteria of non-cardiogenic pulmonary edema and hypoxemia. Furthermore, even when this classification was used, no hemodynamic evaluation was performed to exclude cardiac impairment. The proportions of cardiogenic or lesional edema are, therefore, not known in this condition, and this could lead to an empirical therapeutic approach that may not be the best treatment for all patients. A wider consensus on the classification of pulmonary abnormalities in SAH should be encouraged.

General considerations suggest that volume controlled ventilation be used in the early phase of SAH, to maintain a strict control on $PaCO_2$ levels. Moderate levels of positive end-expiratory pressure (PEEP, up to 8–10 cmH_2O) can be used in normovolemic patients, together with end-tidal CO_2 ($ETCO_2$) and $PaCO_2$ monitoring, and with a 30° head up tilt. Respiratory system compliance should be measured to avoid excessive PEEP in patients with distensible lung, minimizing the transmission of PEEP to the cerebral venous system. According to some authors, lung protective

ventilation could be considered in SAH patients with ARDS, as long as $ETCO_2$, $PaCO_2$ and intracranial pressure are closely monitored [34].

Fever

Fever, defined as a core temperature higher than 38.3 °C, is a common finding after severe neurologic injury, and in SAH the incidence is very high, up to 70 % of patients in the first 10 days [35]. Fever is due to infections in only one half of cases, while up to one in three of the febrile episodes remain unexplained, even after extensive diagnostic efforts.

Studies from animal models found that fever may be induced by many conditions; in particular, the presence of blood within the cerebrospinal fluid (CSF) and tissue ischemia are powerful triggers. Clinical observations have confirmed these data. Fernandez et al. reported that the severity of the initial bleeding event, evaluated by the Hunt-Hess grade, the presence of ventricular hemorrhage, the aneurysm size, and loss of consciousness at the time of the bleeding were all significant admission predictors of fever [36]. Interestingly, a temporal association between vasospasm and the consecutive development of fever after SAH has been observed by several authors, suggesting that cerebral ischemia may be one of the most important determinants of fever [36].

The deleterious effects of fever are well known from both experimental and clinical data. They have been reported in ischemia, as well as in trauma, and were more pronounced in reversible rather than permanent injuries. Even a small increase in temperature further worsens initial cerebral lesions, and these effects are observed both in the acute and delayed settings.

Several large clinical studies observed that after controlling for baseline predictors of poor outcome, any increase in core temperature above 37.0 °C was responsible for a significantly increased risk of death and severe disability [36, 37]. Unfortunately, no prospective randomized study has yet been conducted to demonstrate a beneficial effect of normothermia. This is probably because of the low efficiency of strategies to combat fever that were available up to a few years ago. Recent commercial cooling methods are all very effective at controlling fever and can maintain normothermia even for several days. By using these devices, prospective trials on fever control will be soon available.

Anemia

Despite several studies, the ideal hematocrit at which cerebral oxygen delivery is maximized is still unknown. In the general ICU population and in neurological patients in particular, both anemia and transfusion are associated with a high risk of death and poor outcome. Naidech et al., in 611 SAH patients, found that a good prognosis was associated with a higher mean (11.7 ± 1.5 vs 10.9 ± 1.2, $p < 0.001$) and nadir (9.9 ± 2.1 vs 8.6 ± 1.8, $p < 0.001$) hemoglobin concentration (Hb), after correcting for baseline predictors of poor outcome [38]. Similar results were obtained by Wartenberg et al., who showed that a Hb less than 9 g/dl significantly predicted death and severe disability after SAH [17]. Kramer et al. reported that the association between anemia (Hb less than 10 g/dl) and poor outcome was considerably stronger in patients with vasospasm [39]. These data cannot, however, be inter-

preted as a direct deleterious effect of anemia on prognosis. Patients who developed anemia had more severe diseases, need a longer stay in the ICU, and received a larger number of transfusions. A recent meta-analysis showed that red blood cell (RBC) transfusion increased the risk of developing infections, ARDS, and multiorgan dysfunction syndrome, and was an independent predictor of death [40]. Interestingly, Kramer et al. tried to analyze the independent effects of anemia and transfusion on outcome, and observed that when both variables were introduced together into a logistic regression model, only transfusion remained significantly predictive of death and delayed infarction [39].

While waiting for randomized trials of liberal versus restrictive transfusion thresholds in SAH patients, the need for a RBC transfusion should be individualized, based on a patient's clinical circumstances (cerebral ischemia, cardiac disease, early phase of septic shock) rather than on arbitrary Hb concentrations.

Hyperglycemia

Sustained hyperglycemia is known to exacerbate secondary brain injury and to independently predict poor neurological outcome. While it is now widely accepted that glucose levels persistently above 180 mg/dl can be harmful in such patients, the optimal range for glucose control is not yet clearly defined [41].

In the seminal study by Van den Berghe et al. in surgical patients, there was an improved outcome in patients in whom glucose levels were kept in the 80 – 110 mg/dl range using intensive insulin therapy [42]. The same authors could not replicate these results in medical patients [43], suggesting that glucose control should be individualized for each subgroup of critically ill patients. In neurological patients, some retrospective papers found a beneficial effect of strict glucose control. However, recent studies did not confirm these results. Vespa et al. observed that intensive insulin therapy was associated with an increased incidence of microdialysis markers of cellular distress, namely elevated glutamate, elevated lactate/pyruvate ratio, low glucose, and increased global oxygen extraction fraction measured by positron emission tomography (PET), as if low plasma glucose levels were not sufficient for cerebral metabolism [44]. In effect, after severe brain injury a reduction in cerebral metabolic oxidative metabolism for a direct failure of mitochondrial activity was observed, together with a relative increase in glycolytic metabolic pathways. This may explain the increased need for higher glucose concentrations and the deleterious effect of tight glucose control.

In conclusion, according to Oddo et al., there is presently no substantial evidence to support the use of intensive insulin therapy in critically ill neurological patients [45]. While awaiting the results of large prospective studies, a cautious use of insulin therapy, aimed at a more liberal target for systemic glucose control (100 – 180 mg/dl) may be recommended in SAH patients.

Electrolyte Abnormalities

Hyponatremia, hypernatremia, hypomagnesemia, and hypokalemia are frequent after SAH. Hyponatremia (serum Na < 135 mmol/l) is reported in 30 to 43 % of patients in the acute phase following SAH [46]. Although the prognostic significance of hyponatremia is less pronounced compared to hypernatremia, its diagnosis and

Table 2. Differential diagnosis of hyponatremia

	Cerebral salt-wasting syndrome	Syndrome of inappropriate anti-diuretic hormone
Plasmatic Na^+	Low	Low
Urinary Na^+	High	High
Urinary osmolarity	High	High
Volemia	Low	Normal or high

treatment are crucial to avoid cerebral edema. At least two mechanisms are involved in hyponatremia after SAH: Excessive sodium excretion caused by increased circulating natriuretic peptide activity (cerebral salt wasting, CSW), or an exaggerated increase in antidiuretic hormone (ADH), with consequent water retention, hypervolemia, and secondary natriuresis (syndrome of inappropriate antidiuretic hormone, SIADH) (**Table 2**). Differentiating between these conditions is not simple, and mainly relies on evaluation of the blood circulating volume; in CSW, natriuresis causes hypovolemia, which is not present in SIADH, in which volemia is normal or increased. Laboratory data are not sufficient for diagnosis; in particular urinary sodium concentration is increased in both SIADH and in CSW. In fact, natriuretic factors increase urinary sodium concentration in CSW, while in SIADH, ADH concentrates urine, increasing free water resorption and sodium urine concentration. Urinary osmolarity is not diagnostic either, because it is related to sodium concentrations and is therefore increased in both CSW and SIADH. The cited prevalences of SIADH or CSW are wide; the incidence of SIADH was reported to be 9 to 63 %, and similar data were reported for CSW [46]. Some authors questioned their existence [47].

Other pathophysiologic mechanisms are probably involved in hyponatremia after SAH. The diagnostic criteria for SIADH and CSW include the absence of adrenal insufficiency, but recently we have learned how this condition can be difficult to identify, since it may be present even if normal concentrations of plasmatic cortisol are found. Furthermore some authors have suggested that the so-called 'hyperreninemic hypoaldosteronism syndrome' (HHS), described in critically ill patients, may play a role in the high sodium excretion observed after SAH [48]. In this condition, renin levels are high, while aldosterone is low or normal, as if aldosterone levels were insufficient, and a relative hypoaldosteronism was present. A transient diffuse impairment in the perfusion of the adrenal cortex induced by hypovolemia and the high sympathetic tone after SAH onset has been implicated in the pathogenesis.

The differential diagnosis of hyponatremia is crucial to manage infusional treatment. In fact, in CSW, hypovolemia should be rapidly corrected, while in SIADH a liberal strategy of fluid administration should be avoided. In two reports, hyponatremic patients who were misdiagnosed as having SIADH and treated with water restriction, had a dramatically increased risk of cerebral infarction [49, 50]. The treatment of hyponatremia following SAH, thus relies on hypertonic saline solutions and synthetic mineralocorticoids, regardless of etiology. Careful monitoring should be used to avoid occurrence of hypovolemia and guarantee an adequate cerebral perfusion pressure.

Recently, conivaptan, a non-selective ADH-receptor antagonist, has been approved by the US Food and Drug Administration as an intravenous infusion for the in-hospital treatment of euvolemic or hypervolemic hyponatremia**.** Its efficacy has been assessed in several double-blind, placebo-controlled clinical trials in

patients with acute or chronic heart failure. Although some report suggest that it may be useful in SIADH, clinical experience is still limited, and extreme caution should be paid to avoid its use in hypovolemic patients.

Conclusions

Medical complications may significantly affect the outcome of patients with SAH. Nevertheless, these complications are potentially treatable conditions, for which prompt diagnosis and correct management can achieve important goals, both in terms of mortality and neurological deficits. A 0.4 % per year decrease in the case-fatality of SAH patients has been reported over the last three decades. Good knowledge of the physiopathologic mechanisms that are involved in the organ failure induced by SAH may be crucial for further improvements in outcomes.

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XIII Perioperative Management

Epidural Anesthesia: New Indications for an Old Technique?

A. Gottschalk, C. Ertmer, and M. Westphal

Introduction

Fernand Cathélin (1873 – 1929) and Jean Athanase Sicard (1872 – 1929) were the pioneer researchers who independently tried to establish an analgesic technique via the epidural space. Cathélin, however, was the first to report experiences in blocking the last sacral and coccygeal nerves using an anesthetic solution (which is still unknown). Although Cathélin was able to apply this technique in the treatment of various urological diseases, he failed to produce effective anesthesia for surgical procedures [1]. Now, about one century later, epidural anesthesia is a widely used and accepted technique for perioperative analgesia in thoracic, abdominal, and orthopedic surgery. In addition, epidural anesthesia is often applied in women during labor and delivery and represents a useful approach in the treatment of chronic pain (especially related to pancreatic cancer and pancreatitis). Moreover, besides providing effective pain relief, epidural anesthesia represents a reliable and reversible neural deafferentation technique that effectively contributes to a reduction in the surgical stress response [2]. The clinical effects of thoracic epidural anesthesia are primarily related to a segmental sympathetic blockade [3]. In this context, it is note-

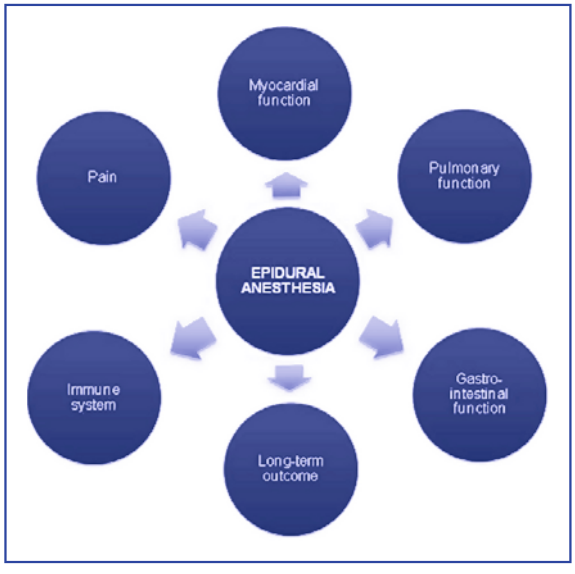

Fig. 1. The effects of epidural anesthesia.

worthy that epidural anesthesia is linked to vasodilation in the blocked area and a reflex increase in sympathetic activity outside the anesthetized segments [4]. Current evidence supports the concept that only thoracic epidural anesthesia exerts positive effects on cardiopulmonary and gastrointestinal functions. This book chapter is not exhaustive, but aims to summarize the current knowledge on the effects of epidural anesthesia on pain management, cardiopulmonary and gastrointestinal functions, as well as the immune system and outcome (**Fig. 1**).

Effects of Epidural Anesthesia on Pain Management

The dictum "pain does not kill" may be dangerously wrong; indeed, "it can mean the difference between life and death" [5]. For thoracic, abdominal and major orthopedic surgery, it has been shown that the efficacy of pain relief with patient-controlled epidural analgesia at rest and during movement is superior compared with intravenous patient-controlled analgesia [6]. Almost without exception, epidural analgesia, regardless of the analgesic agent, epidural regimen, and type and time of pain assessment, provided superior postoperative analgesia compared to intravenous patient-controlled analgesia [7]. For patients undergoing intra-abdominal surgery, in particular, continuous epidural anesthesia is superior in relieving postoperative pain when compared to intravenous opioid-based patient controlled analgesia. [8]. In addition, there is a growing body of evidence to support improved pain management in patients undergoing multi-level and complex spine surgery. Especially in this population, the majority of patients suffers from chronic pain. Mostly, preoperative pain is controlled with opioid analgesics, which may result in tolerance and hyperalgesia, even before the start of surgery. The exact mechanisms underlying the development of acute opioid tolerance and hyperalgesia are still not fully understood, but appear to involve activation of dorsal horn *N*-methyl-d-aspartate (NMDA) systems [9], inactivation of μ-opioid receptors [10], spinal dynorphin release [11], and upregulation of the cyclic adenosine monophosphate (cAMP) pathway [12]. In this context, it has been demonstrated that opioid tolerance in patients undergoing major spine surgery can be attenuated by insertion of an epidural catheter [13 – 15]. In addition, Gauger et al. [16] showed improved quality of analgesia with epidural compared to intravenous analgesia after posterior spinal fusion in pediatric patients. However, these authors [16] reported that 37 % of epidural catheters were ineffective. From these findings, it has been concluded that epidural failure after spinal fusion surgery is a common problem, and may be the result of inadequate dosing and/or catheter positioning. Although the success rate of placing an epidural catheter is very high in adults, there seems to be a need to improve this technique in children.

Effects of Thoracic Epidural Anesthesia on Myocardial Function

In addition to improvement of ventricular function and wall motion, epidural anesthesia modifies the electrical activity of the heart. Improvements in regional blood flow and a reduction in myocardial oxygen consumption play a critical role in attenuating the severity of coronary ischemia. Moreover, it has been shown that high thoracic epidural anesthesia improves regional left ventricular function (mean [SD] global wall motion index, 0.74 [0.18] vs 0.38 [0.16]; $p < 0.05$) [17]. Catheters were

inserted at the C7-T1 level to block the somatosensory level from T1-T5. Along with these findings, it has been reported that cardiac troponin I concentrations, as well as postoperative ischemia, were reduced in patients treated with high thoracic epidural anesthesia after coronary artery bypass grafting (CABG) compared to a control group (general anesthesia without thoracic epidural anesthesia) [17, 18]. Future studies are now needed to clarify whether the beneficial effects of thoracic epidural anesthesia on myocardial function translate into a better overall outcome.

Effects of Thoracic Epidural Anesthesia on Pulmonary Function

A recent meta-analysis by Pöpping et al. [19] elucidated the effects of thoracic epidural anesthesia on pulmonary function. This analysis included 5904 abdominal and thoracic surgical patients from 58 studies published between 1971 and 2006. The primary objective of this analysis was to determine the risk of postoperative pneumonia in patients treated with thoracic epidural anesthesia as compared with systemic analgesia. Notably, thoracic epidural anesthesia not only decreased the risk of pneumonia, but also improved pulmonary function and reduced the risk of prolonged ventilation and re-intubation. Although the mechanisms underlying these positive effects remain inconclusive; it is assumed that the improved outcome is linked to better pain control and subsequent improvement in pulmonary function [19].

Effects of Thoracic Epidural Anesthesia on Gastrointestinal Function

Although the effects of thoracic epidural anesthesia on intestinal perfusion are still not fully understood, improvements in microvascular and regional perfusion seem to play an important role [20]. Since the gut is critically involved in the pathophysiology of sepsis and systemic inflammation, thoracic epidural anesthesia may potentially be a useful technique to attenuate abnormalities in gastrointestinal perfusion [21].

In this context, it has been shown that thoracic epidural anesthesia improves villus blood flow [20] and increases mucosal capillary perfusion in rats suffering from peritoneal sepsis secondary to cecal ligation and puncture [22]. However, conflicting clinical results on the effects of thoracic epidural anesthesia on postoperative complications following abdominal surgery render a final conclusion elusive. Although one retrospective study demonstrated a significant reduction in anastomotic lesions in patients who received thoracic epidural anesthesia [23], a meta-analysis by Fotiadis et al. did not confirm a decrease in anastomotic leakage [24]. Another concern is that the use of thoracic epidural anesthesia in sepsis may aggravate arterial hypotension, thereby possibly threatening organ perfusion. To address this issue, Daudel et al. conducted a prospective, randomized, laboratory experiment and subjected 14 chronically instrumented adult sheep (n = 7 per group) to incremental endotoxin doses to induce a hypotensive-hypodynamic circulation. The thoracic epidural anesthesia group received 0.1 ml/kg of 0.125 % bupivacaine at the onset of endotoxemia, and control animals received normal saline via the epidural catheter. Interestingly, there were no changes in systemic hemodynamics and global oxygen transport beyond the changes caused by endotoxin itself. Conversely, thoracic epidural anesthesia was linked to an increase in urinary output vs control ($p < 0.05$) [25]. The

same investigators evaluated the effects of thoracic epidural anesthesia in the setting of hyperdynamic endotoxemia and reported that from a hemodynamic point of view, thoracic epidural anesthesia presents a safe treatment option [26]. However, future studies are needed to clarify whether or not the use of thoracic epidural anesthesia in sepsis carries the risk of bacterial spread via the epidural catheter.

Effects of Thoracic Epidural Anesthesia on the Immune System

It is well known that perioperative stress negatively affects the immune system [27]. In this context, it has been reported that regional anesthesia, including spinal and epidural anesthesia, markedly reduces the surgical stress response [2], which is believed to be the primary trigger of postoperative immunosuppression [28, 29]. Notably, Wada et al. showed in a mice model that a laparotomy under sevoflurane anesthesia was associated with significantly more liver metastases than one with sevoflurane anesthesia plus spinal anesthesia. Establishing a spinal blockade in addition to sevoflurane anesthesia attenuated the suppression of the tumoricidal function of liver mononuclear cells (presumably by preserving the T helper 1/T helper 2 [Th1/Th2] ratio), thereby limiting tumor metastasis [30]. In this regard, it seems to be important that Th1 cytokines are involved in increasing the cytotoxic activities of T cells, natural killer (NK) cells, interleukin (IL)-4 and IL-10. Th2 cytokines, in turn, promote humoral immunity and suppress the Th1 response. Finally, the Th2-dominant status is thought to play a negative role in oncologic immunity.

A timely retrospective study by Biki et al. [31] investigated the effects of general anesthesia in combination with intravenous morphine versus general anesthesia combined with epidural analgesia in patients with prostate cancer undergoing radical prostatectomy. The authors found that the use of thoracic epidural anesthesia was associated with a 65 % reduction in biochemical recurrence of prostate cancer, as judged by increased prostate specific antigen, postoperatively [31]. Another retrospective study in this area focused on patients' long-term survival after colon-cancer surgery; Christophersen et al. reported that the use of epidural anesthesia in addition to general anesthesia among patients without metastasis was associated with an enhanced survival before 1.46 years. However, epidural anesthesia did not impact on the survival of patients with metastases [32]. Future studies are now needed to elucidate this issue in more detail.

Effects of Thoracic Epidural Anesthesia on Long-term Outcome

The most important question, however, is if and to which degree the anesthetic technique *per se* affects the overall outcome. In contrast to preventable anesthetic mortality, which is rare, all-cause postoperative mortality is surprisingly high. Notably, about 5 % of all surgical patients die within a year of surgery; among those aged > 65 years, mortality is about 10 % [33]. Therefore, mortality in the year after surgery is about 10,000 times more common than preventable anesthetic mortality [34]. A very important question in this regard is, whether or not epidural anesthesia may reduce postoperative mortality. Some studies confirm specific benefits of epidural analgesia including good analgesic efficacy and favorable effects on bowel motility [35]. However, the lack of support for a role in reducing serious surgical morbidity is particularly troublesome.

A meta-analysis published by Rodgers et al. [36] in 2000 suggested that neuraxial blockade reduced the odds of pneumonia by 39 %, deep vein thrombosis by 44 %, transfusion requirements by 50 %, pulmonary embolism by 55 %, and respiratory depression by 59 % (each $p < 0.001$). Overall mortality was reduced by about one third in patients allocated to neuraxial blockade (103 deaths per 4871 patients vs 144 per 4688 patients, odds ratio = 0.70, 95 % confidence interval 0.54 to 0.90, $p = 0.006$) [36]. However, it should be noted that this meta-analysis included studies from 1971 to 1995. Since then, the baseline risk for patients has reduced due to modern antithrombotic medications, antibiotics, and fast track surgery protocols. Since meta-analyses should only be hypothesis generating, future studies adequately powered to address this very important issue are warranted.

Although two randomized controlled trials showed improved analgesia with thoracic epidural anesthesia for high-risk patients undergoing major abdominal surgery [37, 38], they did not demonstrate improved overall outcomes in the thoracic epidural anesthesia group compared with control patients [37, 38]. However, subgroup analyses revealed a significant reduction in respiratory failure [37, 38], myocardial infarction [38], and stroke [38]. A major criticism of the paper by Rigg et al. [37], is the missing information on epidural catheter position. It is also noteworthy that a large number of epidural catheters were withdrawn before termination of the study. In fact, only 50 % of patients in the epidural group received epidural analgesia throughout the entire study period.

Adverse Effects and Potential Risks of Epidural Anesthesia

Epidural analgesia, while apparently safe and providing superior analgesia compared to intravenous analgesia, may contribute to arterial hypotension and bear potential risks, such as infection and epidural hematoma. In this context, it is important to consider that the epidural catheter may provide a track for bacterial contamination and thus facilitate the development of an epidural abscess. In this context, Pöpping et al. reported a risk of symptomatic spinal mass lesions, including epidural hematoma (0.02 %; 1:4741) or epidural abscess (0.041 %; 1:7142), of 1:2857 (0.04 %) after patient controlled epidural anesthesia [6]. Together with data from other studies [39–41], these authors reported that factors, such as advanced age, immunosuppression, and a prolonged duration of catheterization (more than 4 days) were risk factors for the development of an epidural abscess.

Two recent retrospective studies detected a high incidence of epidural hematomas for female patients undergoing lower limb surgery [6, 42]. This adverse effect may potentially be explained by the fact that lower limb arthroplasty is often performed in elderly patients, who often take non-steroidal anti-inflammatory drugs (NSAIDs) and anticoagulants that interfere with platelet function. Alteration in hepatic and renal metabolic function, especially in elderly patients, may also result in a reduced elimination of anticoagulant and antiplatelet agents. In addition, postmenopausal females may suffer from osteoporosis and have a high incidence of osteoporotic or degenerative deformities of the spine, thus necessitating repeated attempts at catheter placement (a significant risk factor for epidural hematoma) [19, 42].

Major issues pertaining to anesthesiology include timing for patients undergoing neuraxial blockade. A particular paradigm shift is the continuation of acetylsalicylic acid in the perioperative period in order to reduce cardiovascular events, especially in patients with recent stent implantation. In the presence of acetylsalicylic acid,

thromboembolism prophylaxis with low molecular weight heparin should be started postoperatively in all patients, especially those undergoing neuraxial blockade [43].

Conclusion

Epidural anesthesia provides better postoperative pain relief compared with intravenous opioids. Thoracic epidural anesthesia reduces central sympathetic activity, with subsequent favorable effects on cardiopulmonary, gastrointestinal, and immune function. To minimize side effects, close supervision by an acute postoperative pain service is mandatory.

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Risk Assessment and Prevention of Perioperative Stroke

A. Papangelou and M. Mirski

Introduction

Perioperative stroke is a potentially devastating medical occurrence that complicates patient management during the postoperative critical care period. Irreversible cerebral ischemia or hemorrhage may be incited either during surgery or in the postoperative period. This latter risk period need not be immediate, as some studies link postoperative stroke up to 30 days following the procedure.

A comprehensive review by Selim [1] on this topic assessed the representative incidences based on surgical procedure. These categories included general surgery (0.08 – 0.7 %), peripheral vascular surgery (0.8 – 3.0 %), resection of head and neck tumors (4.8 %), carotid endarterectomy in symptomatic patients (5.5 – 6.1 %), isolated coronary artery bypass graft (CABG) surgery (1.4 – 3.8 %), combined CABG with valve surgery (7.4 %), isolated valve surgery (4.8 – 8.8 %), double or triple valve surgery (9.7 %), and aortic repair (8.7 %). Beating-heart CABG has a lower incidence of stroke than does CABG on bypass (1.9 % versus 3.8 %, respectively) [2].

The risk of perioperative stroke clearly is dependent on the patient's pre-operative health status as well as on the hazards to intracerebral perfusion implicated by the procedure itself. Preventive management strategies, as will be discussed below, have been employed to reduce the incidence of stroke, including the use of intraoperative neuro-monitoring, novel surgical approaches to reduce cerebral ischemia risk, and development of predictive models. Surgical specialties where appreciable risk exists, and where attention to risk reduction has been most ardent, include general, vascular, and cardiac surgery.

Pathophysiology

Proposed mechanisms for perioperative ischemic stroke include thrombotic, embolic, lacunar, hematologic (hypercoaguable state), and hypoperfusion. Hemorrhagic stroke, far less common than ischemic stroke, is most often a consequence of an acute and intense state of anticoagulation, although extreme hypertension may also be a precipitant. Even given such risks factors, evidence from studies of cardiac surgery support that perioperative hemorrhagic stroke has a very low incidence. For example, Likosky et al. [3] looked at 388 patients who suffered stroke post-isolated CABG surgery. This study used the Northern New England Cardiovascular Disease Study Group classification system and imaging was performed in the form of computed tomography (CT) or magnetic resonance imaging (MRI). The study revealed that 62.1 % of strokes were embolic, 3.1 % lacunar, 1.0 % thrombotic, 8.8 % due to

hypoperfusion, 1.0 % hemorrhagic, 10.1 % multiple etiologies, and 13.9 % unclassified. About 45 % of strokes were detected within the first postoperative (post-op) day, with a slow decrement of detection over time (about 20 % additional by post-op day 2, about 12 % additional by post-op day 3, and less than 5 % beyond post-op day 10).

The sources of emboli (cardiac or artery-to-artery) during any surgery typically include left atrium (as consequence to arrhythmias such as atrial fibrillation), aortic arch atherosclerosis, left ventricle (perioperative myocardial infarction), and physical manipulations of the heart, arch, and carotid arteries [3]. The release of particulate matter from the cardiopulmonary bypass (CPB) pump may also occur. Less common, but a clearly identified risk source, are paradoxical emboli (thrombus or fat emboli) via a patent foramen ovale during orthopedic procedures. In a study of 2,630 CABG patients [4], 2.0 % had postoperative strokes. The event occurred after a mean of 3.7 days. In 19 of 52 patients (36.5 %), atrial fibrillation preceded the stroke, with a mean of 2.5 episodes of atrial fibrillation before the event.

Aggravating the risk of perioperative stroke is the natural transition to a prothrombotic state following visceral tissue injury, which lasts 14 – 21 days postoperatively; this is supported by decreased levels of tissue plasminogen activator and increased plasminogen activator inhibitor type 1 activity, fibrinogen-degradation products, thrombin-antithrombin complex, thrombus precursor protein, and D-dimer. Other factors, such as the use of general anesthesia, under-resuscitation leading to post-op dehydration, and bed rest may all compound the risks of a hypercoaguable state. Often, surgical safety dictates the withholding of antiplatelet and anticoagulant agents, further increasing the acute hypercoaguable state and risk of perioperative stroke. This practice has gradually been modified, and continuation of such medications up to the time of surgery has been found to be safe in a large number of surgical procedures.

Another significant risk factor for ischemic stroke seen during the perioperative period is hypoperfusion. Gottesman et al. [5] examined 98 patients who had MRI scans after a clinical stroke. The group identified watershed infarcts in 68 % of the diffusion-weighted MRI sequences. The superiority of this imaging technique for stroke of this type is clear, as this group only identified such infarctions by CT in 37 % of patients from this same cohort. In fact, 48 % of diffusion-weighted MRIs demonstrated bilateral watershed infarcts, versus 22 % of CTs. Bilateral watershed infarct patients were more likely to have undergone an aortic procedure rather than a coronary bypass procedure (CABG). Reduced perfusion pressures and longer bypass times may have been possible root causes for the enhanced risk of watershed ischemia, on top of the greater risk of embolic stroke from aortic manipulation. Univariate and multivariate logistic regression revealed that patients with a decrease in mean arterial pressure (MAP) of at least 10 mmHg from their preoperative baseline were greater than four times more likely to develop bilateral watershed infarcts as those with a small, or no decrement in blood pressure. Some suggestion has been made that the risk of watershed infarction may also be due to a concerted mechanism of hypoperfusion and embolization. The theory is that a state of reduced perfusion (due to reduced MAP or due to arterial, i.e., carotid, narrowing) may impede washout of microemboli showered during cardiac surgery, and these particulates have a predilection to settle in watershed areas.

In support of this theory, a randomized study of 248 elective CABG patients [6] revealed that patients maintained at a higher MAP (80 – 100 mmHg) during bypass had a lower incidence of stroke. This study has been criticized for lack of power to

draw any widely applicable conclusions. However, van Wermeskerken et al. [7] reviewed outcomes from 2,862 patients undergoing CABG. After controlling for bypass time and preoperative stroke risk index, patients with a lower pressure during bypass (MAP < 50 mmHg) had a decreased incidence of stroke and coma.

In general, hypoperfusion is felt to be an uncommon cause of perioperative stroke. The term hypoperfusion can imply global hypoperfusion (i.e., resulting in bilateral watershed infarctions) or relative hypoperfusion through a preexisting stenosis (i.e., unilateral watershed infarction due to carotid stenosis). The aforementioned study by van Wermeskerken et al. [7] supports a limited role of hypoperfusion. In addition, some studies have concluded that hypoperfusion-induced ischemia is rare during carotid endarterectomy, even when the contralateral carotid is occluded. Naylor et al. [8] reviewed the literature to assess the role of carotid stenosis as a perioperative stroke risk factor after CABG. Ninety-one percent of screened CABG patients had insignificant disease and had a less than 2 % risk of stroke. The risk increased to 3 % for asymptomatic unilateral stenosis of 50 – 99 %, 5 % in bilateral 50 – 99 % stenosis, and 7 – 11 % in those with an occluded carotid. As a consequence of such data, the current practice is to perform carotid endarterectomy prior to CABG or even intraoperatively immediately before CABG.

Studies looking specifically at the mechanisms of stroke in the general surgical population are rare, and on the whole are not contemporary studies. Hart and Hindman [9] performed a retrospective review of 24,500 general surgery patients. Forty-two percent of strokes were felt to be embolic with atrial fibrillation present in 33 % of patients at the time of the events. Interestingly, most perioperative strokes occurred well into the postoperative period, on average on the 7th day. Recent case control studies again reiterate the paucity of intraoperative stroke.

Review of Clinical Studies

In the general surgery population, it is difficult to cross-evaluate the variety of clinical studies undertaken to assess perioperative stroke risk. Prospective randomized trials are rare or non-existent; the best level evidence is from a prospective observational study, with case control investigations being the next highest level of evidence. **Table 1** reviews the most comprehensive data of perioperative stroke in the realm of general surgery. A retrospective analysis of non-carotid vascular surgery patients was also included.

Table 2 compares the existing meta-analyses in cardiac surgery compared to conventional CABG and off-pump CABG in terms of global outcomes. The data in **Table 2** only address stroke. The 2003 analysis [16] included non-randomized trials, but it was felt that the inclusion of these data did not bias their results.

The existing data on perioperative stroke in cardiac surgery are limited to multiple prospectively collected, retrospectively analyzed observational studies. There is also one case control design and multiple retrospective studies in the literature. The data are summarized in **Table 3**, and a small study with similar surgical breakdown [2] has been included for comparison. Also included at the end of the table are two recent larger prospective studies on thoracic aortic surgery, as these studies likely best fit in the cardiac surgery category.

There are several meta-analyses exploring different aspects of perioperative stroke in carotid surgery, and these are reviewed in **Table 4**. These data are applicable to this review only in a broad sense, but are interesting nonetheless. Only the most

Table 1. Perioperative stroke: General surgery

Study year [ref]	Number of subjects	Study design	Stroke incidence	Significant risk factors
1988 [10]	2,463	Prospective, observational	0.2 %	Previous cerebrovascular disease Heart disease Peripheral vascular disease (8 fold increased risk) Hypertension (3 – 4 fold increased risk)
1993 [57]	24,641	Retrospective	0.08 %	Hypertension Smoking Previous neurological symptoms Abnormal rhythm on EKG
1982 [9]	24,500	Retrospective	0.07 %	Atrial fibrillation Cardiac disease
1990 [11]	173 (patients with prior CVA)	Retrospective	2.9 %	Use of preoperative heparin sodium (usually as a substitute for warfarin) General anesthesia (as opposed to regional) [26] Hypotension in recovery room [26]
2004 [12]	2,251 (abdominal aortic aneurysmectomy) 2,616 (aorto-bifemoral bypass) 6,866 (lower extremity bypass) 7,442 (major lower extremity amputation)	Retrospective	0.4 – 0.6 %	Preoperative ventilation (OR 11) Previous stroke or TIA (OR 4.2) Postoperative MI (OR 3.3) Need to return to operating room (OR 2.2)
1998 [13]	61 cases (general surgery) 122 random controls (matched for age, sex, procedure and year of procedure)	Case control	N/A	Previous cerebrovascular disease (AOR_1 12.57; AOR_2 14.70)* COPD (AOR_1 7.51; AOR_2 10.04) PVD (AOR_1 5.35) Higher MAP on admission (AOR_2 1.05) Blood urea at time of stroke (AOR_2 1.04) Postoperative MI (4 cases vs 0 control) Diffuse intravascular coagulation (4 cases vs 0 control)
2000 [14]	1,455 cases (surgery) 1,455 controls (age and gender matched)	Case control	N/A	Perioperative period after general anesthesia extending for 30 days post-op (OR adjusted for known independent stroke risk factor = 3.9 for all surgeries and 2.9 for general surgery)
2005 [15]	172,592	Prospective, observational	0.03 %	Most cases in ASA 3 patients 26 % of stroke cases had prior history of CVA

CVA: cerebrovascular accident, MI: myocardial infarction; MAP: mean arterial pressure; TIA: transient ischemic attack; OR: odds ratio; ASA: anesthesia pre-operative assessment score (1 – 5); COPD: chronic obstructive lung disease; PVD: peripheral vascular disease. * Adjusted odds ratio 1 (AOR_1) is from the univariate analysis; AOR_2 is from the multivariate analysis. Noted values are only those that reached statistical significance.

Table 2. Perioperative stroke: Cardiac surgery – Meta-analyses of conventional coronary artery bypass graft (CABG, control) versus off-pump CABG (intervention)

Study year [ref]	Number of trials	Number of subjects	Intervention (30 day stroke percent)	Control (30 day stroke percent)	Outcomes (OR with confidence interval)
2005 [17]	37 (21 trials included data on stroke)	2,859	0.4	1.0	0.68 (0.33 – 1.40)
2003 [16]	53 (38 trials included data on stroke)	34,126	Not noted	Not noted	0.55 (0.43 – 0.69)

Table 3. Perioperative stroke: Cardiac surgery

Study year [ref]	Number of subjects	Study design	Stroke incidence	Significant risk factors (multivariate analysis unless otherwise noted)
2007 [18]	5,085	Prospective observational	2.6 %	Female sex (OR 1.7); age > 60 (OR 1.2 per 5 yr interval); aortic surgery (OR 3.9); previous stroke (OR 2.1); critical preoperative state (OR 2.5); poor ventricular function (OR 2.0); DM (OR 1.7); PVD (OR 1.8); unstable angina (OR 1.7); pulmonary hypertension (OR 1.8)
2003 [19]	2,972 (1,900 men, 1,072 women)	Prospective observational	2.8 % women, 0.95 % men ($p < 0.001$)	Women: history of stroke (OR 44.5); ascending aortic atherosclerosis (OR 2.1); low cardiac output (OR 6.7); DM (OR 2.2) Men: history of stroke (OR 305.8)
2003 [20]	4,567	Prospective observational	2.5 %	Cerebrovascular disease (OR 2.66); PVD (OR 2.33); number of periods of aortic cross clamping (OR 1.31 for each period); LV dysfunction (OR 1.82); increased age (OR 1.28 for each 10 years); non-elective surgery (OR 1.83, $p = 0.08$)
2007 [21]	720	Prospective observational	3.9 % in men; 1.3 % in women ($p = 0.066$)	Prior cerebral infarction (OR 1.987 per grade); atherosclerosis of ascending aorta (OR 1.990 per grade)
2001 [22]	6,682	Prospective observational	1.5 %	Age > 70 (OR 5.4); LVEF < 40 % (OR 4.1); history of CVA/TIA (OR 3.0); normothermic CPB (OR 2.2); diabetes (OR 1.9); PVD (OR 1.9)
2000 [23]	1,987 CABG only, 84 CABG and carotid endarterectomy	Prospective observational	1.7 % CABG; 4.7 % combo	Age-76 vs 71.9 yrs (OR 1.09); hypertension (OR 2.67); extensively calcified aorta (OR 2.82); prolonged bypass time (OR 1.01, CI 1.00 – 1.02)
1996 [24]	189	Prospective	4.76 % by 1 wk post-op	Univariate analysis on aortic atheromatous grade by TEE: Advancing aortic atheroma grade was a predictor of CVA ($p = 0.00001$)
1992 [25]	130	?Prospective	3.85 %	Protruding aortic arch atheroma (OR 5.8, CI 1.2 – 27.9)

Table 3. cont.

Study year [ref]	Number of subjects	Study design	Stroke incidence	Significant risk factors (multivariate analysis unless otherwise noted)
2006 [26]	810	Prospective observational	CVA and TIA 1.85 %	Redo cardiac surgery (OR 7.45); unstable cardiac status (OR 4.74); history of cerebrovascular disease (OR 4.14); PVD (OR 3.55); preoperative use of statins (OR 0.24, CI 0.07 – 0.78)
2003 [27]	11,825	Prospective	1.5 %	Prediction model incorporated known preop risk factors: Age, DM, urgent surgery, EF < 40 %; creatinine ≥2.0. Additional intra-op and post-op risk factors: CPB 90 – 113 min (OR 1.59); CPB ≥ 114 min (OR 2.36); atrial fibrillation (OR 1.82); prolonged inotrope use (OR 2.59)
2002 [28]	2,711	Prospective observational	2.7 %	Past stroke (OR 2.11); hypertension (OR 1.97); age 65 – 75 (OR 2.39); age ≥ 75 (OR 5.02)
1999 [29]	4,518	Prospective observational	2.0 % CVA; 0.7 % TIA	Known cerebrovascular disease (OR 2.5); renal failure (OR 1.6); MI (OR 1.5); DM (OR 1.5); age > 70 (OR 1.5); also associated with post-op low EF and atrial fibrillation
2000 [30]	472	Prospective	3.4 %	Severity of extracranial carotid artery stenosis (OR 6.59)
2003 [2]	16,184 total: Group 1 – 8,917 CABG only; Group 2 – 1,842 beating heart CABG; Group 3 – 1,830 AV surgery; Group 4 – 708 MV surgery; Group 5 – 381 multiple valve surgery; Group 6 – 2,506 CABG + valve surgery	Prospective observational	4.6 % overall; 3.8 % in 1; 1.9 % in 2; 4.8 % in 3; 8.8 % in 4; 9.7 % in 5; 7.4 % in 6	History of cerebrovascular disease (OR 3.55); PVD (OR 1.39); DM (OR 1.31); hypertension (OR 1.27); urgent operation (OR 1.47); preoperative infection (OR 2.39); prior cardiac surgery (OR 1.33); CPB time > 2 hrs (OR 1.42); intraoperative hemofiltration (OR 1.25); high transfusion requirement (OR 6.04); beating heart CABG (OR 0.53, CI 0.37 – 0.77)
2002 [31]	4077 (45 stroke = cases; 4032 'no stroke'= controls)	Prospective, case-control	1.1 %	Increasing age (OR 1.06 per yr); unstable angina (OR 2.69); preoperative creatinine > 150 μmol/l (OR 2.64); previous CVA (OR 2.26); preexisting PVD (OR 2.99); salvage operation (OR 16.1)
1999 [32]	2,972	Prospective observational	1.6 % (0.6 % early and 1.0 % delayed)	Early stroke (immediately after surgery): history of stroke (OR 11.6); ascending aortic atherosclerosis (OR 2.0); duration of CPB (OR 1.1); female sex (OR 6.9) Delayed stroke: history of stroke (OR 27.6); DM (OR 2.8); female sex (OR 2.4); ascending aortic atherosclerosis (1.4); combined end points of atrial fibrillation and low cardiac output (OR 1.7)

Table 3. cont.

Study year [ref]	Number of subjects	Study design	Stroke incidence	Significant risk factors (multivariate analysis unless otherwise noted)
2005 [33]	4,380	Prospective observational	1.2 %	History of stroke (OR 6.3); DM (OR 3.5); older age (OR 1.1); temperature of CPB was insignificant.
2000 [34]	19,224	Prospective	1.4 %	Calcified aorta (OR 3.013); prior stroke (OR 1.909); increasing age-null of 60 (OR 1.522 per 10 yrs); pre-existing carotid artery disease (OR 1.590); duration of CPB (OR 1.27 per 60 min); renal failure (OR 2.032); PVD (OR 1.62); cigarette smoking in past year (OR 1.621); DM OR 1.373)
2001 [35]	16,528	Prospective observational	2.0 %	CRI (OR 2.8); recent MI (OR 2.5); previous stroke (OR 1.9); carotid artery disease (OR 1.9) hypertension (OR 1.6); DM (OR 1.4); age > 75 yrs (OR 1.4); preoperative moderate/severe LV dysfunction (OR 1.3); post-op low cardiac output syndrome (OR 2.1); post-op atrial fibrillation (OR 1.7)
2005 [36]	783 total: Group 1 – 582 CABG only; Group 2 – 101 Single VR ; Group 3 – 70 combined CABG+VR; Group 4 – 30 multi VR	Retrospective	CVA and TIA 1.7 % in 1; 3.6 % in 2; 3.3 % in 3; 6.7 % in 4	Previous neurological event (OR 6.8); age > 70 (OR 4.5); preoperative anemia (OR 4.2); aortic atheroma (OR 3.7); duration of myocardial ischemia (OR 2.8); number of bypasses (OR 2.3); LV-EF < 0.35 (OR 2.2); insulin-dependent DM (OR 1.5)
2007 [37]	171 serial TEVAR cases	Prospective observational	5.8 %	Prior stroke (OR 9.4); involvement of the proximal descending thoracic aorta (OR 5.5); CT demonstrating severe atheromatous disease of aortic arch (OR 14.8)
2007 [38]	606 stent/graft cases	Prospective observational	3.1 % stroke; 2.5 % paraplegia	Stroke: duration of the intervention (OR 6.4); female sex (OR 3.3). Paraplegia: left subclavian artery covering without revascularization (OR 3.9); renal failure (OR 3.6); concomitant open abdominal aorta surgery (OR 5.5); three or more stent grafts used (OR 3.5)

AV: aortic valve; CI: cardiac index; CPB: cardiopulmonary bypass; CRI: chronic renal insufficiency; CVA: cerebrovascular accident (stroke); DM: diabetes mellitus; EF: ejection fraction; LV: left ventricular; MI: myocardial infarction; MV: mitral valve; OR: odds-ratio; PVD: peripheral vascular disease; TEE: transesophageal echocardiography; TEVAR: thoracic endovascular aortic repair; TIA: transient ischemic attack; VR: valve replacement

recent meta-analyses on this topic were included. **Table 5** includes the major multicenter randomized clinical trials for carotid endarterectomy.

The data presented clearly demonstrate the magnitude of the health problem in terms of perioperative stroke and the desire to capture and define the breadth of this disease process. Nonetheless, the data are difficult to capture in pure form, or in the

Table 4. Perioperative stroke: Summary of meta-analyses on carotid surgery

Study year [ref]	Number of trials	Number of subjects (intervention/no intervention)	Intervention	Control	Outcomes
1999 [39]	23 publications from 3 randomized studies (NASCET, ECST, VACSP)	6078 (3777/2301)	Surgery	Medical treatment	Stenosis 70–99 % (absolute RR 6.7 %, NNT 15-to prevent stroke or death) Stenosis 50–69 % (absolute RR 4.7 %, NNT 21) Stenosis < 49 % (absolute risk increase 2.2, NNH 45)
2004 [40]	7 randomized; 41 non-randomized	554 in randomized; 25622 in non-randomized	Local anesthesia for CEA	General anesthesia for CEA	Meta-analysis of non-randomized studies showed significant reduction in risk of stroke (31 studies), but this was not shown in analysis of randomized studies. Conclusion is that there is insufficient evidence.
2004 [41]	7 randomized	1281 operations	Carotid patch angioplasty during CEA	Primary closure	Patch angioplasty associated with reduced risk of stroke of any kind ($p = 0.004$), ipsilateral stroke ($p = 0.001$), perioperative stroke or death ($p = 0.007$), long-term stroke or death ($p = 0.004$), perioperative arterial occlusion ($p = 0.0001$), long-term decreased recurrent stenosis ($p < 0.0001$)
2005 [42]	62 (16 studies evaluated perioperative CVA and gender differences)	9131 female; 17559 male	Female	Male	Female gender (OR 1.28; CI 1.12–1.46). Also evaluated risk of non-fatal perioperative CVA based on age: age ≥75 (OR 1.01, CI 0.8–1.3); aged ≥ 80 (OR 0.95)
2005 [43]	3 (asymptomatic carotid stenosis)	5223	CEA	Medical	Peri-op CVA or death rate: 2.9 %. Peri-op CVA or death or subsequent ipsilateral CVA: benefit for CEA (RR 0.71, CI 0.55–0.90)

CEA: carotid endarterectomy; CI: confidence interval; CVA: cerebrovascular accident (stroke); ECST: European Carotid Surgery Trial; NASCET: North American Symptomatic Carotid Endarterectomy Trial; NNH: number needed to harm; NNT: number needed to treat; OR: odds-ratio; PVD: peripheral vascular disease; RR: risk reduction; TIA: transient ischemic attack; VACSP: Veterans Affairs Cooperative Studies Program

Table 5. Perioperative stroke: Summary of randomized controlled trials of carotid endarterectomy.

Study year [ref]	Number of subjects (intervention/no intervention)	Study design	Intervention	Control (no intervention)	Outcomes
1998 [44] NASCET	1,108 intervention; 1,118 no intervention	RCT of symptomatic carotid stenosis (50 – 69 %)	CEA	Medical management	Perioperative CVA risk: 6.16 % Univariate analysis: contralateral carotid occlusion (RR 2.3); left sided carotid disease (RR 2.3); daily dose of less than 650 mg ASA (RR 2.3); absence of history of MI or angina (RR 2.2); lesion on imaging ipsilateral to operative artery (RR 2.0); DM (RR 2.0); diastolic BP > 90 mm Hg (RR 2.0)
1998 [45] ECST	1,811 intervention; 1,213 no intervention	RCT of all symptomatic carotid stenosis	CEA	Medical management (as long as possible)	Perioperative CVA risk: 6.8 % Cox proportional-hazards model of major stroke or death within 5 days post-op: Female sex (Hazards ratio: 2.39); Age in years at randomization (HR 0.959 per year); Occluded symptomatic carotid (HR 12.77)
1999 [46] ACE	1,395 'intervention'; 1,409 'no intervention'	Double-blind RCT of all patients scheduled for CEA	Low dose ASA (81 or 325 mg)	High dose ASA (650 or 1300 mg)	Perioperative any CVA/death (30 d): 4.7 % in low dose and 6.1 % in high dose (RR 1.29, CI 0.94 – 1.76). Univariate analysis for perioperative stroke/death: contralateral carotid occlusion (RR 2.3); hx of DM (RR 1.9); taking ≥ 650 mg ASA (RR 1.8); endarterectomy of the left carotid (RR 1.6); ipsilateral TIA or CVA in prior 6 months (RR 1.4); history of contralateral CVA (RR 1.47); insulin therapy (RR 1.78)
2004 [47] ACST	1,560 intervention/1,560 no intervention	RCT of asymptomatic carotid stenosis ≥ 60 %	Immediate CEA	Medical management	Perioperative CVA (30 d): 2.79 %. Perioperative CVA RF not assessed. Conclusion: In those < 75 years of age with asymptomatic stenosis of 70 % or more, CEA cut 5 year stroke risk from 12 % to 6 %.
1991 [48] ECST	Mild stenosis (0 – 29 %): 219 intervention/ 155 no intervention; Severe stenosis (70 – 99 %): 455 intervention/323 no intervention	RCT of symptomatic carotid stenosis	CEA	No CEA	Perioperative CVA/death (30 d): 3.7 % severe stenosis, 2.3 % mild stenosis adverse 30 day outcome predicted by: high blood pressure (SBP > 160 mm Hg); rapid surgery (less than 1 hour)

Table 5. cont.

Study year [ref]	Number of subjects (intervention/no intervention)	Study design	Intervention	Control (no intervention)	Outcomes
1995 [49] ACAS	825 intervention; 834 no intervention	RCT of asymptomatic carotid stenosis ≥ 60 %	CEA	Medical management	Perioperative CVA/death (30 d after randomization): 2.3 % Trend toward better outcome in men, but not statistically significant ($p = 0.1$) NNT 19 (to prevent 1 stroke in 5 yrs)
1991 [50] NAS-CET	328 intervention; 331 no intervention	RCT of severe (70 – 99 %) symptomatic (TIA or non-disabling CVA within past 120 days) carotid stenosis	CEA	Medical management	Perioperative CVA (30 d): 5.5 % absolute risk reduction for intervention group for 2 years: 17 % medical management group*: 0 – 5 RF-17 % risk CVA in 2 yrs 6 RF-23 % risk CVA in 2 yrs ≥ 7 RF-39 % risk CVA in 2 yrs

ASA: aspirin; BP: blood pressure; CEA: carotid endarterectomy; CHF: congestive heart failure; CI: confidence interval; CVA: cerebrovascular accident (stroke); DM: diabetes mellitus; NNH: number needed to harm; NNT: number needed to treat; OR: odds-ratio; PVD: peripheral vascular disease; RCT: randomized controlled trial; RF: risk factor; RR: risk reduction; TIA: transient ischemic attack.

* Selected risk factors=age> 70, male sex, systolic blood pressure > 160 mmHg, diastolic blood pressure > 90 mmHg, recency (< 31 d), recent event was stroke not TIA, degree of stenosis (> 80 %), presence of ulceration on angio, history of smoking, hypertension, MI, CHF, DM, intermittent claudication, elevated lipids.

best fashion such as large randomized studies. Hence, most of the information we have is from suboptimally-derived clinical series, with difficulty in between-group statistical comparisons and translating such data to an accurate risk formulation for specific surgical procedures. Clearly delineated in these investigative efforts is the identification of premorbid risk factors for perioperative stroke: prior history of cerebrovascular accident (CVA), heart disease, hypertension, diabetes, peripheral vascular disease and atrial fibrillation; the most powerful predictor appears to be a prior history of CVA [13].

In the cardiac literature, the concept of increased surgical risk in women is prevalent and unique. In addition, older age, a diseased proximal aorta, peripheral vascular disease, history of stroke, poor cardiac function, chronic renal insufficiency, hypertension, diabetes, atrial fibrillation, urgent surgery and prolonged bypass time are prevalent risk factors in multivariate analyses. The most powerful predictors again are prior CVA, surgery on the aorta, aortic disease burden, and perhaps female gender [19, 32]. The two studies on aortic surgery also reveal female sex and surgery on the proximal aorta as substantial risk factors [37, 38].

Perhaps the clinical question most often raised regarding stroke in cardiac surgery is whether off-pump CABG reduces perioperative stroke. This was assessed by two meta-analyses. It appears that off-pump CABG has a trend toward being superior to conventional CABG in preventing perioperative stroke. It is also likely that a 'no touch' technique substantially reduces stroke risk in those with a heavily dis-

eased aorta. In addition to technique, additional controversies revolve around intraoperative technologies to help prevent stroke (e.g., transesophageal echocardiography [TEE], epi-aortic ultrasound, intra-aortic filtration devices).

The carotid surgery literature reveals that increased disease burden on the surgical side as well as contralateral occlusion (which will lessen collateral flow) are substantial factors for stroke. Prior stroke or transient ischemic attack (TIA, on the surgical side), hypertension (especially diastolic > 90 mmHg), diabetes, and left carotid surgery are also significant risk factors. Finally, it appears that women do not benefit from carotid surgery as much as men; this has been a constant significant finding or trend across nearly all studies.

One question that was raised years ago and persists to this day regarding carotid surgery is whether the use of local anesthesia instead of general anesthesia reduces stroke risk. Unfortunately, more prospective studies are required to reach a conclusion, although there is a suggestion that local anesthesia may be superior [40]. With respect to the use of aspirin, the North American Symptomatic Carotid Endarteriectomy Trial (NASCET) showed that a daily dose of aspirin of less than 650 mg was associated with a higher relative risk of stroke [44]. That recommendation was repealed following The ASA and Carotid Endarterectomy (ACE) study [46], which clearly demonstrated the opposite result, that conventional low dose treatment was safer. Hence, current practice guidelines are to use 81 or 325 mg of aspirin [46]. Much of the current research in carotid endarterectomy is focused on identifying the patient population who will benefit the most from surgery.

In a retrospective review of 6038 patients after carotid endarterectomy in Ontario [51], the perioperative 30-day death or non-fatal stroke rate was 6 %. This study specifically aimed to identify predictors of stroke and reviewed substantially more surgical cases than any of the randomized controlled trials above. In this study, a history of TIA or stroke (OR 1.75), atrial fibrillation (OR 1.89), contralateral carotid occlusion (OR 1.72), congestive heart failure (OR 1.80), or diabetes (OR 1.28) were found to be independent predictors of a perioperative event.

Preventive Strategies

Surgical patients have an aggregate risk of 0.08 – 0.7 % of having a perioperative stroke [1]. A clear and obvious consequence of a perioperative CVA is worsened outcomes, particularly in terms of neurological functional outcome, but also in terms of overall in-hospital mortality. A case-mix average for hospital mortality following CABG is about 24.8 % [34] and about 33 % for thoracic endovascular aortic repair [37]. In another large database of 35,733 patients, the one-year survival following stroke in the CABG population was 83 % [52]. Additionally, intensive care unit (ICU) stay and hospital length-of-stay (LOS) stay were increased, as well as total health cost expenditure.

The risk of perioperative stroke is clearly also altered by the presence or absence of risk factors (as noted in **Table 1**). This basic risk of an ischemic complication likely overlaps into all surgical procedures, including CABG and carotid endarterectomy. The success of the many predictive scales for post-op stroke relies on an accurate accounting for such risk elements. The augmented risk in CABG and carotid endarterectomy is likely from technical aspects of the surgery itself (accounting for the immediate postoperative ischemic events), as well as the more tumultuous post-op course (electrolyte abnormalities, dehydration, arrhythmias, infections, redo procedures, etc).

Attention to the substantive risk of stroke during and following cardiac surgery has led to continued improvements in techniques and protocol implementation based on guidelines as listed below. There is, therefore, optimism that future studies will describe even lower incidences of perioperative cerebral ischemia, with improved utilization of alternate techniques and multiple new available technologies. As one example, off-pump CABG may have a lower stroke risk as compared to conventional CABG [16, 17], and one study demonstrated an exceptionally low risk rate of stroke/TIA of 0.14 %.

Another area of interest in cardiac surgery is the reduction of emboli associated with aortic cross-clamping. It has been recognized that atheroma is a risk for major vascular occlusion leading to overt stroke, as well as for post-operative cognitive dysfunction due to the presumptive 'showering' of micro-emboli. Studies suggest that cerebral emboli, as detected by intraoperative transcranial Doppler, are associated with atheroma from the ascending aorta and arch but not the descending aorta. It would seem feasible that curtailing use of cross-clamping in high risk individuals or the institution of aortic filtration may greatly reduce such postoperative complications. Studies in fact have demonstrated that intra-aortic filtration appeared to be associated with improved neurological outcome. In one study by Schmitz et al., 402 patients were assigned intra-aortic filtration; although the predicted number of strokes was estimated to have been 13.7 via use of the Stroke Risk Index, only six perioperative events were identified [53].

Both TEE and epi-aortic ultrasound have been used to assess clot burden of the ascending aorta and aortic arch. In cases where aortic atheroma is severe (> 5 mm), an alternative technique such as the 'no touch', off pump method may reduce the stroke rate. In cases of moderate disease (3 – 5 mm), careful choice of aortic cannulation site and minimal cross-clamping (single clamp) appears to improve outcomes. There is also evidence that a 'no touch' technique in the right setting may improve overall outcome, aside from overt stroke. In a review of 640 off-pump CABG cases, 84 had their surgeries modified with a 'no touch' technique [54]. In the 'no touch' group, the post-op delirium rate improved (8 % versus 15 %, $p = 0.12$), and there was a lower incidence of stroke (0 % versus 1 %), although numbers were too small to reach statistical significance.

In the field of carotid surgery, stroke reduction will likely revolve around optimal patient selection and timing, as well as the type of procedural intervention. Currently, consensus opinion advocates that severe (70 – 99 %) symptomatic carotid stenosis benefits the most (5 year absolute risk reduction of 16 %); followed by moderate (50 – 69 %) symptomatic stenosis (5 year absolute risk reduction of 4.6 %); and finally, asymptomatic carotid stenosis of 60 – 99 % (small benefit). Also, it is currently advocated to perform carotid endarterectomy within six weeks of a non-disabling, carotid-related ischemic stroke. The strongest data for this recommendation come from The Carotid Surgery for Ischemic Stroke Trial [55], where the perioperative stroke and death rate was 6.7 %, comparable to the European Carotid Surgery Trial (ECST) and NASCET. Interestingly, higher American Society of Anesthesiology (ASA) grades of III-IV, as well as decreasing age, were predictive of higher perioperative risk, especially if surgery was done in the first 3 weeks. The perioperative risk was 14.6 % in the first three weeks versus 4.8 % beyond the first 3 weeks.

Carotid artery stenting first came into clinical practice approximately a decade ago, and has since become common if not standard practice to treat asymptomatic and symptomatic carotid disease. Unfortunately, little evidence establishing efficacy was accrued in the early years to defend or refute the procedural practice. Certainly,

the surgical sparing procedure appears easy to perform, and likely has some niche(s) to fill in cerebrovascular disease management. A recent meta-analysis of seven trials (1,480 patients randomized to carotid endarterectomy, 1,492 to carotid angioplasty with or without stenting) significantly favored carotid endarterectomy over carotid artery stenting with regards to risk of death, any stroke or myocardial infarction at 30 days, ipsilateral stroke at 30 days, any stroke at 30 days, death or stroke at 6 months, and the risk of procedural failure [56]. Carotid stenting, however, may be suitable in patients with concomitant coronary disease awaiting revascularization, and in those patients with contralateral carotid occlusion.

Finally, one must mention the possibility of identifying, using, and/or developing novel neuroprotective drugs. There is evidence that preoperative use of statins may be protective for cardiac surgery [26]. In addition, the results from one study suggested that perioperative beta-blockade during cardiac surgery may reduce the risk of neurological injury. Several anesthetic agents, such as thiopental and isoflurane, may also provide some level of neuroprotection.

For now, we must rely on identifying those patients at highest risk for perioperative stroke. A commonly used scale for cardiac surgery is the Multicenter Study of Perioperative Ischemia (McSPI) stroke risk index (SRI). This scale is likely not quite ideal, however, as was shown by a recent study attempting to validate the SRI. Other scales have also been developed; please note, however, that a different scale may be ideal for each surgical specialty. It is our hope that the contents of this chapter may help guide management of all patients at risk for stroke in the perioperative period.

Conclusion: Proposed/useful Clinical Perioperative Guidelines

- Detailed preoperative history, especially with regards to stroke risk factors of previous stroke/TIA, diabetes, hypertension, atrial fibrillation.
- Preoperative optimization of blood pressure, heart rate, glucose control
- Consider initiation of statin therapy before CABG [26].
- Continuation of anti-platelet and anti-coagulation whenever feasible.
- Preoperative echocardiogram in patients with atrial fibrillation (heart failure and atrial fibrillation in combination also increases risk of stroke).
- Consider use of local anesthesia instead of general anesthesia when feasible.
- Intraoperatively: Maintain MAP as near as possible to preoperative baseline.
- Intraoperatively: Maintain glycemic control as per American Diabetes Association guidelines (as close as possible to 110 mg/dl, but at least less than 180 mg/dl is almost universally advocated). Studies support this goal in cardiac surgery, but evidence remains controversial. Preoperative cardiac surgery patients: Carotid ultrasound screening.
- Cardiac surgery: Consideration of pre-emptive carotid endarterectomy in appropriate high-risk patients with high-grade ipsilateral stenosis or contralateral occlusion.
- Cardiac surgery patients: Intraoperative use of TEE and/or epi-aortic ultrasound to optimize aortic cannulation and clamping (versus use of 'no touch' technique).
- Cardiac surgery patients: Consider perioperative use of beta blockade. Postoperative cardiac surgery: 3-day monitor for atrial fibrillation – consider anticoagulation for 30 days after return of sinus rhythm.

- Post-op CABG and carotid endarterectomy: Initiate anti-platelet therapy, as this can reduce risk of perioperative CVA without increasing bleeding risk [52].
- Prompt neurological consultation once a potential deficit is identified. Depending on surgical procedure, options such as intravenous tissue plasminogen activator (tPA), intra-arterial tPA, mechanical thrombectomy, and clot retrieval may be considered.

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Overview of Chronic Post-thoracotomy Pain: Etiology and Treatment

P. K. Battu, T.D. Priest, and F. Gao-Smith

Introduction

The first reference to chronic post-thoracotomy pain was in 1944 by United States Army surgeons who noted 'chronic intercostal pain' in men who had thoracotomy for chest trauma during the Second World War [1]. Chronic post-thoracotomy pain is defined by the International Association for the Study of Pain as pain that recurs or persists along a thoracotomy incision at least 2 months following the surgical procedure [2]. It is typically burning and dysesthetic in nature and has many features of neuropathic pain [3, 4]. Post-thoracotomy pain also may result, at least in part, from a non-neuropathic origin (myofascial pain) [5]. Several studies have estimated the incidence of post-thoracotomy pain as ranging from 25–60 % which makes post-thoracotomy pain the commonest complication of thoracotomy. Thoracotomy, along with limb amputation, is considered to be the procedure that elicits the highest risk of severe chronic postoperative pain [6]. This chapter outlines the prevalence of this condition and then discusses the potential etiological factors and treatment strategies and possible future research.

Prevalence

The prevalence of post-thoracotomy pain is variable, but high. The majority of patients experience only mild pain, but 3–16 % experience moderate to severe pain [6, 7]. Pain has been reported more profoundly around the surgical site or scar [8, 9]. When chronic post-thoracotomy pain persists, physical activity is reduced [10] and even low levels of pain have been associated with reduced physical and social activity as well as global perceptions of decreased health [11].

Pathology

Tissue injury results in the release of local inflammatory mediators, such as prostanoids, which result in peripheral sensitization. These actions activate intracellular signalling pathways on nociceptive terminal membranes reducing threshold and increasing excitability [12, 13]. This hypersensitivity reduces the intensity of the peripheral stimulus needed to activate nociceptors at the site of inflammation (primary hyperalgesia).

The hyperexcitable state of the spinal cord dorsal horn that follows release of humoral signals from noxious peripheral stimuli is referred to as central sensitiza-

tion. Prolonged central sensitization can lead to long-lasting alterations in the central nervous system (CNS) and can contribute to chronic pain long after withdrawal of the acute painful stimulus [14]. Sustained input from the peripheral neurons can trigger glial activation, resulting in release of 'pro-inflammatory cytokines', which have been shown to be critical mediators of exaggerated pain. These can lead to death of inhibitory neurons and replacement with new afferent excitatory neurons along with establishment of aberrant excitatory synaptic connections [15, 16].

Thoracotomy is associated with surgical trauma to the intercostal nerves. Injured primary sensory neurons begin to fire action potentials spontaneously as a result of increased or novel expression and altered trafficking of sodium channels [17–19]. This altered activity contributes to spontaneous pain, heightens pain sensitivity, and produces tactile allodynia [20]. There are also changes in the expression of neurotransmitters and receptors that modify transmission and responsiveness [21]. When a nerve is damaged, it heals by fibrosis and neuroma formation, which can lead to abnormal signal transduction and transmission to the CNS, generating both neuronal and glial responses, including the elevation of spinal prostaglandin (PGE_2) concentrations [22]. A number of studies [23–27] have implicated intercostal nerve trauma in the etiology of chronic post-thoracotomy pain, and suggest that chronic post-thoracotomy pain is a neuropathic pain, but the damage may be subtle and is not always apparent [28].

Preoperative Factors

Demographic Factors

The risk of chronic pain following certain types of surgical procedures is increased in women and decreased in the elderly [6]. Preoperative assessment of the endogenous analgesia system (diffuse noxious inhibitory control [DNIC]) may help predict postoperative pain responses [29].

Genetics

It has been recognized that genetic factors may be important in pain perception and several pain genes have been identified including genes for catechol-O-methyl transferase (COMT), voltage gated calcium channels, GTP cyclohydrolase, and tetrahydrobiopterin among others [30–32].

Psychosocial Factors

Two studies [28, 33] explored the role of preoperative anxiety/depression in relation to development of post-thoracotomy pain, both showing no relationship.

Preoperative Pain

There is conflicting evidence regarding preoperative pain, the development of chronic post-thoracotomy pain, and the use of preoperative analgesics [9, 10, 28, 34].

Intraoperative Factors

Surgery

The simple relationship between the extent of tissue damage and the severity of pain is obscured by the development of central sensitization [14]. It is logical to ask whether aggressive analgesia and meticulous surgery can affect the development of sensitization in chronic post-thoracotomy pain [35]. Two studies [36, 37] compared muscle sparing posterolateral thoracotomy versus traditional posterolateral thoracotomy and found no difference in the incidence of post-thoracotomy pain syndrome. The anterior access resulted in reduced post-thoracotomy pain when compared to the classical, posterior access [38, 39].

Two prospective trials, one comparing muscle-sparing postero-lateral thoracotomy to video-assisted thoracic surgery [40] and the other comparing postero-lateral thoracotomy to video-assisted thoracic surgery [41], found no differences in the incidence of post-thoracotomy pain syndrome, but a retrospective study [4] reported that video-assisted thoracic surgery was associated with reduced post-thoracotomy pain syndrome compared to muscle sparing thoracotomy.

Analgesia

A meta-analysis of 66 studies and 3261 patients drawn from different surgical specialities concluded that a pre-emptive effect on acute pain could be observed with epidural analgesia, wound infiltration with local anesthesia, and the administration of non-steroidal anti-inflammatory drugs [42]. Katz et al. [33] and Doyle and Bowler [43] found no differences in post-thoracotomy pain syndrome when investigating the timing of intercostal nerve block.

Thoracic epidural analgesia is widely used as a component of anesthesia for thoracic surgery. A meta-analysis of pre-emptive use of thoracic epidural analgesia [44] concluded that it offered improved postoperative analgesia in the first 48 hours after surgery, but had no impact on chronic post-thoracotomy pain.

Other techniques such as intrapleural analgesia, paravertebral block, cryoanalgesia, and infiltration at the incision site did not effect the incidence of post-thoracotomy pain syndrome [45].

Postoperative Factors

Although several studies from other surgical procedures have demonstrated that the intensity of acute postoperative pain is a risk factor for persistent post-surgical pain, Wilgaard et al. in their review concluded that lack of attention to important pre-, intra- and postoperative aspects of the etiology of post-thoracotomy pain syndrome make conclusions impossible on the exact relationship between acute and chronic post thoracotomy pain [45].

Others

Factors that have been suggested to contribute to post-thoracotomy pain include neuroma formation, healing rib fracture, frozen shoulder, local infection/pleurisy, costochondritis/costochondral dislocation, local tumor recurrence, and psychological overlay [4, 46].

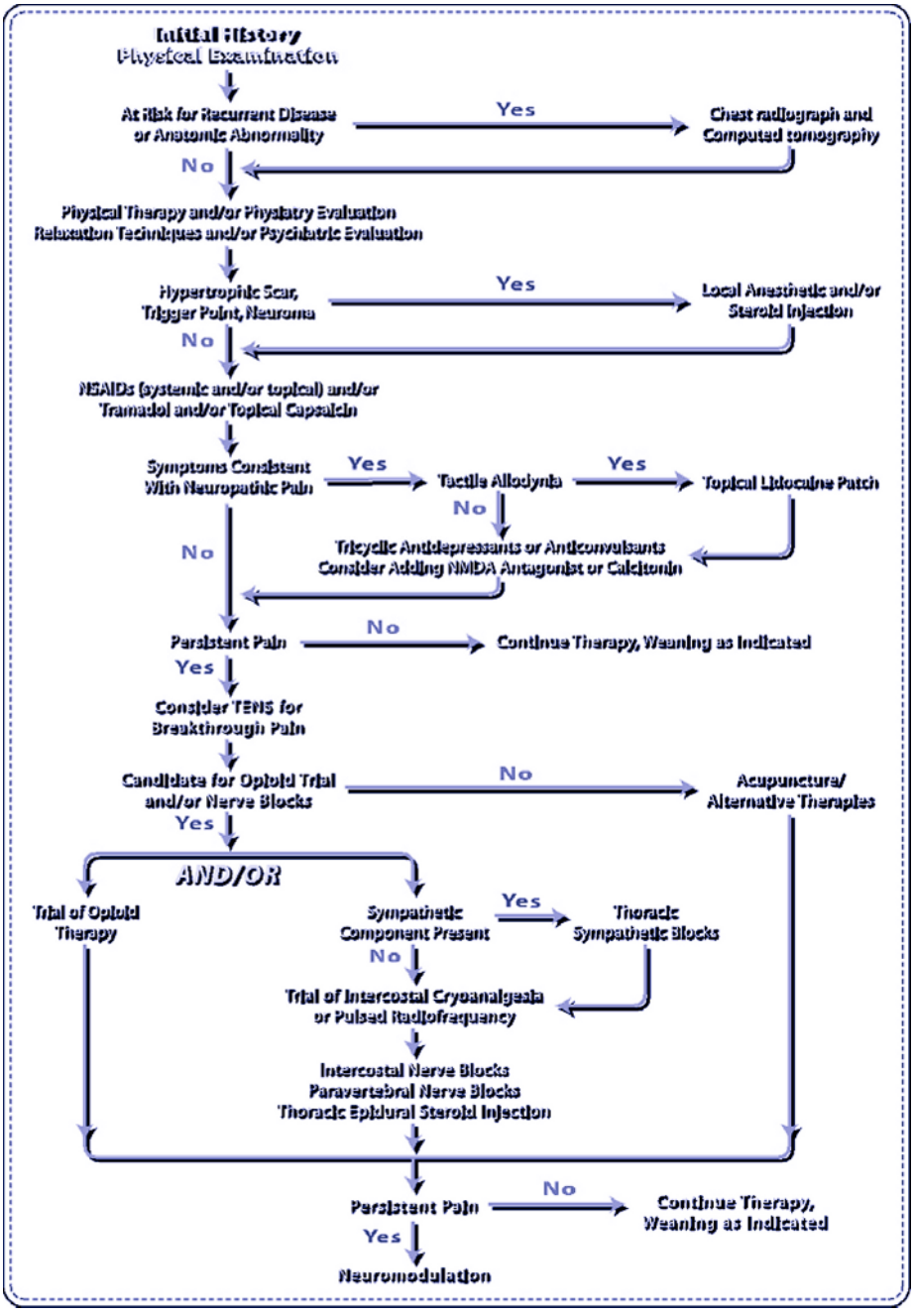

Fig. 1. Flow diagram for management of acute perioperative pain associated with thoracic surgery. From [23] with permission

Strategies for Treating Long Term Pain

After a comprehensive evaluation, an individualized treatment plan should be adopted using one or more pharmacological, interventional, and behavioral options as shown in **Figure 1** [23].

Although pre-emptive effects of gabapentinoids in reduction of postoperative morphine usage and opioid related adverse effects such as nausea, vomiting, and urinary retention have been established, their role in the prevention of long term pain has not been fully explored.

Conclusion

Chronic post-thoracotomy pain is the most common complication following a thoracotomy but is less widely appreciated. Its impact on social and economic costs is unknown. The origins of chronic post-thoracotomy pain have been sought in surgical trauma to the intercostal nerves, followed by development of peripheral and central sensitization in the nociceptive pathways. Modified surgical techniques and multimodal analgesia applied pre-emptively or preoperatively have done little to affect the incidence of chronic post-thoracotomy pain. Chronic post-thoracotomy pain can be treated with analgesics (opioids, tricyclic anti depressants, gabapentinoids, and local anesthetics). As we gain further insight into the mechanisms of development of post-surgical pain, there is a possibility that we may pre-emptively reduce the incidence of chronic post-thoracotomy pain.

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XIV Abdominal Compartment Syndrome

The Polycompartment Syndrome: What's all the Fuss About?

M.L.N.G. Malbrain, I. De Laet, and J. De Waele

Introduction

A compartment syndrome exists when the increased pressure in a closed anatomic space threatens the viability of enclosed and surrounding tissue [1]. Within the body there are four major compartments: The head, the chest, the abdomen, and the extremities. Within each compartment an individual organ or a region with multiple organs can be affected by a compartment syndrome. **Table 1** summarizes the different compartments and their related pathologies [2]. A compartment syndrome is not a disease; as such it can have many causes and can develop within many disease processes.

Scalea et al. was the first to allude to the term multiple compartment syndrome in a study of 102 patients with increased intra-abdominal (IAP), intrathoracic, and intracranial (ICP) pressure after severe brain injury [3], suggesting that the different compartments within the body are not isolated and independent entities but instead are intricately connected. Since the term multi- or multiple compartment syndrome is mostly used in relation to multiple limb trauma with compartment syndrome needing fasciotomy and in order to avoid confusion, the term polycompartment syndrome was finally coined [4]. This article will briefly discuss the different compartment syndromes as well as their interactions.

Pathophysiology

Increased compartment pressure will exert a direct force on the original compartment and its contents by increasing venous resistance and decreasing perfusion pressure, as well as on distant compartments (**Fig. 1**). The impact on end-organ function and viability within and outside the original compartment can be devastating.

Orbital Compartment Syndrome

Acute orbital compartment syndrome is a rare but treatable complication of increased pressure within the confined orbital space. This increased intraorbital pressure may cause pressure-related decreased ocular perfusion pressure similar to that caused by mass lesions or Graves' disease. If the mean arterial pressure (MAP) is the sum of one third of the systolic blood pressure plus two thirds of the diastolic blood pressure, the ocular perfusion pressure can be calculated as follows:

Ocular perfusion pressure = MAP – intraorbital pressure

Table 1. The four compartments

	Head		Chest		Abdomen	Extremities
	Brain	Eye	Thorax	Heart		
Primary physiologic parameter	Intracranial pressure (ICP)	Intraorbital pressure (IOP)	Intrathoracic pressure (ITP)	Filling pressure (CVP, PAOP)	Intra-abdominal pressure (IAP)	Extremity compartment pressure (ECP)
Secondary parameter	Cerebral perfusion pressure (CPP) = MAP – ICP	Orbital perfusion pressure (OPP) = MAP – IOP	Peak (Ppeak), plateau (Pplat) or mean (Pmean) airway pressure	Coronary perfusion pressure (CoPP) = DBP – PAOP = DBP – ITP	Abdominal perfusion pressure (APP) = MAP – IAP	Peripheral arterial perfusion pressure, tissue perfusion pressure (TPP) = capillary pressure – ECP
CP measurement	Fluid filled ventriculostomy, air filled balloon-tipped catheter, parenchymal solid state microchip transducer	Orbital tissue tension manometry	Esophageal pressure measurement via a balloon-tipped catheter Palv (Ppeak, Pplat, Pmean)	Via deep venous or Swan-Ganz catheter	Via bladder (FoleyManometer, AbViser valve) via stomach (Spiegelberg, Pulsion Medical Systems)	Via a needle connected to a fluid-filled pressure transducer system
Syndrome	Intracranial hypertension (ICH): ICP > 15 mmHg	Intraorbital hypertension (IOP > 17 mmHg)	ITP > 15 mmHg	CVP > 20 mmHg PAOP > 25 mmHg	Intra-abdominal hypertension (IAH): IAP > 12 mmHg	Extremity hypertension: ECP > 15 mmHg
	Intracranial compartment syndrome (ICS) – cerebral herniation: ICP > 25 mmHg	Orbital compartment syndrome (OCS): IOP > 30 mmHg	Thoracic compartment syndrome (TCS): ITP > 25 mmHg	Cardiac compartment syndrome (CCS) – cardiac tamponade	Abdominal compartment syndrome (ACS): IAP > 20 mmHg	Extremity compartment syndrome: ECP > 30 mmHg
Etiology	Primary (tumor, hematoma,...) Secondary (auto-PEEP, hypoxia or hypercarbia, hyper-tension, ventilation, seizures, ,...) Postoperative (edema, mass lesion,...)	Intrinsic (glaucoma) Extrinsic (traumatic retrobulbar hemorrhage) Combination (burn injury)	Post cardiac surgery, spontaneous mediastinal or pleural hemorrhage, tumor, COPD with dynamic hyperinflation, tension pneumothorax	Trauma, tumor, spontaneous bleeding, fluid resuscitation	Primary IAH: associated with injury or disease in the abdomino-pelvic region Secondary IAH: does not originate from the abdomino-pelvic region Recurrent IAH: chronic state of IAH	Crush injury Trauma with fractures Bleeding disorders Burns

Table 1 (*Continued*)

Potential implications	Brain death	Blindness	Cardiopulmonary collapse	Cardiac collapse, electromechanical dissociation	Multiple organ dysfunction	Extremity loss
Therapeutic intervention	Lower ICP: CSF drainage Increase CPP: vasopressors, fluids	Lower IOP Increase OPP	Lower ITP escharotomy, chest tube	Evacuate pericardiac effusion Pericardiac tube,	Lower IAP: ascites drainage Increase APP: vasopressors, fluids	Lower ECP Increase TPP
Resuscitative plan	Open compartment Decompressive craniectomy	Open compartment Ocular decompression	Open compartment Decompressive sternotomy	Open compartment Decompressive pericardectomy	Open compartment Decompressive laparotomy	Open compartment Decompressive fasciotomy
Importance	Adaptation of ventilatory support essential	Recognition of syndrome can be eye saving	Recognition of syndrome can be life saving	Recognition of syndrome can be life saving	Prevention of bacterial translocation and MODS can be life saving	Recognition can be limb saving
Effect on	IOP, cardiorespiratory function (SVR, PVR)	–	Lung (Palv), ICP, IAP, CVP, PAOP	Lung, ICP	All other compartments (Lung, ICP, ITP, CVP, PAOP,...)	Kidney (rhabdomyolysis), lungs, heart
Affected by	intracardiac pressures (CVP, PAOP), ITP, PEEP and IAP	ICP, ITP, PEEP, IAP	IAP (abdomino-thoracic transmission 50 % on average), mechanical ventilation (PEEP)	ITP, IAP (abdomino-thoracic transmission 50 % on average), mechanical ventilation (PEEP)	ITP, mechanical ventilation (PEEP)	IAP (diminished venous return)

CP: compartment pressure; CPP: cerebral perfusion pressure; CSF: cerebrospinal fluid; CVP: central venous pressure; DBP: diastolic blood pressure; MAP: mean arterial pressure; MODS: multiple organ dysfunction syndrome; OPP: orbital perfusion pressure; PAOP: pulmonary artery occlusion pressure; PEEP: positive end-expiratory pressure; PVR: peripheral vascular resistance; SVR: systemic vascular resistance;

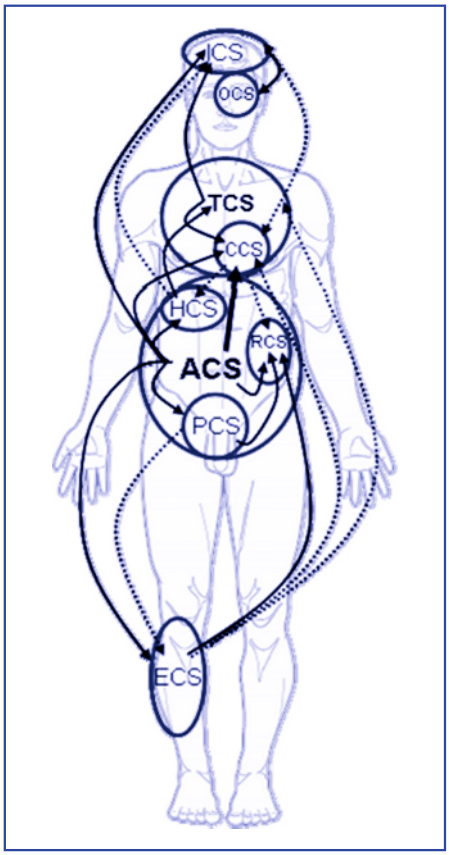

Fig. 1. Interactions between different compartments. The arrows indicate possible interactions between different compartments. Solid lines show direct effects by mechanical pressure forces. Dotted lines show indirect distant effects between compartments. ACS: abdominal compartment syndrome. CCS: cardiac compartment syndrome; ECS: extremity compartment syndrome; HCS: hepatic compartment syndrome; ICS: intracranial compartment syndrome; RCS: renal compartment syndrome; OCS: orbital compartment syndrome; PCS: pelvic compartment syndrome; TCS: thoracic compartment syndrome. Adapted from [2].

Acute orbital compartment syndrome presents with recognizable physical findings (eye pain, reduced ocular motility, pro-optosis, diplopia) and progressive visual deficit. Recognition and prompt treatment may prevent blindness. A recent study in burn patients showed that increased intraorbital pressure was significantly ($p=0.015$) associated with the amount of fluids given during the first 24 hours (37.2 ± 14.4 l vs 24.6 ± 12.3 l) and with the presence of periocular burns [5]. Emergent orbital decompression resulted in a drop in intraorbital pressure from 59.4 ± 15.9 mmHg to 28.6 ± 8.2 mmHg. Conditions that can be associated with orbital compartment syndrome are infection, inflammation, spinal surgery, optic nerve sheath compression (tumor or meningeoma), vascular problems with ophthalmic artery or retinal vein occlusion, traumatic asphyxia syndrome, bleeding diathesis or even after orbital extravasation of X-ray contrast material. This intraorbital compartment syndrome needs to be differentiated from intraocular compartment syndrome as seen with glaucoma.

Intracranial Compartment Syndrome

A unique feature of the brain is that the intracranial contents are confined within a rigid bony cage. Because the volume of the cranial cavity is limited, any change in

the size of any intracranial compartment leads to a reciprocal change in the size of the remaining compartments. When compensation mechanisms are exhausted, volume increase can lead to alterations in cerebral perfusion pressure (CPP) and ICP.

$$CPP = MAP - ICP$$

Many studies have been published regarding the best treatment options for intracranial hypertension either focusing on lowering ICP (by evacuation of cerebrospinal fluid [CSF] or a variety of other techniques aimed at decreasing brain tissue edema) or by raising CPP (by maintaining correct MAP with fluids or vasopressors). However, fluid therapy used to support CPP may cause retroperitoneal and visceral edema, ascites accumulation and increased IAP, which in turn can further increase ICP [6]. Therefore, in patients with severe traumatic brain injury (TBI), treatment decisions may result in a vicious cycle that increases pressures in various compartments [3]. The effects of IAP and intrathoracic pressure (ITP) on ICP have not been extensively studied to date, and remain a challenging area for laboratory and clinical investigators [7–14]. **Figure 2** shows a clinical example of abdomino-cranial pressure transmission. In a study by Scalea et al. [3], 78 patients had an intracranial compartment syndrome and underwent decompressive craniectomy, resulting in a significant decrease in ICP from 24 to 14 mmHg. The other 24 patients had a multiple or poly-compartment syndrome and underwent a decompressive craniectomy and a decompressive laparotomy. The combination of decompressive craniectomy and decompressive laparotomy in these 24 patients led to a decrease in ICP from around 32 to 14 mmHg after decompressive craniectomy and from 28 to 19 mmHg after decompressive laparotomy (the effect being different depending on whether decompressive craniectomy or decompressive laparotomy was performed first). After decompressive laparotomy, the IAP decreased from 28 to around 18 mmHg and mean airway pressure from 37 to 27 cmH_2O. The authors concluded that increased ICP can result from primary TBI as well as from increased IAP, which has been documented before [6, 8, 9]. Patients with polycompartment syndrome received significantly more fluids during the first 7 days of ICU stay, around 63 ± 21 l vs 40 ± 13 l ($p < 0.001$); they also stayed longer in the ICU, about 25 ± 13 days vs 17 ± 12 days ($p = 0.01$) and in the hospital, 29 ± 16 days vs 21 ± 14 days ($p = 0.05$). While there was a trend towards higher mortality in these patients (42 % vs 31 %), it did not reach statistical significance. Polycompartment syndrome should, therefore, be considered in multiple trauma patients with increased ICP that does not respond to therapy [3].

Thoracic Compartment Syndrome

Thoracic compartment syndrome has traditionally been described in adult and pediatric patients undergoing cardiac surgical procedures. In the setting of substantial myocardial edema, acute ventricular dilatation, mediastinal hematoma, or non-cardiogenic pulmonary edema, sternal closure may precipitate cardiac tamponade leading to hemodynamic instability or collapse [15, 16]. Theoretically thoracic compartment syndrome could also occur in patients with thoracic trauma; however, it is rarely seen due to the limited survival of patients whose injuries were significant enough to result in massive tissue edema after resuscitation, although traumatic cardiac tamponade due to bleeding could be seen as a hyperacute primary compartment syndrome. In the intensive care unit (ICU), increased ITP is seen most commonly in relation to sepsis, capillary leak, fluid resuscitation, positive pressure ven-

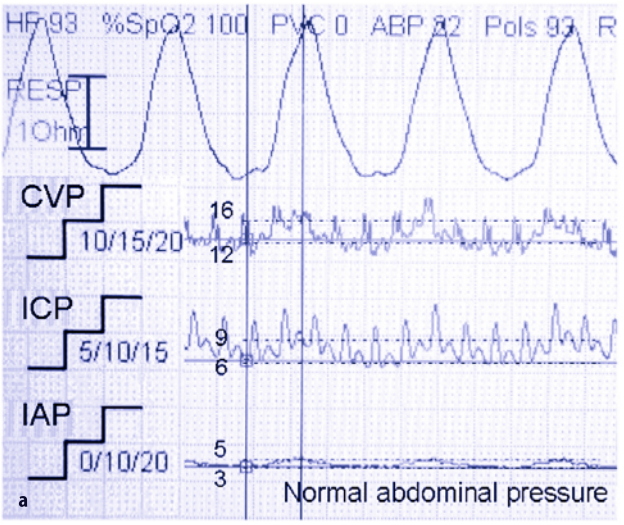

Fig. 2. Bedside example of abdomino-cranial pressure transmission. Simultaneous tracings of respiration (RESP), central venous pressure (CVP), intracranial pressure (ICP) and intra-abdominal pressure (IAP) in a patient with combined head and abdominal trauma. The patient was mechanically ventilated via BiPAP mode with a RESP of 20 breaths per minutes, inspiratory pressure was set at 32 cmH_2O with a positive end-expiratory pressure (PEEP) of 5 cmH_2O. Paper tracing speed at 6.25 mm/sec. The respiratory in- and end-expiratory variations in the pressure tracings can be observed. Panel **a** Screenshot taken from bedside Philips IntelliVue monitor during normal (baseline) IAP of 4 mmHg. Panel **b** Screenshot taken from bedside Philips IntelliVue monitor during increased IAP of around 19 mmHg (abdominal compression with velcro belt for prevention of incisional hernia). The Table lists the different compartment pressures obtained from the IAP, ICP and intravascular or intrathoracic (CVP) compartments at end-expiration (ee) and at end-inspiration (ei) at baseline conditions and after abdominal compression in a single patient (as an illustrative example). Abdominal compression resulted from the use of a Velcro belt. Average abdomino-thoracic transmission was around 60 % while the abdomino-cranial transmission was almost 100 %. ITee: index of transmission during expiration; ITei: index of transmission during inspiration; Δee: difference between end-expiratory value during abdominal compression and baseline value; Δei: difference between end-inspiratory value during abdominal compression and baseline value; ΔRES: end-inspiratory minus end-expiratory value. Adapted from [4]

	Baseline			Compression			Index of transmission			
	ee	ei	ΔRES	ee	ei	ΔRES	Δee	Δei	ITee	ITei
IAP (mmHg)	3	5	2	17	21	4	14	16	–	–
ICP (mmHg)	6	9	3	21	24	3	15	15	107%	94%
CVP (mmHg)	12	16	4	20	25	5	8	9	57%	56%

tilation with high positive end-expiratory pressure (PEEP) or dynamic hyperinflation, pneumothorax, chronic obstructive pulmonary disease (COPD) with auto-PEEP, diminished chest wall compliance (e.g., morbid obesity or eschars), lung fibrosis, and acute respiratory distress syndrome (ARDS). The most important strategy to prevent thoracic compartment syndrome or decrease the ITP and to facilitate sternal closure (providing all obvious space-occupying lesions have been evacuated) is the limitation of resuscitation fluid therapy through the use of hypertonic saline or colloid solutions. Increasing ITP, mean, or peak inspiratory pressure during thoracic wall closure may serve as an early warning that the patient is at risk for thoracic compartment syndrome. Increased ITP (normal < 5–7 mmHg), which can be measured via a balloon-tipped catheter positioned in the lower third of the esophagus, will exert effects on the lungs, the heart and the brain (by limiting venous return). Since increased ITP, like IAP, is most commonly related to superfluous fluid resuscitation, IAP and ITP go hand in hand [17, 18].

Some key-issues to remember are:

- Best PEEP should be set to counteract ITP and IAP while at the same time avoiding over-inflation of already well-aerated lung regions (**Fig. 3**)
  – Best PEEP (cmH_2O) = IAP (mmHg)
- During lung protective ventilation, plateau pressures (Pplat) should be limited to transmural plateau pressures ($Pplat_{tm}$) less than 35 cmH_2O otherwise endtidal CO_2 will increase (**Fig. 4**)
  – $Pplat_{tm}$ = Pplat – ITP = Pplat – IAP/2 < 35 cmH_2O
- Increased ITP and IAP increase lung edema; within this concept, monitoring of extravascular lung water index (EVLWi) seems warranted [19]

Cardiac Compartment Syndrome

Within the thorax, the heart can develop an isolated compartment syndrome also called cardiac tamponade. Cardiac tamponade occurs when there is accumulation of fluid or air in the pericardium caused by trauma, hemorrhage, infection or tumor causing impaired filling of the ventricles and decreased cardiac output. As little as 250 ml of fluid can cause acute cardiac tamponade whereas under chronic conditions greater amounts of fluid can accumulate as the cardiovascular system can slowly adjust. The same effect on the heart can occur via transmission of increased ITP either directly as seen with thoracic compartment syndrome or indirectly as seen with abdominal compartment syndrome, due to the cephalad movement of the diaphragm. In case of increased ITP or IAP, coronary perfusion pressure is lowered:

Coronary perfusion pressure = DBP – PAOP = DBP – ITP

where DBP is the diastolic blood pressure and PAOP the pulmonary artery occlusion pressure. The increase in ITP will also result in a difficult preload assessment because traditional filling pressures will be erroneously increased. When ITP or IAP increase above 10–12 mmHg, cardiac output decreases due to an increase in afterload (systemic vascular resistance, SVR) and a decrease in preload and left ventricular compliance [20–23]. Tachycardia may develop, MAP will decrease and a pulsus paradoxus (or increase in pulse pressure variation [PPV]) may occur. Cardiovascular dysfunction and failure (low cardiac output, high SVR) are common in conditions of increased ITP or IAP [24, 25]. Finally, hepatomegaly (backward failure) may develop in chronic cases, so that cardiac tamponade may have a distant effect on other organs (**Fig. 1**).

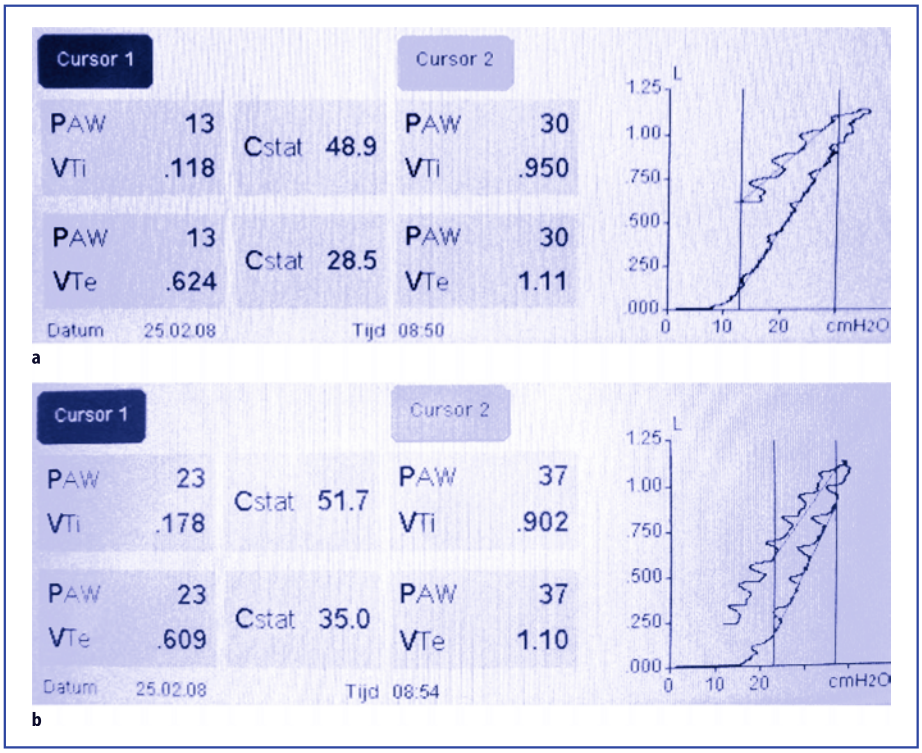

Fig. 3. Relation between IAP and lower inflection point. Low flow pressure volume (PV) loop in a patient with combined head and abdominal trauma. The patient was mechanically ventilated via BiPAP mode at 24 breaths per minute, inspiratory pressure was set at 32 cmH_2O with a positive end-expiratory pressure (PEEP) of 12 cmH_2O. The low flow PV loop maneuver was performed with an Evita XL ventilator (Dräger, Lubeck, Germany). The flow was set at 4 l/min, the maximal pressure alarm at 55 cmH_2O and the tidal volume alarm at 1200 ml. Panel **a** Screen shot obtained during baseline IAP of around 12 mmHg. The tidal volume was 650 ml, hence the dynamic compliance was calculated as 32.5 ml/cmH_2O. The static compliance obtained with the low flow PV loop was 48.9 ml/cmH_2O, and the lower inflection point was 13 cmH_2O. Panel **b** Screen shot obtained during increased IAP of around 24 mmHg (with abdominal compression with velcro belt for prevention of incisional hernia). The tidal volume was 430 ml, hence the dynamic compliance was calculated as 21.5 ml/cmH_2O. The static compliance obtained with the low flow PV loop was 51.7 ml/cmH_2O, and the lower inflection point was 23 cmH_2O. Adapted from [69].

XIV

Some key-issues to remember are:

- Our understanding of traditional hemodynamic monitoring techniques and parameters, must be re-evaluated in conditions of increased ITP or IAP since pressure-based or 'barometric' estimates of intravascular volume, such as PAOP and central venous pressure (CVP), are erroneously increased.
- The clinician must be aware of the interactions between ITP, IAP, PEEP, and intracardiac filling pressures as illustrated in **Figure 5** [4]
- misinterpretation of the patient's minute-to-minute cardiac status may result in the institution of inappropriate and potentially detrimental therapy

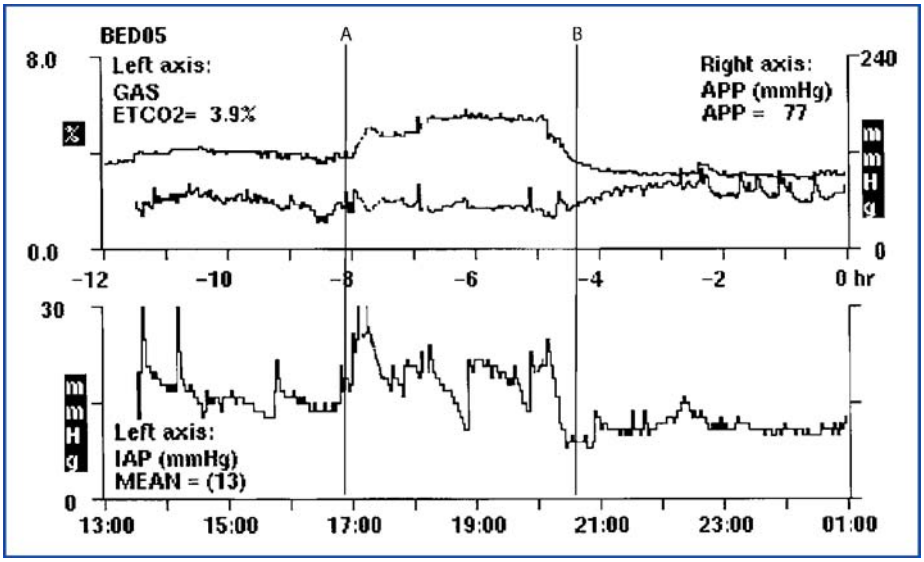

Fig. 4. Bedside example of interactions between the thoracic and abdominal compartments. Upper panel: Trend tracing of endtidal CO_2 ($ETCO_2$) on the left axis and abdominal perfusion pressure (APP) on the right axis in a mechanically ventilated patient in BiPAP mode on Evita XL (Dräger, Lubeck, Germany). Lower panel: Trend tracing of continuous intra-abdominal pressure (IAP) monitoring obtained with Spiegelberg balloon-tipped stomach catheter and monitor (Spiegelberg, Hamburg, Germany). Line A (16:50) marks the beginning of ventilator dyssynchrony due to fighting and abdominal muscle contractions with increased IAP up to 30 mmHg, increased PCO_2 and $EtCO_2$ and decreased APP. Line B (20:40) marks the end of dyssynchrony with normalization of all parameters after the start of a continuous infusion with cisatracurium. This case nicely demonstrates the interactions between the abdominal and thoracic compartments.

- Transmural (tm) filling pressures, calculated as the end-expiration value (ee) minus the ITP better reflect preload [18, 21]:
  $CVP_{tm} = CVP_{ee} - ITP$
  $PAOP_{tm} = PAOP_{ee} - ITP$
- A quick estimate of transmural filling pressures can also be obtained by subtracting half of the IAP from the end-expiratory filling pressure [26]
  $CVP_{tm} = CVP_{ee} - IAP/2$
  $PAOP_{tm} = PAOP_{ee} - IAP/2$
- 'Volumetric' estimates of preload status, such as right ventricular end-diastolic volume index (RVEDVi) or global end-diastolic volume index (GEDVi), are especially useful in the conditions of changing ventricular compliance due to elevated ITP [23, 27–30].
- The cardiovascular effects are aggravated by hypovolemia and the application of PEEP [31–35], whereas hypervolemia has a temporary protective effect [13].

XIV

Limb or Extremity Compartment Syndrome

Extremity compartment syndrome is a condition in which the compartment pressure within the closed muscle compartment increases to a level that reduces capillary blood perfusion below the level necessary for tissue viability. Permanent loss of function and contracture may occur. Extremity compartment pressure can be mea-

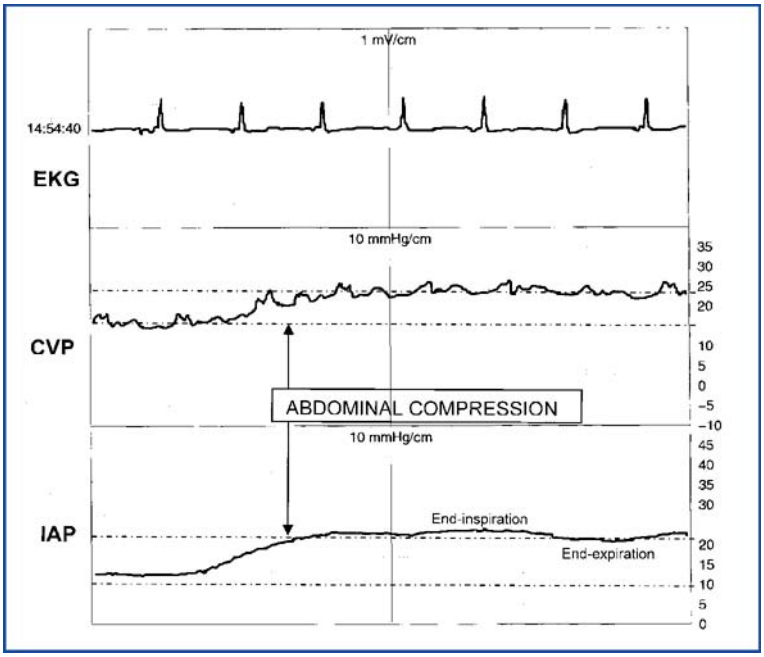

Fig. 5. Calculation of abdomino-thoracic index of transmission at the bedside. Simultaneous electrocardiogram (EKG), central venous pressure (CVP) and intra-abdominal pressure (IAP) tracing before and during abdominal compression with a Velcro belt used to prevent incisional hernia. The abdomino-thoracic transmission can be calculated as follows:
The change in endexpiratory CVP: $\Delta CVP = 22 - 15 = 7$ mmHg
The change in endexpiratory IAP: $\Delta IAP = 23 - 12 = 11$ mmHg
The index of abdomino-thoracic transmission = $\Delta CVP/\Delta IAP = 7/11 = 63\,\%$

sured via a needle connected to a fluid-filled pressure transducer system. Normal compartment pressure should be below 20 mmHg and can be used to guide the need for surgical intervention.

Tissue perfusion pressure = capillary pressure – extremity compartment pressure

A crush injury with subsequent edema and increased compartment pressure can be caused by the patient's own weight in case of unconsciousness related to poisoning, drug overdose, strenuous exercise, or during prolonged anesthesia, especially if the patient has a high body mass index (BMI). External causes of increased extremity compartment pressure are mainly related to trauma with fractures (especially of the tibia) and tight plaster casts, muscle contusions, bleeding disorders, burns (with eschars), venous obstruction, and arterial occlusion with post ischemic swelling, all causing muscle compression and further crush injury. The extremity compartment syndrome will result in muscle compression and rhabdomyolysis which may cause hypovolemia, acute kidney injury (AKI) and failure, coagulopathy, acute lung injury (ALI), and shock. Hence, increased extremity compartment pressure may have a distant effect on other organs (**Fig. 1**). In case of established extremity compartment syndrome, the only definitive treatment is decompressive fasciotomy with muscle debridement in case of necrosis. Fluid resuscitation can be used to counteract the deleterious effects of

extremity compartment syndrome on distant organ function but it can also lead to increased edema formation and further rise in compartmental pressures. Increased IAP related to abdominal or pelvic compartment syndrome can have an effect on extremity compartment syndrome due to the diminished venous return from the extremities to the central circulation causing further limb swelling.

Hepatic Compartment Syndrome

Within the capsule of the liver itself, local hematoma formation caused by trauma or bleeding diathesis (oral anticoagulants, liver cirrhosis,...) may have an adverse affect on tissue perfusion causing a local hepatic compartment syndrome. Furthermore, the liver appears to be particularly susceptible to injury in the presence of elevated surrounding pressures, this especially in cases of intra-abdominal hypertension (IAH) or abdominal compartment syndrome. Animal and human studies have shown impairment of hepatic cell function and liver perfusion even with only moderately elevated IAP of 10 mmHg [36, 37]. Acute liver failure, decompensated chronic liver disease and liver transplantation are frequently complicated by IAH and abdominal compartment syndrome [38, 39]. Close monitoring and early recognition of IAH, followed by aggressive treatment may confer an outcome benefit in patients with liver disease. In the management of these patients it might be useful to monitor the plasma disappearance rate (PDR) for indocyanine green (ICG) as this correlates not only with liver function and perfusion but also with IAP [40, 41]. Cytochrome P450 function may be altered in IAH/abdominal compartment syndrome, which may have important but as of yet unstudied clinical implications regarding drug dosing. Increased IAP leads to decreased hepatic arterial flow, decreased venous portal flow, and increases in the portacollateral circulation, causing physiological effects with decreased lactate clearance, altered glucose metabolism and altered mitochondrial function.

Renal Compartment Syndrome

IAH has been associated with renal impairment for over 150 years [42]. The exact nature of the relationship between IAP and kidney injury has only been studied intensively in recent years and further work certainly needs to be done [43–45]. Elevated IAP significantly decreases renal artery blood flow and compresses the renal vein leading to renal dysfunction and failure [46]. Oliguria develops at an IAP of 15 mmHg and anuria at 25 mmHg in the presence of normovolemia and at lower levels in the patient with hypovolemia or sepsis [47, 48]. Renal perfusion pressure and renal filtration gradient have been proposed as key factors in the development of IAP-induced renal failure.

$$\begin{aligned}\text{Renal perfusion pressure} &= \text{MAP} - \text{renal vein pressure}\\ \text{Renal filtration gradient} &= \text{glomerular filtration pressure} - \text{proximal tubular pressure}\\ &= \text{renal perfusion pressure} - \text{proximal tubular pressure}\\ &= (\text{MAP} - \text{renal vein pressure}) - \text{renal vein pressure}\\ &= \text{MAP} - 2 \times \text{renal vein pressure}\end{aligned}$$

In conditions of increased IAP, the renal vein pressure may be substituted by IAP, thus:

$$\begin{aligned}\text{Renal perfusion pressure} &= \text{MAP} - \text{IAP}\\ \text{Renal filtration gradient} &= \text{MAP} - 2 \times \text{IAP}\end{aligned}$$

Changes in IAP seem to have a greater impact on renal function and urine production than changes in MAP. It should not be surprising, therefore, that decreased renal function, as evidenced by development of oliguria, is one of the first visible signs of IAH. An increasing number of large clinical studies have identified that IAH (≥ 15 mmHg) is independently associated with renal impairment and increased mortality [43, 44, 49, 50]. The etiology of these changes is not well established, however, it may be multifactorial: Reduced renal perfusion, reduced cardiac output, increased SVR, and alterations in humeral and neurogenic factors. Within the capsule of the kidney itself, local hematoma formation (caused by trauma or bleeding diathesis) may have an adverse affect on tissue perfusion causing a local renal compartment syndrome [51, 52].

Pelvic Compartment Syndrome

In the pelvic region, three major compartments (gluteus medius-minimus compartment, gluteus maximus compartment, and iliopsoas compartment) can be distinguished from the smaller compartment of the tensor fasciae latae muscle. Pelvic compartment syndromes are rare and a clear history of trauma is often lacking [53–55]. The pelvic compartment syndrome is often associated with drug and alcohol abuse, infections (necrotising fasciitis) and the use of anticoagulant therapy [54]. Increased pelvic compartment pressure may eventually increase IAP and affect kidney function due to bilateral ureteral obstruction and renal failure caused by a massive intrapelvic hematoma with increased retroperitoneal pressure. Decompressive fasciotomy of the gluteal compartment is the treatment of choice.

Abdominal Compartment Syndrome

In analogy with the head, the abdomen can be considered as a closed box like the skull, with partially rigid sides (spine and pelvis), an anchorage above (costal arch), and partially flexible sides (abdominal wall and diaphragm). Like the skull, the abdomen is filled with organs (small and large intestine, liver, kidneys, spleen) perfused by arterial, venous, and capillary capacitance blood vessels (the mesenteric vessels) and filled with a fluid, like the CSF in the skull (**Table 2**), but which only becomes apparent in pathologic circumstances (ascites). In real life the analogy is complicated by the movable diaphragm, the shifting costal arch, the contractions of the abdominal wall, and the intestines that may be empty or filled with air, liquid or fecal matter.

The term 'abdominal compartment syndrome' was first used by Fietsam et al. in the late 1980s to describe the pathophysiologic alterations resulting from IAH secondary to aortic aneurysm surgery: "In four patients that received more than 25 liters of fluid resuscitation increased IAP developed after aneurysm repair. It was

	Cranium	Abdomen
Organ (s)	Brain	Abdominal organs, intestines
Fluid (s)	Cerebrospinal fluid	Ascites
Enclosure	Skull	Abdominal cage
Lesions	Tumor, hematoma	Blood, edema, ascites, air, tumor
Pressure	ICP	IAP
Perfusion	CPP = MAP – ICP	APP = MAP – IAP

Table 2. The cranial and abdominal compartments

ICP: intracranial pressure; IAP: intra-abdominal pressure; CPP: cerebral perfusion pressure; MAP: mean arterial pressure; APP: abdominal perfusion pressure

manifested by increased ventilatory pressure, increased central venous pressure, and decreased urinary output. This set of findings constitutes an abdominal compartment syndrome caused by massive interstitial and retroperitoneal swelling... Opening the abdominal incision was associated with dramatic improvements..." [56].

The World Society of the Abdominal Compartment Syndrome (WSACS – www.wsacs.org) was founded in 2004 to serve as a peer-reviewed forum and educational resource for all healthcare providers as well as members of the industry who have an interest in IAH and abdominal compartment syndrome. Recently the first consensus definitions have been published [1, 57]. **Table 3** summarizes these consensus definitions: A sustained increase in IAP equal to or above 12 mmHg defines IAH, and abdominal compartment syndrome is defined by sustained IAP above 20 mmHg with new onset organ failure. **Table 4** lists some possible risk factors for the development of IAH.

Table 3. Consensus definitions (adapted from [1])

Definition 1	Intra-abdominal pressure (IAP) is the steady-state pressure concealed within the abdominal cavity.
Definition 2	APP = MAP – IAP
Definition 3	FG = GFP – PTP = MAP – 2 * IAP
Definition 4	IAP should be expressed in mmHg and measured at end-expiration in the complete supine position after ensuring that abdominal muscle contractions are absent and with the transducer zeroed at the level of the mid-axillary line.
Definition 5	The reference standard for intermittent IAP measurement is via the bladder with a maximal instillation volume of 25 ml of sterile saline.
Definition 6	Normal IAP is approximately 5 – 7 mmHg in critically ill adults.
Definition 7	Intra-abdominal hypertension (IAH) is defined by a sustained or repeated pathologic elevation of IAP $\geq$ 12 mmHg.
Definition 8	IAH is graded as follows: • Grade I: IAP 12 – 15 mmHg • Grade II: IAP 16 – 20 mmHg • Grade III: IAP 21 – 25 mmHg • Grade IV: IAP > 25 mmHg
Definition 9	Abdominal compartment syndrome is defined as a sustained IAP > 20 mmHg (with or without an APP < 60 mmHg) that is associated with new organ dysfunction/failure.
Definition 10	Primary abdominal compartment syndrome is a condition associated with injury or disease in the abdomino-pelvic region that frequently requires early surgical or interventional radiological intervention.
Definition 11	Secondary abdominal compartment syndrome refers to conditions that do not originate from the abdomino-pelvic region.
Definition 12	Recurrent abdominal compartment syndrome refers to the condition in which abdominal compartment syndrome redevelops following previous surgical or medical treatment of primary or secondary abdominal compartment syndrome.

APP: abdominal perfusion pressure; FG : filtration gradient ; GFP: glomerular filtration pressure ; MAP: mean arterial pressure; PTP: proximal tubular pressure

Table 4. Risk factors for the development of intra-abdominal hypertension and abdominal compartment syndrome

A. Related to diminished abdominal wall compliance
- Mechanical ventilation, especially fighting with the ventilator and the use of accessory muscles
- Use of positive end-expiratory pressure (PEEP) or the presence of auto-PEEP
- Basal pleuroneumonia
- High body mass index
- Pneumoperitoneum
- Abdominal (vascular) surgery, especially with tight abdominal closures
- Pneumatic anti-shock garments
- Prone and other body positioning
- Abdominal wall bleeding or rectus sheath hematomas
- Correction of large hernias, gastroschisis or omphalocele
- Burns with abdominal eschars

B. Related to increased intra-abdominal contents
- Gastroparesis
- Gastric distention
- Ileus
- Volvulus
- Colonic pseudo-obstruction
- Abdominal tumor
- Retroperitoneal/abdominal wall hematoma
- Enteral feeding
- Intra-abdominal or retroperitoneal tumor
- Damage control laparotomy

C. Related to abdominal collections of fluid, air or blood
- Liver dysfunction with ascites
- Abdominal infection (pancreatitis, peritonitis, abscess,...)
- Hemoperitoneum
- Pneumoperitoneum
- Laparoscopy with excessive inflation pressures
- Major trauma
- Peritoneal dialysis

D. Related to capillary leak and fluid resuscitation
- Acidosis* (pH below 7.2)
- Hypothermia* (core temperature below 33 °C)
- Coagulopathy* (platelet count < 50000/mm^3 OR an activated partial thromboplastin time (APTT) more than 2 times normal OR a prothrombin time (PTT) below 50 % OR an international standardized ratio (INR) more than 1.5)
- Polytransfusion/trauma (> 10 units of packed red cells/24 hours)
- Sepsis (as defined by the American – European Consensus Conference definitions)
- Severe sepsis or bacteremia
- Septic shock
- Massive fluid resuscitation (> 5 l of colloid or > 10 l of crystalloid/24 hours with capillary leak and positive fluid balance)
- Major burns

* The combination of acidosis, hypothermia and coagulopathy has been forwarded in the literature as the deadly triad [70, 71].

Monitoring of intra-abdominal pressure

Since the abdomen and its contents can be considered as relatively non-compressive and primarily fluid in character, behaving in accordance to Pascal's law, the IAP measured at one point may be assumed to represent the IAP throughout the abdomen [58, 59]. IAP increases with inspiration (diaphragmatic contraction) and decreases with expiration (diaphragmatic relaxation). In the strictest sense, the normal IAP ranges from zero to 5 mmHg [60]. Certain physiologic conditions, however, such as morbid obesity [61, 62], ovarian tumors, cirrhosis or pregnancy, may be associated with chronic IAP elevations of 10 – 15 mmHg to which the patient has adapted without significant pathophysiology. In contrast, children commonly demonstrate low IAP values [63]. The clinical importance of any IAP must be assessed in view of the baseline steady-state IAP for the individual patient. The gold standard IAP measurement method is via the bladder with a Foley manometer (Holtech Medical, Copenhagen, Denmark) or an AbViser valve (Wolfe-Tory, Utah, USA), while continuous IAP measurement can be performed via a balloon-tipped catheter in the stomach (Spiegelberg, Hamburg, Germany or CiMON, Pulsion Medical Systems, Munich, Germany). Continuous monitoring allows respiratory variations in the IAP tracing to be identified, which may indirectly give an estimate of the abdominal wall compliance (**Fig. 6**) [64].

Abdominal perfusion pressure measurement

Analogous to the widely accepted and clinically utilized concept of cerebral perfusion pressure, calculated as MAP – ICP, abdominal perfusion pressure, calculated as MAP – IAP, has been proposed as a more accurate predictor of visceral perfusion and a potential endpoint for resuscitation by considering both arterial inflow (MAP) and restrictions to venous outflow (IAP) [9, 24, 65, 66].

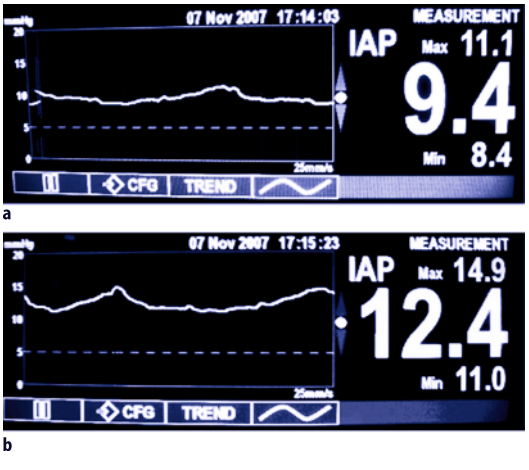

Fig. 6. Respiratory variations in intra-abdominal pressure (IAP) as an indirect measure for abdominal wall compliance. Screenshot of continuous IAP monitoring with CiMON (Pulsion Medical Suystems, Munich, Germany) in a mechanically ventilated patient showing breath-to-breath variations in IAP. Panel **a** Initial ventilator settings with an inspiratory positive airway pressure (IPAP) of 20 cmH_2O and positive end-expiratory pressure (PEEP) set at 5 cmH_2O. Mean IAP was 9.4 mmHg; IAP was 8.4 mmHg at end-expiration and 11.1 mmHg at end-inspiration (?IAP = 2.7 mmHg). Panel **b** Change of ventilator settings one minute later, to an IPAP of 35 cmH_2O with a PEEP of 15 cmH_2O. Mean IAP increased from 9.4 to 12.4 mmHg, IAP was 11 mmHg at end-expiration and 14.9 mmHg at end-inspiration (ΔIAP = 3.9 mmHg). The higher ΔIAP suggests a lower compliance of the abdominal wall.

Clinical Management

The management of patients with polycompartment syndrome is based on 3 principles [67, 68]:

- Specific medical and surgical procedures to reduce the compartment pressure (**Table 5**)
  - Improvement of compartment wall compliance
  - Evacuation of intra-compartment contents
  - Correction of capillary leak and positive fluid balance
  - Specific treatments
  - Rescue treatments
- General and organ support (intensive care) of the critically ill patient
- Optimization and prevention of specific adverse events after surgical decompression (ischemia/reperfusion)

Table 5. Treatment options for compartment syndrome

1. Improvement in compartment wall compliance
- Sedation
- Pain relief (not fentanyl!)
- Neuromuscular blockade
- Body positioning
- Negative fluid balance
- Skin pressure decreasing interfaces
- Weight loss
- Percutaneous abdominal wall component separation
- Escharotomies

2. Evacuation of intra-compartmental contents
- Gastric tube and suctioning
- CSF, ascites, pleural or pericardial drainage
- Rectal tube and enemas
- Chest tube and suctioning
- Endoscopic decompression of large bowel
- Colostomy or ileostomy
- CT- or ultrasound-guided aspiration of abscess
- CT- or ultrasound-guided aspiration of hematoma
- pericardectomy

3. Correction of capillary leak and positive fluid balance
- Albumin in combination with diuretics (furosemide)
- Correction of capillary leak (antibiotics, source control,...)
- Colloids (hypertonic-Voluven®) instead of crystalloids
- Dobutamine (not dopamine!)
- Dialysis or CVVH with ultrafiltration
- Ascorbinic acid in burn patients

4. Specific therapeutic interventions
- Continuous negative external pressure (VAC®)
- Targeted compartment perfusion pressure

5. Rescue therapy
- Intracranial compartment syndrome: decompressive craniectomy
- Abdominal compartment syndrome: decompressive laparotomy
- Thoracic compartment syndrome: decompressive sternotomy
- Extremity compartment syndrome: decompressive fasciotomy
- Pelvic compartment syndrome: decompressive gluteal fasciotomyy
- Renal compartment syndrome: renal decapsulation
- Hepatic compartment syndrome: hepatic decapsulation
- Cardiac compartment syndrome: decompressive pericardiotomy
- Orbital compartment syndrome: orbital decompression

CSF: cerebrospinal fluid; CT: computed tomography; CVVH continuous veno-venous hemofiltration

Conclusion

First suggested in 2007, the polycompartment syndrome is a constellation of the physiologic sequelae of increased compartment pressures in multiple compartments of the body [3, 4]. Recent observations suggest an increasing frequency of this complication in all types of patient and increased compartment pressures are independently associated with morbidity and mortality. Even chronic elevations in compartment pressure seem to affect the various organ systems in the body. In spite of this, research on this syndrome is still in its infancy, making it poorly recognized and thus poorly treated in some cases. Diagnosis relies largely on compartment pressure measurement. Within the polycompartment syndrome, the abdomen plays a central role and the effect of IAH on different organ systems has been described, along with recommendations to compensate for these effects. The ultimate goal of treatment is not only to decrease the compartment pressure, but also to improve organ function and to decrease mortality. Decompressive craniectomy, sternotomy, fasciotomy and laparotomy are the only treatment options that have been shown to reach most of these goals today. However, some less invasive techniques and some medical treatment strategies have shown promise in achieving compartment pressure reduction as well as organ function improvement. Another major issue is that crystalloid overresuscitation may cause (iatrogenic) secondary abdominal compartment syndrome, while the cautious administration of colloids not only seems to decrease the incidence of abdominal compartment syndrome in burn and trauma patients but also abdominal compartment syndrome-associated complications and mortality as well as the complications related to increased pressures in other compartments. The timing, type and amount of fluid resuscitation will play a major role in the future treatment and prevention of polycompartment syndrome. The take home message is not to give too much fluid, but to give the right fluids right...

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Laparostomy: Why and When?

A.K. Leppäniemi

Introduction

Laparostomy is a surgical treatment method in which the peritoneal cavity is opened anteriorly and deliberately left open, hence often called 'open abdomen'. The abdominal contents are exposed and protected with a temporary coverage. The term does not include full-thickness abdominal wall defects resulting from partial excision due to tumor or necrotizing infection, or incisional hernias.

Laparostomy is currently used in many severely ill or injured patients to facilitate healing or prevent complications, most notably the development of abdominal compartment syndrome. It is, however, a morbid procedure with postoperative care that requires good knowledge and skills to prevent even more severe complications. It is also resource intensive, often requiring multiple visits to the operating room and extensive nursing care. With improved understanding of the pathophysiology of common abdominal emergencies, such as abdominal sepsis, severe acute pancreatitis, and major abdominal trauma, as well as their relation to abdominal compartment syndrome, the number of patients with laparostomy can be expected to increase in general and surgical intensive care units.

Who Started Laparostomy?

In modern times, the idea of leaving the abdomen open dates back to the 1970s when patients with septic abdomens were treated with laparostomy, in analogy to incision and drainage of an abscess. Similarly to draining an abscess with a large incision and leaving it to heal by secondary intention, open management with frequent dressing changes to clear the infection was used in patients with peritonitis or pancreatitis [1–3].

Although the concept of packing the liver after severe trauma was already described in the early 1900s by Pringle and Halsted, the current practice was defined in the 1990s with the concept of damage control surgery, a staged approach to abdominal trauma patients with severe physiological derangement [4]. An important part of the initial, life-saving operation to control bleeding and contamination is to leave the abdomen open for planned relaparotomy 1–2 days later.

Finally, with the recognition of the risks of intra-abdominal hypertension (IAH), and the full-blown abdominal compartment syndrome, opening the abdomen and leaving it open has multiplied the numbers of patients with laparostomies [5].

Temporary Abdominal Cover

After the initial decision to open the abdomen and/or to leave it open, the exposed viscera must be covered with a protective dressing of some sort to prevent drying and unintentional injury, and to prevent or reduce the risk of infection. Ideally, this dressing should be easy to apply and remove, allow easy nursing care, not damage the fascia or the skin, be readily available and inexpensive, and maintain the abdominal domain. Furthermore, providing easy access to the abdominal cavity and a high rate of subsequent closure of the abdomen, especially the fascia, are additional points to consider.

Excluding the application of a simple dressing used in the early days, the first and easiest method to cover and protect the laparostomy wound was the application of a plastic silo (the 'Bogota bag'). This system is inexpensive, readily available and preserves the intact fascia when sutured to the skin edges. However, because the plastic silo does not provide sufficient traction to the wound edges and allows the fascial edges to retract laterally, the abdominal cavity loses part of its volume or domain resulting in difficult fascial closure under significant tension, especially if the closure is delayed beyond the first week.

In 1995, the vacuum pack method utilizing a polyethylene sheet tucked between the parietal peritoneum and the bowel was introduced. The improvement with this technique compared to earlier methods was related to the prevention of the formation of adhesions between the abdominal wall and the bowel [6]. A further improvement described in 2001 was the introduction of the vacuum-assisted wound management concept [7]. The application of vacuum-assisted wound closure techniques to open abdomens helps nursing care and is associated with the highest rate of subsequent delayed primary fascial closure and lowest mortality [8]. Even in the management of the most severe complication of the open abdomen, the exposed enteric fistula, vacuum-assisted wound management is able to control fistula secretion allowing the wound around it to heal [9]. A variety of 'self-made' topical negative pressure dressings utilizing the same principle has been described [10].

In some institutions, absorbable mesh is used for temporary cover of laparostomies, but the risks of prosthesis infection and fistula formation are still considerable. In a single institution, prospective randomized study comparing polyglactin 910 mesh and vacuum-assisted closure in 51 patients with laparostomy [11], the fistula rate was 21 % after vacuum-assisted closure and 5 % after mesh (statistically not significant). There were no differences in mortality, intra-abdominal infection, or delayed primary fascial closure rates (26 % and 31 %). The authors found both methods to be useful and equally likely to produce delayed fascial closure [11].

The likelihood of fascial closure is also related to the underlying etiology. In a study of 71 patients requiring laparostomy for gastrointestinal sepsis, pancreatitis or trauma, only 20 % achieved definitive fascial closure [12]. The likelihood of fascial closure was significantly higher in trauma patients.

A recent modification combines the use of a mesh and vacuum-assisted closure by using a temporary mesh sutured to the fascial edges under the vacuum with gradual tightening of the mesh at dressing changes until the fascia can be closed primarily [13]. Currently, this technique is the preferred method of temporary abdominal closure at our institution (**Fig. 1**).

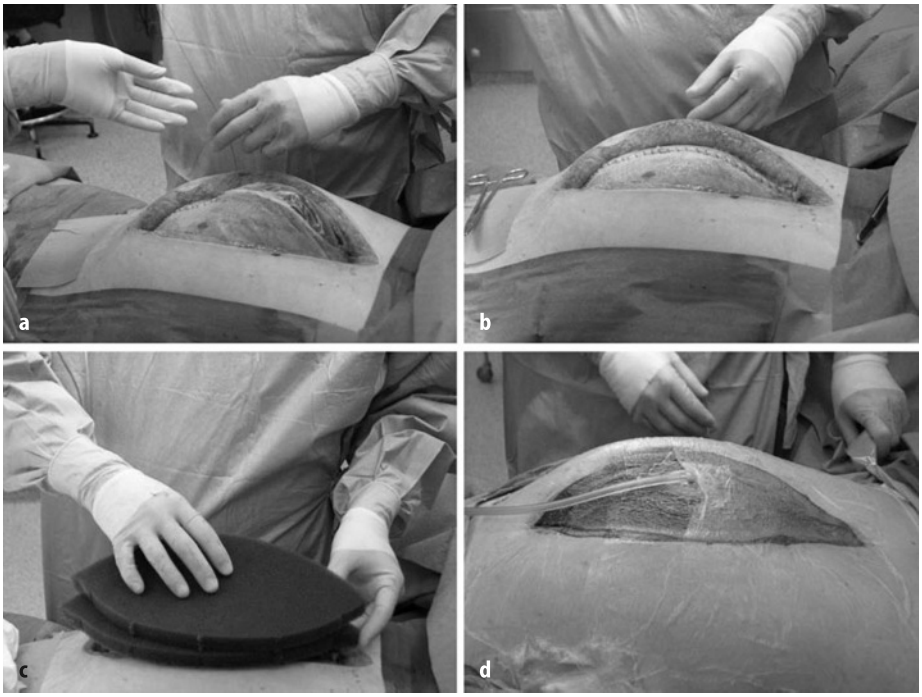

Fig. 1a-d. Mesh-assisted vacuum-assisted closure dressing

Classification of Open Abdomen

Because of the multitude of conditions leading to open abdomen, the comparison of different series and treatment outcomes has been difficult. Recently, a consensus group established a new classification system for open abdomen [14]. The criteria for different categories are based on the degree of contamination and adherence between bowel and abdominal wall or 'fixity' (lateralization of the abdominal wall). Among the four categories, Grade 1 refers to clean (1A) or contaminated (1B) wound without adherence, and 2A and 2B to clean and contaminated wounds with adherence, respectively. Grade 3 is an open abdomen complicated by fistula formation, and grade 4 a frozen abdomen.

Definitive Abdominal Wall Closure

The primary aim in managing laparostomy patients is to achieve primary fascial closure as soon as possible without causing recurrent abdominal compartment syndrome or other complications associated with premature closure. If the infection source has been controlled and even if a relaparotomy might be needed in the near future, every effort should be made to achieve primary fascial closure during the initial hospitalization period and avoid the significant morbidity associated with leaving the abdomen open for delayed reconstruction. Gradual fascial closure, often mesh-assisted, seems currently to be the best available technique, but other possibil-

ities, such as the components separation technique at an early stage [15], or fascial closure with a mesh prosthesis can be considered when there is no infection and enough skin to cover the prosthesis. However, if primary fascial closure is not possible, an early decision to resort to the planned hernia strategy is a good option.

A planned hernia approach aims at skin coverage with subsequent delayed abdominal wall reconstruction. The skin closure is most often achieved with autologous split-thickness skin grafting over the exposed bowel. Conditions favoring a planned hernia strategy include the inability to re-approximate the retracted abdominal wall edges, sizeable tissue loss, risk of tertiary abdominal compartment syndrome, inadequate infection source control, anterior enteric fistula, and poor nutritional status of the patient. The maturation of the skin graft requires about 9–12 months, after which the grafted skin can be easily removed from the bowel surface without additional iatrogenic lesions. Large abdominal wall defects can be reconstructed with pedicular or microvascular flaps. The most commonly used is the tensor fascia lata (TFL)-flap [16].

Does Laparostomy Improve Outcome?

The potential benefits of laparostomy have been most extensively studied in patients with secondary peritonitis. In a small randomized study of 40 patients comparing open treatment utilizing a polypropylene mesh for temporary cover with closed treatment, there was no significant difference in postoperative acute renal failure, duration of mechanical ventilatory support, need for total parenteral nutrition, rate of residual infection, or need for reoperation for residual infection [17]. Even though the difference in mortality (55 % vs 30 % favoring closed treatment) was not statistically significant, the study was terminated at the first interim analysis due to the clear tendency (relative risk and odds ratio for death 1.83 and 2.85 higher in the open group) toward a more favorable outcome after closed treatment. The authors concluded that closed management of the abdomen may be a more rational approach.

The benefits of laparostomy in intra-abdominal sepsis are conceptually related to the policy toward relaparotomies; should a relaparotomy be performed as a planned second look decided on already at the initial operation, or should relaparotomy only be performed on-demand after identifying a surgical complication (abscess, suture line or anastomotic leak) not amenable to percutaneous drainage. A recent, well-conducted randomized study comparing an on-demand to a planned relaparotomy strategy in patients with severe peritonitis showed that the on-demand group had a substantial reduction in relaparotomies, health care utilization, and medical costs [18]. There were, however, no significant differences in mortality or major peritonitis-related morbidity.

The current consensus does not support laparostomy and planned relaparotomy as the routine strategy in secondary peritonitis [19]. There are, however, some patient groups where laparostomy is unavoidable or practical. As has been lineated by Moshe Schein, one of the true pioneers in open abdomen, there are abdomens that cannot be closed due to major abdominal wall tissue loss, poor condition of the fascia, or extreme visceral or retroperitoneal swelling, and there are abdomens that should not be closed either to avoid abdominal compartment syndrome or because of a planned reoperation within a day or two (why lock the gate through which you are to re-enter very soon?) [20].

Infected pancreatic necrosis is an established indication for surgical necrosectomy in patients with severe acute pancreatitis. Although minimally invasive necrosectomy is feasible in some patients, the golden standard is still open necrosectomy [21, 22]. While open necrosectomy is performed in a more or less identical fashion, there are four techniques, differing in the way they provide exit channels for further slough and infected debris: Open packing, planned relaparotomies, closed packing, and closed continuous lavage [22]. Although mortality rates below 15 % have been reported after all four techniques, necrosectomy and subsequent closed continuous lavage of the lesser sac seems to be associated with the lowest morbidity [22].

The benefits of laparostomy in the management of abdominal compartment syndrome in patients with severe acute pancreatitis have not been reliably demonstrated. Although there is no question that opening the abdomen reduces intra-abdominal pressure (IAP) in this patient group, the indications for, techniques used, subsequent management of the open abdomen, and potential risk of increased infectious complications are highly controversial. In a collective review of 250 patients undergoing midline laparostomy, decompression had an overall positive effect on hemodynamic, respiratory, and renal functions [23]. Central venous pressure (CVP) and pulmonary artery pressure decreased, most likely caused by the direct effect of the decrease in IAP on the thoracic cavity. Cardiac function improved in the majority of the patients. There was an improvement in PaO_2/FiO_2 ratio and a decrease in peak airway pressure, but the respiratory function remained severely impaired in most patients. Significant improvement in urinary output was observed in all but two studies.

In a report from our institution, among the 26 patients with severe acute pancreatitis undergoing surgical decompression for abdominal compartment syndrome during the past 6 years, mostly using a full-thickness midline laparostomy, the median sequential organ failure assessment (SOFA) score at the time of decompression was 12, interquartile range (IQR) 10 – 15, and the median IAP was 31.5 (IQR 27 – 35) mmHg [24]. After decompression, 14 (54 %) patients had improved renal or respiratory functions. The overall mortality rate was 46 %, but in 17 patients in whom decompression was performed within the first 4 days from disease onset, the mortality rate was 18 %. We concluded that in patients with severe acute pancreatitis and abdominal compartment syndrome, surgical decompression may improve renal or respiratory functions, and when performed early surgical decompression is associated with reduced mortality [24].

Leaving the abdomen open after a damage control procedure for trauma is an essential component of the abbreviated laparotomy and planned reoperation strategy. Although there are no randomized studies showing that the damage control approach improves outcome in abdominal trauma patients with severely deranged physiology, cumulative material from 1001 damage control patients demonstrated a 50 % mortality rate [25]. This seems high, but a 50 % survival rate in this very sick patient population is remarkable. More recent studies have shown other benefits of damage control in trauma patients. In a series of patients with severe abdominal injuries compared with historical controls from Atlanta, damage control use increased from 7 % to 18 % and the overall mortality decreased from 76 % to 27 % [26]. A similar decrease was noted in another study from Philadelphia where the mortality rate after the paradigm change decreased from 42 % to 10 % [27].

Survival after damage control, however, comes with a price. In a series of 334 damage control patients, 276 of whom survived to abdominal closure, there was a 25 % incidence of wound infections, abscesses, and enteric fistulas [28]. In the two

studies mentioned previously, the incidence of abscesses was 14 % and 18 %, and of fistulas 18 % and 14 %, respectively [26, 27]. In a series of 56 trauma patients with early mortality of 27 %, 31 patients required subsequent treatment for complications related to the open abdomen; overall, 58 late operations for complications were performed, most commonly for infection (46 %), hernia (41 %) and enteric fistula (34 %) [29].

Conclusion

Open abdomen is a situation that is encountered increasingly frequently in trauma and emergency surgery, and is often the price to be paid for saving severely ill or injured patients. Current evidence supports the use of laparostomy in all patient groups with severe abdominal compartment syndrome. Obviously, the inability to close the abdomen due to tissue loss or extreme swelling is a mandatory indication for laparostomy. Open abdomen treatment of patients with secondary peritonitis or infected pancreatic necrosis to facilitate the clearing of the infection seems unwarranted. A relative indication for laparostomy is the planned return to the operating room for relaparotomy within 1 – 2 days where closing the wound at the initial operation requires more time and poses an additional risk to the integrity of the fascia. With modern techniques of temporary abdominal closure, the risks of enteric fistulas or failure to close the fascia are acceptable.

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XV Drug Distribution and Clearance

Augmented Renal Clearance: Unraveling the Mystery of Elevated Antibiotic Clearance

A.A. Udy, J.A. Roberts, and J. Lipman

Introduction

The prescription of pharmaceuticals in the critically ill represents a significant challenge, largely due to the scarcity of knowledge concerning the pharmacokinetic implications of the underlying disease state [1]. Dynamic changes in organ function can be remarkable in this population, driven by both the primary pathophysiological disturbance, and as a consequence of therapy provided. Vascular tone, capillary permeability, fluid status, cardiac output, and major organ blood flow can be significantly altered, with substantial follow-on effects on the volume of distribution and clearance of many agents.

Augmented renal clearance refers to the enhanced renal elimination of circulating solute and is being increasingly described in subsets of critically ill patients [2–8]. Defining and recognizing this process, however, in terms of routinely available measures of renal function is problematic, as there are many controversies on how best to estimate or measure glomerular filtration, let alone what is considered as the upper limit of normal.

From a pharmacokinetic point of view, augmented renal clearance can significantly elevate the elimination of renally cleared antibiotics, resulting in potentially sub-therapeutic dosing, treatment failure, or the selection of resistant microorganisms [9]. Notably, this is rarely considered in clinical practice, and as such doses are infrequently revised.

Defining Augmented Renal Clearance

The most widely accepted descriptor of renal function in health and disease is the glomerular filtration rate (GFR), with 'normal' values around 130 ml/min/1.73m^2 in young men and 120 ml/min/1.73m^2 in young women [10]. Augmented renal clearance refers to the enhanced renal elimination of solute and, therefore, can largely be defined on the basis of an elevated GFR. However, accurately quantifying this process is complex, as there is no clear consensus on the upper limit of 'normal', and significant controversy exists on the most robust way to estimate or measure GFR in clinical practice.

Sunder-Plassmann and Horl suggested a categorization system for elevated glomerular filtration, which they termed 'glomerular hyperfiltration' [11], defined as a GFR ≥ 120 ml/min/1.73m^2 (> 149 ml/min/1.73m^2 in young adults). However, this system is potentially flawed, as it does not differentiate between genders and may in fact represent values within the normal range for some patients. Furthermore, the

term 'glomerular hyperfiltration' is perhaps better suited to chronic kidney disease, and is a poor descriptor of the process in critical illness.

Recently we have completed an observational study of creatinine clearance in traumatic brain injured patients, employing a definition of augmented renal clearance using values 10 % above the upper limit of normal, namely a measured creatinine clearance > 160 ml/min/1.73m^2 in men and > 150 ml/min/1.73m^2 in women (unpublished data). The use of measured or calculated creatinine clearance as a descriptor of augmented renal clearance, is underscored by a number of authors identifying this factor as a key pharmacokinetic covariate for predicting the clearance of many antibiotics [5, 8, 12 – 14]. As such, defining this process, using a readily available measure of GFR, is a key step in identifying sub-populations 'at risk' of sub-therapeutic antibiotic exposure.

Assessing Renal Function in Critical Illness

The most clinically accurate, routinely available method of assessing GFR is still uncertain. Creatinine is an amino-acid derivative (molecular mass 113 Da) that is freely filtered by the glomerulus, and secreted by proximal tubular cells. As such, serum creatinine concentrations are routinely used as an index of renal function, although isolated results within the 'normal' reference range are insensitive indicators of GFR in the intensive care unit (ICU) [15]. Clinically, an acute rise in serum creatinine concentration is frequently interpreted as representing renal dysfunction, especially in conjunction with a poor urine output. In contrast, a serum creatinine concentration within the 'normal' reference range is regarded as representing 'normal' renal function, particularly in the absence of oliguria. This interpretation, however, may not always be correct, such as in situations where protein stores or intake may be low (for example, the elderly, malnourished, or debilitated), or at term pregnancy.

In an effort to more accurately quantify renal function using serum creatinine values, numerous equations have been developed to estimate GFR using simple laboratory and demographic measures. The Modification of Diet in Renal Disease (MDRD) equation was developed using data from 1628 patients with chronic kidney disease and calculates an estimated GFR adjusted to body surface area [16]. The Cockcroft-Gault equation, first used in 1973, was derived from a smaller cohort of 249 male patients [17], and calculates an estimated creatinine clearance using the patient's weight, sex, age and serum creatinine concentration.

Although potentially more useful than serum creatinine concentrations alone, particularly early in the ICU admission [18], clinicians should be cautious in using such equations to modify dosing regimes, as they ignore the substantial effects of disease pathophysiology. In addition, the limitations of relying solely on serum creatinine concentrations are embedded within the use of these equations, and increasing evidence supports the assertion that both MDRD and Cockroft-Gault-derived estimates of GFR are flawed in critically ill patients [5, 15, 19]. Rather, because of the established correlation with drug clearance [6, 8], and ease of measurement in the ICU, it should be considered that a timed urinary creatinine clearance is the most appropriate and convenient method for estimating GFR.

Four- [7], eight- [8], and 24-hour [6] urine collections have been used in the ICU, although given the dynamic nature of critical illness, more frequent measurements may be necessary. Two hour collections appear to be just as accurate [18], although

any cyclical variation needs further investigation. If the clinician does not have ready access to therapeutic drug monitoring as a means to optimize antibiotic dosing, we recommend regular measurement of creatinine clearance to allow the implementation of improved dosing schedules.

Changes in Critical Illness Contributing to Augmented Renal Clearance

The systemic inflammatory response syndrome (SIRS), a part of the innate immune response to cellular trauma, describes a series of physiological and laboratory derangements that can be identified commonly in the critically ill [20]. Significantly, the syndrome is very non-specific, and can be recognized in trauma, pancreatitis, burn injury, autoimmune disorders, ischemia, and post major surgical procedures. Sepsis is then considered as the presence of infection in addition to SIRS [20].

A hyperdynamic circulation, defined by a low systemic vascular resistance index (SVRI) and high cardiac output, is typical of this syndrome. The release of endogenous cytokines and inflammatory mediators, in addition to the relative cellular dysoxia, drive these systemic perturbations. This hyperdynamic state can lead to augmented blood flow to major organs, and in a large animal model of sepsis, renal blood flow was documented to increase in concert with cardiac output [21].

Measures to improve cardiovascular function in the critically ill commonly involve the administration of intravenous resuscitation fluids and the use of vasoactive medications, both of which may exacerbate these changes. Recent animal research has confirmed that crystalloid administration can result in an increase in creatinine clearance [22], and that cardiac output, renal blood flow, and creatinine clearance increase with norepinephrine administration [23].

Previously investigators have also demonstrated that the GFR increases after the ingestion of a protein rich meal [24]. This ability of the kidneys to respond to a protein load has been termed the 'renal reserve', and implies the human kidney is not working at full capacity under basal conditions. The mechanisms underlying this phenomenon are not entirely clear, but may include a population of 'dormant nephrons' that can be recruited at times of biological stress. Although unproven, this may help to explain the augmented clearances seen in hematological malignancy and/or febrile neutropenia. **Figure 1** schematically illustrates the potential mechanisms underlying augmented renal clearance in the critically ill.

Prevalence and Natural History of Augmented Renal Clearance in the Critically Ill

In a single center ICU observational study, Fuster-Lluch et al. report a 17.9 % incidence of glomerular hyperfiltration on admission to the ICU, with a mean creatinine clearance of 142 ml/min/1.73m^2. Patients with an elevated creatinine clearance were primarily multi-trauma victims or postoperative patients, younger, with lower APACHE II scores, and higher urine outputs [7]. Augmented renal clearance has also been demonstrated in more specific populations, and **Table 1** lists those sub-groups where augmented clearances appear to be common.

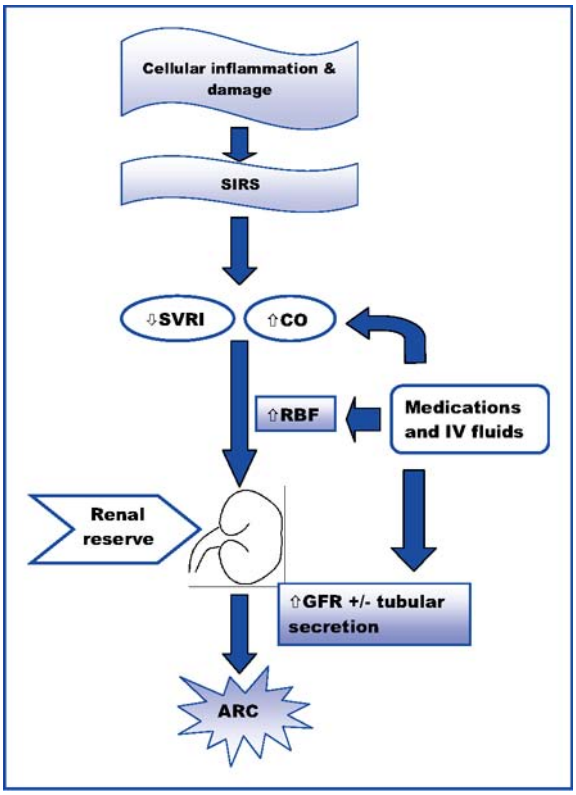

Fig. 1. Potential mechanisms underlying augmented renal clearance (ARC). SIRS: systemic inflammatory response syndrome; SVRI: systemic vascular resistance index; CO: cardiac output; RBF: renal blood flow; GFR: glomerular filtration rate

- Young patients (age < 60 years)
- Multi-trauma
- Traumatic brain injury
- Burns injury
- Postoperative patients
- Sepsis (with normal renal function)
- Hematological malignancy (febrile neutropenia)
- Hypoalbuminemia

Table 1. Sub-groups of critically ill patients at risk of augmented renal clearance

Traumatic Brain Injury

Albanese et al. previously documented elevated creatinine clearance in a sub-group of isolated traumatic brain injured patients receiving norepinephrine [2]. Significantly, clearances were elevated prior to the institution of the vasopressor and remained elevated for the twenty-four hour period of the study. A similar result was noted by Benmalek and colleagues in their paper investigating the effects of dopamine in addition to norepinephrine in the management of post-traumatic intracranial hypertension [3].

Recently, in a cohort of young severely head injured patients requiring osmotherapy (hypertonic saline) and/or norepinephrine infusion for the maintenance of a desired cerebral perfusion pressure (CPP), we documented an incidence of aug-

mented renal clearance of 85 % during the ICU stay (unpublished data). Of note, clearances were elevated both on and off CPP therapy, although norepinephrine use, saline loading, mean arterial pressure (MAP) and central venous pressure (CVP) predicted creatinine clearance on the day of measurement in a multivariate model.

Surgery and Trauma

In a small cohort of young trauma patients, Brown and colleagues reported elevated creatinine clearance values, peaking at an average of 190 ml/min/1.73m^2 in the post-operative period [4]. In support of this finding, increased clearance of ceftazidime has been documented in trauma patients [25], while Shikuma et al. reported wide inter-patient variation in key pharmacokinetic parameters, and markedly elevated clearance of piperacillin in a young cohort of surgically critically ill patients with sepsis [26]. Specific creatinine clearance values and hemodynamic parameters were not provided, although a moderate correlation was reported between drug elimination and estimated creatinine clearance [26].

In contrast, previous work examining the administration of cefpirome to traumatized patients with SIRS as compared to matched healthy controls, failed to demonstrate any significant alterations in key pharmacokinetic parameters [27]. Of note, estimated creatinine clearance values were elevated in the trauma group (median = 147 ml/min), but did not reach statistical significance. Importantly, several features of this study [27] must be noted. In particular, cefpirome was administered on average 9 days into the ICU stay, no hemodynamic data were reported, and patients requiring vasopressor administration were excluded [27].

Burns

Burns injury appears to be another unique population where augmented renal clearance is likely to be common. The acute phase of this injury lasts approximately 48 hrs and is characterized by intravascular hypovolemia secondary to loss of protein-rich fluid across the capillary membrane. Following adequate fluid resuscitation, major burn injury is then characterized by a hypermetabolic state, with a subsequent increase in renal blood flow and GFR. Recent data have confirmed that a significant percentage (42 %) of patients will manifest elevated creatinine clearance (> 120 ml/min/1.73m^2) during this phase and that serum creatinine concentrations and/or estimates of GFR are inaccurate in predicting renal function in this setting [5].

The clearance of most hydrophilic and moderately lipophilic antibiotics is expected to increase during this second phase [28 – 30] and, as such, higher doses of aminoglycosides are required in burn patients [29] and more frequent dosing of glycopeptides may be necessary. Regular measurement of trough concentrations and subsequent dose adjustment is essential to avoid sub-therapeutic levels.

Hematological Malignancy

Hematological malignancy also represents a possible risk factor for augmented renal clearance. In 22 leukemic patients receiving high dose teicoplanin as empirical therapy for febrile neutropenia, Pea et al. observed elevated creatinine clearance results, with a moderate to good inverse linear relationship between trough levels and estimated creatinine clearance [31]. Significantly, standard dosing regimes resulted in

much lower concentrations compared with healthy volunteers. Fernandez De Gatta et al. demonstrated similar results with vancomycin dosing in hematological malignancy [32], while Romano et al. observed that the clearance of amikacin was significantly increased in the presence of acute myeloblastic leukemia [33].

Hypoalbuminemia

Hypoalbuminemia is frequently encountered in the critically ill, either independently as a marker of underlying disease (e.g., hepatic failure), or as a consequence of protein capillary leak, fluid loading, increased catabolism, and poor nutrition. Previous work investigating the pharmacokinetics of ceftriaxone (protein binding ~ 90 %) for severe sepsis has demonstrated an almost doubling of drug clearance in this setting [34]. The increase in the free drug concentration facilitates renal elimination, and augmented clearances have been demonstrated with other highly protein bound agents [13, 35].

The natural history of augmented renal clearance in the critically ill is still largely uncertain, and many patients may develop this phenomenon during their ICU admission. In a study by Fuster-Lluch et al., the prevalence of a creatinine clearance > 120 ml/min/m^2 was greatest on day 5 of the study [7], while Brown and colleagues reported peak creatinine clearance levels on the fourth postoperative day [4]. In our recent observational study in traumatic brain injury, peak creatinine clearance values were recorded after a mean of 4.7 days of treatment (unpublished data).

What are the Clinical and Dosing Implications of Augmented Renal Clearance?

The ramifications of augmented renal clearance relate primarily to enhanced antibiotic elimination, resulting in sub-therapeutic drug exposure, the selection of resistant mutants, and potentially treatment failure [9]. However, how augmented renal clearance influences antibiotic prescription largely depends on the pharmacokinetic-pharmacoynamic factors most relevant for bacterial kill. **Table 2** broadly categorizes antibiotics on this basis and provides recommendations for dosing modification in this setting.

Concentration-dependent Killing

Aminoglycosides

As drugs are excreted almost entirely unchanged by glomerular filtration, drug elimination is likely to be enhanced in the setting of augmented renal clearance, although any change in the apparent volume of distribution in the critically ill is likely to be more important, as this may significantly alter maximum plasma concentrations (Cmax). However, there is no benefit in doses > 7 mg/kg (for gentamicin), as this typically confers a Cmax/minimum inhibitory concentration (MIC) ratio of at least 10, maximizing bacterial killing [1]. Some consideration to increasing the frequency of dosing to 18-hrly may be appropriate, although trough concentrations should be measured frequently to avoid toxicity.

Reviewing dosing schedules of aminoglycosides is paramount in the critically ill, as investigators have previously shown a significant impact of ICU interventions on pharmacokinetic parameters [36], in addition to augmented drug clearances in sep-

Table 2. Antibiotic categorization by kill characteristic and implications of augmented renal clearance

	Concentration-dependent killing	Time-dependent killing	Concentration- and time-dependent
Antibiotic class	Aminoglycosides Nitroimidazoles Polymyxins	β-lactams Lincosamides Some macrolides Oxazolidinones	Glycopeptides Fluoroquinolones Tetracyclines
Examples	Gentamicin Amikacin Metronidazole Colistin	Penicillins Cephalosporins Carbapenems Clindamycin Erythromycin Linezolid	Vancomycin Teicoplanin Ciprofloxacin Levofloxacin Tigecycline
PK-PD factor	Cmax/MIC	T > MIC	AUC_{0-24}/MIC
Effect of augmented renal clearance	Increased CL, Lower Cmin	Lower Cmin, Less T > MIC	Lower AUC_{0-24}
Potential dose modification	More frequent dosing	More frequent/extended interval/continuous infusions dosing	More frequent dosing/ continuous infusion

Cmax/MIC: ratio of maximum serum concentration to the minimum inhibitory concentration of the microorganism; T > MIC: Time for which the drug concentration remains above the minimum inhibitory concentration for bacterial growth; AUC_{0-24}/MIC: ratio of the area under the concentration time curve to minimum inhibitory concentration; PK-PD: pharmacokinetic-pharmacodynamic; CL: drug clearance; Cmin: minimum serum concentration

sis [37], hematological malignancy [33], and burns [29]. Therapeutic drug monitoring has an established role in the prescription of aminoglycosides, and consequently the impact of augmented renal clearance can be clearly observed and doses modified appropriately.

Time-dependent Killing

β-lactam antibiotics

The β-lactam group of antibiotics includes the penicillins, cephalosporins, carbapenems, and monobactams. Because of the absence of any significant post-antibiotic effect for most of these agents, dosing schedules should aim to keep serum concentrations a factor 4 – 5 times above the MIC for 90 – 100 % of the dosing interval [1]. The effects of augmented renal clearance on drug exposure are likely to be significant as most β-lactams are eliminated through a mixture of glomerular filtration and tubular secretion. Recent data support this assertion, in that creatinine clearance was identified as a key covariate in piperacillin elimination in the critically ill, with a strong inverse relationship between creatinine clearance and trough concentrations [6]. Augmented clearances have also been documented in burns [30], trauma [25], and sepsis [8, 26].

The carbapenems (meropenem, imipenem, panipenem, ertapenem, doripenem, and biapenem), because of their inherent post-antibiotic effect, require less time at concentrations > MIC (T>MIC) [1], although in common with other β-lactams, creatinine clearance is a key covariate in predicting drug elimination [12]. Of note,

drug clearance has been reported to be significantly elevated in the critically ill, leading to potentially sub-therapeutic levels for large portions of the dosing interval [13].

In regards to the potential clinical implications of augmented renal clearance, work by Noel et al. investigating the new broad-spectrum cephalosporin, 'ceftobiprole', is worthy of close consideration. Although yet to be published in a peer-reviewed format, inferior cure rates were documented in patients who were either young (< 45 years) or had an elevated creatinine clearance at baseline (≥ 150 ml/min) when compared to the combination linezolid/ceftazidime for the treatment of ventilator-associated pneumonia (VAP) [38]. Importantly, no pharmacokinetic data were provided, and the implications of this work need further study.

Cumulative pharmacokinetic data serve to highlight augmented renal clearance as an important consideration in effectively dosing β-lactam antibiotics in the critically ill, and raise questions as to the optimal dosing strategy in this setting. Given their time-dependent kill characteristic and the increased clearances reported, maintaining adequate drug concentrations through more frequent, extended, or continuous dosing must be considered. Although pharmacokinetic-pharmacodynamic data largely support administration by extended or continuous infusion [1], a recent systematic review of continuous dosing strategies in different sub-sets of hospitalized patients failed to demonstrate any clinical advantage [39]. Continuous infusion of β-lactams, however, remains an attractive strategy to maintain adequate drug concentrations, and any specific role in augmented renal clearance requires further investigation.

Oxazolidinone antibiotics

Linezolid is a time-dependent antibiotic with activity against multi-resistant Gram-positive pathogens. Conflicting data regarding the possible implications of augmented renal clearance have been reported, with recent work observing increased drug clearance in the critically ill, and a pharmacokinetic advantage to dosing by continuous infusion [40]. However, separate authors have presented data reporting no difference in key tissue and plasma pharmacokinetic parameters in severe sepsis and septic shock compared with healthy volunteers [41], and as such, no specific dose modification can be recommended.

AUC_{0-24}/MIC antibiotics

Glycopeptides

The glycopeptides have a pharmacokinetic-pharmacodynamic profile that is not fully understood, although an AUC_{0-24}/MIC ratio ≥ 400 has been associated with superior clinical and bacteriological cure in patients treated with vancomycin for methicillin-resistant *Staphylococcus aureus* (MRSA) lower respiratory tract infection [42]. Vancomycin is cleared through a combination of glomerular filtration and renal tubular secretion, and a significant correlation between drug clearance and creatinine clearance has been confirmed in the critically ill [43].

Altered creatinine clearance is thought to account for > 50 % of the variability in vancomycin clearance in this population, and pharmacokinetic modeling has suggested that doses higher than those regularly prescribed in the critically ill are needed to achieve the desired AUC_{0-24}/MIC targets, particularly with intermediate or drug-resistant strains [14]. These data are in agreement with other authors reporting higher dose requirements in patients receiving vasoactive medications

[44], in addition to augmented clearances in burns [28] and hematological malignancy [32]. Teicoplanin has a similar spectrum of activity to vancomycin, although its longer elimination half-life allows for once a day dosing. Drug clearance can be correlated with estimated creatinine clearance, and enhanced elimination has been demonstrated in the settings of hypoalbuminemia [35] and febrile neutropenia [31].

Despite an increasing volume of data on the relevant pharmacokinetic-pharamcodynamic properties of vancomycin, the optimal dosing strategy in the ICU remains uncertain. Current levels of bacterial resistance require trough levels of at least 15 – 20 mg/l, and in those manifesting augmented renal clearance, increased frequency or continuous infusion dosing may be appropriate. Continuous infusion has been proposed as the optimal dosing regimen to achieve target steady-state concentrations, although to date the data remain conflicted [45, 46]. Any specific role for alternative dosing regimes in those with augmented renal clearance remains to be determined.

Quinolone antibiotics

The fluoroquinolones include ciprofloxacin, moxifloxacin, gatifloxacin, and levofloxacin, and dosing strategies to achieve an $AUC_{0-24}/MIC > 125$ are required for superior clinical outcomes with Gram-negative infections [1]. Presently there are only limited data exploring the impact of augmented renal clearance on fluoroquinolone pharmacokinetics in the critically ill, although it must be recognized that this may be limited, as these agents have a large apparent volume of distribution.

Recently Conil et al. reported pharmacokinetic-pharmacodynamic data for ciprofloxacin in 70 critically ill patients receiving the drug as either directed or empirical antibiotic therapy. Total drug clearance was closely related to estimated creatinine clearance, although drug elimination is complex in this setting, as ciprofloxacin displays significant non-renal clearance [47]. In a small study (n = 10), Pea and colleagues examined the pharmacokinetic profile of levofloxacin in early onset VAP and demonstrated significantly elevated clearances secondary to enhanced renal elimination of the unchanged drug [48].

The implications of augmented renal clearance on dosing of fluoroquinolone antibiotics remains uncertain. Although it has previously been shown that 8-hourly administration of ciprofloxacin is safe and effective in patients with severe sepsis and normal serum creatinine concentrations [49], this regime could still fail to reach the desired AUC_{0-24}/MIC targets [50]. As such, higher doses or alternative dosing strategies may be recommended in the future, particularly for those agents that are renally excreted. Further research is urgently needed to address the paucity of knowledge in this area.

Therapeutic Drug Monitoring

Therapeutic drug monitoring is well established in the prescription of aminoglycosides, where Cmax and trough concentrations can be used to improve efficacy and limit toxicity. In addition, trough levels have regularly been used to guide vancomycin and teicoplanin prescribing in the critically ill [1], although outside of these classes, therapeutic drug monitoring has been infrequently available. However, with improving knowledge of the pharmacokinetic-pharmacodynamic properties of many antibiotics and the capability to measure serum concentrations with increasing accuracy, therapeutic drug monitoring has a central role in optimizing dosing regimes for many additional agents.

Furthermore, due to the dynamic nature of critical illness and the rapid changes in organ function often encountered, dosing schedules should be regularly evaluated, in order to minimize the chances of therapeutic failure or toxicity. As such, therapeutic drug monitoring should be regarded as an important component of antibiotic prescribing in the ICU, and ideally should be available for a wide range of pharmaceutical agents. If such a service is not readily available, we would strongly recommend the routine measurement of creatinine clearance as a surrogate of drug elimination, so that appropriate antibiotic dose modification can be made.

Conclusion

Determining the optimum dosing strategy for any drug is clearly important. But this is of even greater relevance for those pharmaceuticals where clinical response is either difficult to monitor or delayed, and sub-optimal drug exposure can result in inferior outcomes. Such is the case with the prescription of antibiotics in the critically ill.

Accurate assessment of renal function in the ICU is often confused, and usually focuses on identifying renal dysfunction. However, a growing body of evidence confirms that 'normal' serum creatinine concentrations are associated with augmented clearances, particularly in young trauma patients, and patients with burns, sepsis, and hematological malignancy. Current data also raise questions concerning the validity of a number of routinely used equations to estimate GFR in this setting. As such, a timed creatinine clearance remains the most robust and readily available method of assessing GFR in this population, and should be routinely employed as a surrogate of renal drug elimination.

The implications of augmented renal clearance in terms of enhanced drug elimination are significant, such that sub-therapeutic levels for substantial periods of the dosing interval may result in treatment failure or the selection of resistant organisms. As this has largely been neglected in clinical practice, more frequent creatinine clearance measures are warranted to allow improved optimization of dosing regimens. Further research should now focus on identifying readily measurable predictors of augmented renal clearance in the critically ill, on the validation of bed-side tests to allow more frequent measurement, and on empirical adjustment of dosing regimens in this setting.

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Drug Distribution: Is it a more Important Determinant of Drug Dosing than Clearance?

M. Ulldemolins, J.A. Roberts, and J. Rello

Introduction

Appropriate drug dosing in critically ill patients remains an unresolved challenge for clinicians. Severity of disease and aggressive medical management of patients admitted to the intensive care unit (ICU) are known to drive to changes in patient physiology that lead to important variations in pharmacokinetics [1]. However, despite an increasing awareness of differential dosing requirements for critically ill patients, dose-finding studies continue to be performed in healthy volunteers or non-critically ill patients.

It is accepted that the different requirements for critically ill patients are usually multifactorial. Pharmacokinetically, variations in drug clearance and volumes of distribution can both change significantly [2, 3]. However, the relative importance of these two factors for dosing is yet to be clarified. To maintain appropriate serum and target site drug concentrations, dose-adjustments are required. The need for drug dosing modifications due to increases or decreases in drug clearance has been identified in previous papers [4, 5], but increases in drug volume of distribution have been studied to a lesser extent, despite being commonly seen in critically ill patients.

The aim of this chapter is to contrast the effect of altered volume of distribution with clearance on drug dosing and highlight the reasons why some drugs may develop a higher volume of distribution in critically ill patients.

Overview of Pharmacokinetic and Pharmacokinetic/pharmacodynamic Parameters

Pharmacokinetics studies the relationship between dose and serum concentrations over time. Further, pharmacodynamics aims to assess the relationship between concentrations at the target site and pharmacologic effect. The gap between pharmacokinetics and pharmacodynamics is bridged by the pharmacokinetic/pharmacodynamic approach, which aims to link dose with pharmacological effect (**Fig. 1**).

The most relevant pharmacokinetic parameters are [6]:

- Cmax: Peak concentration achieved after a dose
- Tmax: Time after administration when the peak concentration is achieved
- Volume of distribution (Vd): Apparent volume into which a drug distributes into the body after equilibrium.
- Clearance (CL): Measures the irreversible loss of drug from the body by metabolism and/or excretion.

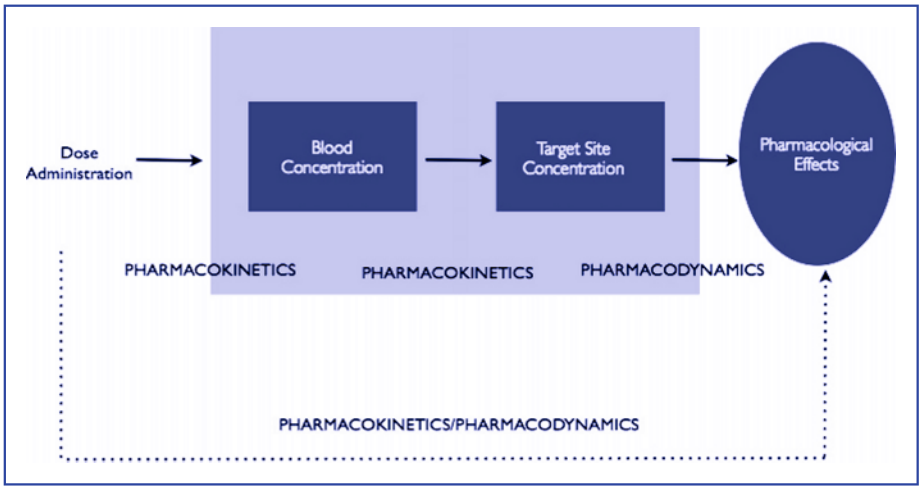

Fig. 1. Interrelationship between pharmacokinetics and pharmacodynamics and link between the two concepts by pharmacokinetics/pharmacodynamics

- Elimination half-life ($t_{1/2}$): Time taken for the serum concentration to fall by one-half. Half-life depends on both clearance and volume of distribution.
- Protein binding: Extent that the drug binds to plasma proteins (mainly albumin and α- acid glycoprotein). This binding is a reversible equilibrium that depends on the drug-protein affinity, drug concentration, and protein concentration. Only unbound drug can pass through most cell membranes, as the protein-drug complex is too large.
- AUC: Total area under the concentration-time curve. AUC can be calculated from the integration of the concentration/time function (f(x)) and gives information about drug exposure and clearance.

Volume of Distribution versus Clearance: How do they Affect Serum Drug Concentration and Half-life?

From pharmacokinetic first principles, concentration and half-life are secondary parameters derived from volume of distribution and clearance.

$$t_{1/2} = \ln 2 \times Vd/CL \qquad \text{(Equation 1)}$$

$$C = Dose/Vd \qquad \text{(Equation 2)}$$

Increased clearance and/or volume of distribution affect serum drug concentrations in the same fashion, decreasing the values of the concentration-over-time curve (Fig. 2).

However, understanding the effect of increased clearance and volume of distribution on elimination half-life is more challenging. Mathematically, an increased clearance in Equation 1 produces a decrease in half-life. On the other hand, a longer half-life is derived from an increased volume of distribution. In between the two extremes, a constellation of possible half-life values exist. Physiologically, increased drug volume of distribution and clearance interfere with the dynamic and variable process of equilibrium between serum and interstitial fluid and tissue concentrations.

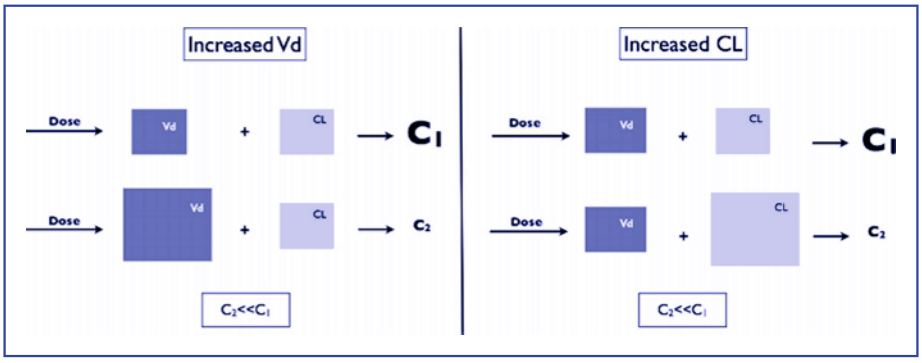

Fig. 2. Changes in drug concentrations due to increased clearance (CL) and volume of distribution (Vd). In the left panel, the lower schematic shows that increased volume of distribution leads to decreased serum concentration (C_2) compared with that observed with a smaller volume of distribution (C_1). In the right panel, increased clearance causes a lower serum concentration (C_2) compared with that resulting from the lesser clearance denoted by C_1.

Briefly, the distribution process endeavors to reach a concentration equilibrium among serum, peripheral tissues, and extracellular fluid [7], and depends on the hydrophilicity (or lipophilicity) of the drug. When the volume of distribution is increased, the extent of distribution is increased because of the additional volume to be saturated, with greater movement of the drug molecules from the central compartment (bloodstream) to the peripheral compartments (tissues and interstitial fluid). The volume of distribution is, therefore, inversely correlated with serum drug concentrations.

Paradoxically perhaps, increased volume of distribution and lower serum drug levels are also directly correlated with larger half-lives. However, the physiology of distribution and elimination can also explain this phenomenon. Elimination processes only occur to the drug molecules present in the central compartment [6]. As the kidneys/liver extract these molecules from the bloodstream, an inverse movement of drug from the tissues back into the bloodstream occurs to re-establish the concentration equilibrium. A larger volume of distribution means that a greater amount of drug is distributed into the tissues. Therefore, drug in the peripheral compartments acts as a reservoir and will replace drug that has been cleared from the central compartment. It follows that the effective drug half-life is longer because whilst clearance is occurring, the serum concentration may not reflect the level of clearance because cleared drug is replenished by re-distributed drug.

On the other hand, the effect of high clearance on half-life is slightly more understandable. Higher clearance results in faster removal of the drug from the serum and, therefore, decreases the serum concentration faster, being inversely proportional to the half-life.

Causes and Consequences of Increased Volume of Distribution

Volume of distribution is a parameter heavily influenced by the physicochemical properties of a drug. Chemically, the octanol/water partition coefficient will help to describe the level of hydrophilicity (or lipophilicity) of a drug. Depending on this

Table 1. Examples of lipophilic and hydrophilic drugs frequently used in intensive care and emergency medicine

Hydrophilic Drugs	Lipophilic Drugs
Antibiotics • Glycopeptides (vancomycin) • Aminoglycosides (gentamycin) • β-lactams (penicillins, cephalosporins, carbapenems, monobactams) • Linezolid • Daptomycin • Colistin	**Antibiotics** • Fluoroquinolones • Lincosamides • Macrolides • Metronidazole • Tetracyclines and Tigecycline • Rifampicin
Antiarrythmics • Digoxin • β-blockers (atenolol)	**Antiarrythmics** • Amiodarone • β-blockers (metoprolol, propranolol) • Milrinone
Sedatives, Analgesics and Anticonvulsivants • Opioids (morphine, oxycodone)	**Sedatives, Analgesics and Anticonvulsants** • Barbiturates • Benzodiazepines • Dexmedetomidine • Valproic acid • Opioids (fentalyl and sulfentanyl) • Phenytoin • Propofol
Anticoagulants, antiplatelets • Salicylates • Warfarin, Acenocoumarol • Heparin • Enoxaparin	

affinity, drug molecules will distribute to one compartment or another. **Table 1** shows some examples of hydrophilic and lipophilic drugs commonly used in critically ill patients. Hence, different conditions can affect drug volumes of distribution differently. **Figure 3** summarizes the physiological/pathological situations likely to cause increases in volume of distribution, classified as acute or chronic.

Chronic Increases in Volume of Distribution

Obesity

The incidence of obesity is rising alarmingly, estimated to be between 6 and 31 % in European countries [8] and about 35 % in the USA [9]. Obese patients in the ICU are well-known to be at increased risk of nosocomial infections, ventilation complications, and other morbidities [10]. Moreover, the dosing requirements of certain drugs can be significantly different in obese patients. Obesity is particularly important in the pharmacokinetics of lipophilic drugs, because the extent of distribution massively increases in the presence of adipose tissue. This phenomenon has been well documented with drugs such as benzodiazepines and opioids. Greenblatt and colleagues found a 3-fold increase in the volume of distribution of midazolam when comparing obese versus non-obese patients (311 l vs 114.1 l), which demonstrated increased distribution of midazolam into adipose tissue. Clearance was not different between groups, but half-life was extended significantly (8.4 vs 2.7 h) as could be anticipated [11]. The same effect was observed in a study with sufentanil, which reported a volume of distribution of 547 l in obese patients compared with 346 l in non-obese patients [12]. Drug half-

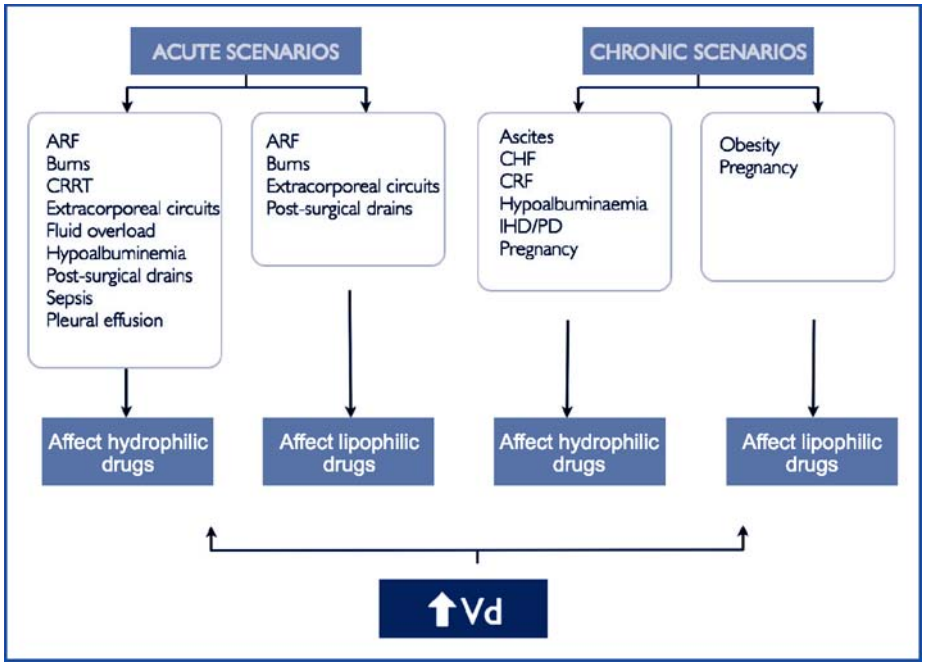

Fig. 3. Classification of the increases in volume of distribution as acute or chronic, and drugs likely to be affected by each situation due to their physicochemical characteristics. AKI: Acute kidney injury; CRRT: Continuous renal replacement therapy; CHF: Congestive heart failure; CKD: Chronic kidney disease; IHD: Intermittent hemodialysis; PD: Peritoneal dialysis

life was also extended significantly in this study (3.5 vs 2.3 h) and correlated statistically with total volume of distribution ($r = 0.70$) [12]. For antibiotics, there is evidence that suggests that the volume of distribution of even hydrophilic drugs (i.e., aminoglycosides, glycopeptides) is increased in obese patients due to the increased interstitial fluid and muscle mass that also accompany obesity [13–16].

Chronic organ dysfunctions

Chronic kidney disease and congestive heart failure (CHF) are two common pathologies that cause a constellation of different signs and symptoms. Fluid retention in the interstitial space is common in both syndromes which generally causes an increase in the volume of distribution of hydrophilic drugs [17, 18]. Ascites derived from severe hepatic failure and portal hypertension is also recognized to produce increases in the volume of distribution of some hydrophilic drugs. A study on the pharmacokinetics of the monobactam, aztreonam, in patients with severe cirrhosis and ascites demonstrated a vast increase in the volume of distribution (2.57 l/kg vs 0.16 l/kg from healthy volunteer data) [19, 20]. Similar results were observed with ampicillin, vancomycin, and gentamicin [21–23], evidencing the importance of this third space in drug pharmacokinetics.

Other scenarios

Pregnancy is another clinical scenario associated with increases in the volume of distribution of hydrophilic drugs due to edema and distribution to the fetus, pla-

centa, uterus and amniotic liquid [17, 24]. Systemic fluid volume has been estimated to increase between 6 and 8 l (80 % distributing to extracellular space and 20 % to intracellular space). Moreover, as body fat has been also reported to increase about 3–4 kg, the volume of distribution of lipophilic dugs is also likely to increase, although is unlikely to be clinically significant [24]. This increased volume of distribution makes the management of pregnant critically ill patients even more complex and is a topic that merits further research. Another well-known factor for increases in volume of distribution is hypoalbuminemia. Chronic causes of hypoalbuminemia include malnutrition, aging, chronic hepatic failure, malignancies and pregnancy and such presentations to the ICU are common [24–28]. The effects of hypoalbuminemia on drug volume of distribution are described in the following section.

Acute Increases in Volume of Distribution

Acutely increased volumes of distribution are frequently observed in critically ill patients and are primarily related to a movement of water from the intravascular compartment to the extravascular space. Compelling evidence shows that different pathologies and therapeutic procedures are factors responsible for the increases in the volume of distribution that affect mainly hydrophilic drugs.

Severe sepsis

The pathophysiology and management of severe sepsis is complex and still controversial [29]. The lipopolysaccharide (LPS) of Gram-negative bacteria (endotoxin) activates a host response that induces changes in the vascular permeability that lead to hypotension and capillary leakage of fluids to the extravascular space [30].

Moreover, patients with septic shock in the ICU have been reported to receive up to 12 l of fluid during their first two days of stay in the ICU [31], which also contributes considerably to increased volume of distribution. Many studies have demonstrated the variable pharmacokinetics of different drug classes in critically ill patients with sepsis. For instance, the volume of distribution of hydrophilic antibiotics such as aminoglycosides has been shown to increase in septic patients, correlating with severity of sickness [32]. Glycopeptides and β-lactams have similar behavior to aminoglycosides [33–36]. Linezolid also displays this characteristic [37].

Burns

Burn patients are also likely to receive large amounts of fluid and inotropes during the resuscitative phase and the subsequent hypermetabolic phase is well recognized to cause variations in pharmacokinetics. In these patients, increased clearance and volume of distribution should be expected for hydrophilic drugs [38]. Increased volumes of distribution have also been observed with lipophilic drugs, such as fentanyl and propofol [39].

Hypoalbuminemia

Some 40–50 % of critically ill patients have been reported to have albumin levels less than 25 g/l [40], and sufficient evidence shows that this presentation considerably affects the volume of distribution of highly protein-bound drugs such as salycilates, ceftriaxone, sulfonamides, daptomycin, and ertapenem among others [34, 35, 41–43]. The increases in the unbound drug concentration due to hypoalbuminemia lead to enhanced movement of unbound molecules from the central compartment to peripheral compartments, thereby increasing the volume of distribution [43].

Other scenarios

Critical illness embraces a wide range of signs, symptoms and syndromes that potentially can increase the volumes of distribution of different drugs. The purpose of this chapter is not to describe each of them, but to give an overview of the more frequent situations likely to alter this parameter. Common clinical scenarios that can potentially vary drug volume of distribution are acute renal failure, continuous renal replacement therapy (CRRT), the presence of surgical drains, and extracorporeal circuits and pleural effusions among others [3]. There are still sparse data focused on this aspect, and more research is definitely warranted.

Measurement of Volume of Distribution in Critically Ill Patients

Several methods exist to determine body composition. The information obtained from these tools allows estimating the likely volume of distribution of each drug depending on its physicochemical proprieties.

Bioelectrical impedance: This method measures the opposition to the electric current flow by the tissues, which is the opposite to electrical conductivity, and gives information about extracellular water and total body water by the application of these electrical currents throughout the body. At low frequencies, the bioelectrical current flows through the extracellular water but is unable to penetrate inside the cells. On the other hand, at high frequencies, the bioelectrical current can penetrate all body tissues completely and flow through the extracellular and intracellular electrolyte solutions. The information obtained from this measurement allows clinicians to, for example, identify increased extracellular volumes due to fluid shifts [44].

Sodium bromide test: The anion bromide (Br^-) distributes deeply into extracellular fluids, but does not penetrate into the cells. The intravenous administration of sodium bromide and measure of the peak concentration gives information about the extracellular water volume [45].

Indocyanine green (ICG) test: ICG is a compound that rapidly binds to albumin once in the bloodstream, does not distribute to the extravascular or the intracellular water, and is entirely cleared by the liver. The intravenous administration of ICG and subsequent monitoring of the disappearance rate from blood gives information about intravascular (plasma) volume and hepatic function [46].

However, performance of these tests is not always possible at the bedside, and they are still predominantly restricted to research purposes. The daily determination of volume of distribution by clinicians is much more empirical, based on nature and severity of sickness, fluid balance, individual patient characteristics (age, weight, height), clinical management and concomitant medication known to alter volume of distribution.

Clinical Significance and Recommended Dose Strategies

Increases in the volume of distribution are likely to decrease Cmax and drug concentrations over-time. This can lead to potential underdosing, which will affect the attainment of pharmacodynamic targets linked with the desired effect and produce therapeutic failure. **Figure 1** illustrates how pharmacodynamics are dependent on pharmacokinetics. If pharmacokinetics are altered, there will be a subsequent effect on pharmacodynamics and, therefore, on the pharmacological effect. For drugs with

pharmacodynamics that are difficult to clinically measure, such as antibiotics, the determination of potentially increased volume of distribution is essential to guide appropriate initial dosing. Given that the primary site of most infections is the tissues, it is essential to administer initial loading doses that properly saturate the tissues in order to achieve therapeutic concentrations at the target site. For critically ill patients, there is compelling evidence on the importance of appropriate and early antibiotic treatment on patient outcomes [47]. Clinicians must take into account the clinical scenarios discussed above when prescribing in order to design the most appropriate dose regimen to achieve the best patient outcomes. For lipophilic drugs, initial dosing should be based on total body weight (TBW), as this accounts for the increased adipose tissue that is likely to increase the volume of distribution of these drugs. For hydrophilic drugs the use of lean body weight would be more appropriate, always taking into account the likely acute increases in volume of distribution associated with severe sickness and clinical management in the ICU. After volume of distribution has been used to guide initial dosing, data on drug clearance can be used to guide maintenance dosing.

Conclusion

Outcomes of drug therapy in critically ill patients are heavily dependent on achieving therapeutic concentrations in the target sites. There are compelling data that show that increments in the volumes of distribution of hydrophilic and lipophilic drugs are commonly found in critically ill patients. The impact of these larger volumes on drug pharmacokinetics are lower concentrations than expected, which can significantly affect the attainment of pharmacodynamic breakpoints in the target site and lead to therapeutic failure. It is of paramount importance that clinicians are aware of the constellation of scenarios likely to produce increases in volumes of distribution and choose the dose regimen and loading doses most appropriate for saturating this volume depending on the physicochemistry of each drug, in order to avoid underdosing and achieve the pharmacodynamic targets associated with therapeutic success. After tissue saturation has occurred, dosing based on known, or estimated, drug clearance can occur. It follows that volume of distribution and clearance are equally important determinants of drug dosing, but given the importance of effective initial therapy for critically ill patients, perhaps volume of distribution is more important than clearance?

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XVI Risk Stratification

Risk Stratification in Severe Sepsis: Organ Failure Scores, PIRO or Both?

R.P. Moreno, P. Metnitz, and P. Bauer

"*It's more important to know*
what sort of person this disease has,
than what sort of disease this person has"

William Osler 1849 – 1919

Introduction

The use of all-cause hospital mortality as the sole or major endpoint for the evaluation of clinical trials in intensive care was challenged in the mid 1980s, in the aftermath of a very long series of negative clinical trials in patients with sepsis, severe sepsis, and septic shock [1]. This outcome measure, until then viewed as the golden standard in clinical trials in intensive care, is, beyond any doubt, a very relevant endpoint both for researchers and for clinicians. Its use has been contested because hospital policy can and does change the location of deaths (e.g., discharging patients to the ward to die) and mortality rates can, therefore, be significantly underestimated in hospitals that discharge patients very early in the course of their disease to other facilities [2].

Moreover, the absence of stratification in the process of selecting two groups of patients, one assigned to receive the intervention under study and the other assigned to receive the placebo, has been criticized. The absence of stratification according to patient demographic or biological characteristics before randomization can often result in unbalanced groups and in the presence of confounding; an impossibly high number of patients would therefore need to be enrolled in order to demonstrate a significant difference between patient groups. Also, interactions between certain patient characteristics at baseline and the effect of treatment can be obscured, as happened in the Monoclonal Anti-TNF: A Randomized Clinical Sepsis (MONARCS) trial, in which the administration of afelimomab was able to lower circulating levels of tumor necrosis factor (TNF) and interleukin (IL)-6, accelerate the resolution of organ dysfunction, and reduce 28-day all-cause mortality but only in patients with elevated IL-6 levels at baseline [3].

For all these reasons, some investigators proposed at that time that patients should be stratified according to several factors, not all of them included in the American College of Chest Physicians (ACCP)/Society of Critical Care Medicine (SCCM) definitions of sepsis or sepsis syndrome. These included the use of a validated scoring system for organ dysfunction that could be incorporated into sepsis studies, such that major morbidities (and not only 28-day all-cause mortality) should be considered as primary end points [4].

Soon after the publication of the Protein C Worldwide Evaluation in Severe Sepsis (PROWESS) trial by Gordon Bernard and co-workers [5], the presence of several confounders and effect modifiers became evident. The most important of these was the baseline severity of illness and the site of infection [5, 6]. These potential confounders, in addition to later publications with discrepant results either in controlled [7] or uncontrolled settings [8, 9], have raised such a debate [10], that the

drug is now being assessed in a risk-stratified population, the so-called PROWESS-SHOCK study [11].

Results of the Corticosteroid Therapy of Septic Shock (CORTICUS) study, comparing the use of hydrocortisone with placebo in patients with septic shock, were published in 2008 by Charles Sprung and co-workers [12]. Again, baseline severity of illness and possibly other baseline- and infection-related factors played an important role in the interpretation of results. These factors could be responsible for the negative results of the intervention on all-cause 28-day mortality, compared to another study with almost the same design, but done in a cohort of more severely ill patients [13]. This effect is even more striking, because hydrocortisone, despite having no effect on all-cause 28-day mortality, did reduce the reduce the length of shock and the severity of multiple organ failure (MOF), specifically the amount of cardiovascular failure [14].

Authors, such as Petros and colleagues, questioned almost 15 years ago the adequacy of all-cause mortality as an endpoint [15]. A meaningful endpoint can only be chosen when a direct relation between an event and its consequences is known. In the case of sepsis (and MOF), our knowledge is very limited and no direct relationship can be established. Moreover, the use of this outcome variable without prior patient stratification implies the need for large samples to have a fair chance to achieve an adequate balance between groups, creating problems in reliability of data collection, heterogeneity of enrolled patients, duration of the trial, and associated costs. Patients in intensive care units (ICUs), even with very strict inclusion criteria for sepsis or septic shock, do not constitute a homogeneous sample. Patients have different ages, chronic illnesses (chronic health, comorbidities), diagnoses, time-courses, sites of infection and invading microorganisms, and are enrolled in trials with different degrees of physiologic dysfunction resulting in a large dispersion of mortality risks, as demonstrated in the mid 1990s [16, 17]. Several methods have been proposed by different authors to deal with such huge variation [17–19], but these usually lead to complex, extensive (and expensive) data collection systems and are thus not feasible.

Two approaches have been proposed and tested to cope in a more intuitive way with this complex problem of patient selection and stratification. This includes the development and validation of organ dysfunction scores (based on the presence and severity of organ dysfunction/failure in some organs and systems) and the so-called PIRO-scores.

Organ Dysfunction/Failure Scores

The awareness of the importance of evaluating and considering MOF as an important confounder and/or effect modifier in the evaluation of patients with sepsis lead the Working Group on Sepsis Related Problems of the European Society of Intensive Care Medicine (ESICM), under the leadership of Professor Jean-Louis Vincent, to organize in December 1994, in Paris, a consensus meeting to create the so-called sepsis-related (later renamed sequential) organ failure assessment (SOFA) score [20]. The rationale behind this decision was the need to find an objective and simple way to describe individual organ dysfunction/failure in a continuous form, from mild dysfunction to severe failure, that could be used over time to measure the evolution of individual (or aggregated) organ dysfunction in clinical trials on sepsis or for the clinician at the bedside. A retrospective evaluation of the application of this score to the first 24 hours in the ICU on 1,643 patients with early sepsis on an international

database was quickly published [20] and a very good relation between the aggregated score and mortality was reported with an acceptable distribution of the patients among the several groups (sepsis, severe sepsis, and septic shock). To confirm these retrospective findings, a prospective, multinational study was initiated.

Later on, with further analysis and derived knowledge, more complex measures have been built based on this concept, such as the total maximum SOFA score and the delta SOFA score (total maximum SOFA minus admission total SOFA, or the magnitude of organ dysfunction appearing during the ICU stay) and have been demonstrated to behave even better as descriptors and/or predictors of outcome in patients with MOF (most of them septic) in ICUs around the world [21].

Other similar systems were developed shortly thereafter, such as the Multiple Organ Dysfunction Score (MODS), developed by John Marshall et al. [22], and the Logistic Organ Dysfunction (LOD) System (LOD), developed by Jean-Roger Le Gall et al. [23]. All of these systems have been designed with similar principles in mind, as summarized by Jean-Louis Vincent [20]:

- organ failure is not a simple all-or-nothing phenomenon, it is a spectrum or continuum of organ dysfunction from very mild altered function to total organ failure;
- organ failure is not a static process and the degree of dysfunction varies with time during the course of disease;
- the variables chosen to evaluate each organ need to be objective, simple and available but reliable, routinely measured in every institution, specific to the organ in question, and independent of patient variables, so that the score can be easily calculated on any patient in any ICU.

Although there is no general agreement about the best system or the optimal way to use a certain system, all widely used systems include six key organ systems (cardiovascular, respiratory, hematological, central nervous, renal, and hepatic), evaluated through a combination of physiologic (e.g., PaO_2) and therapeutic (e.g., use of vasopressor agents) variables. The major difference among them is the method chosen for the evaluation of cardiovascular dysfunction: SOFA uses blood pressure and the level of adrenergic support, MODS uses a composed variable, the so-called pressure-adjusted heart rate (heart rate x central venous pressure/mean arterial pressure) and the LOD score the heart rate and the systolic blood pressure.

Mixed models, integrating organ failure assessment scores and general severity scores have been published as well [24, 25] but they never gained widespread acceptance.

From Multiple Organ Dysfunction/Failure Scores to the PIRO Concept

In 2001, several European and American critical care societies organized a second International Consensus Conference to address the weaknesses of the existing systemic inflammatory response syndrome (SIRS) and sepsis definitions, that have been discussed over the past decade [26]. The aim of that Conference was to further improve the early identification and stratification of patients with sepsis [27]. The result of this conference was the adoption of systemic inflammatory response syndrome as a broader definition of inflammation.

Furthermore, minor changes were added to the definition of severe sepsis and septic shock. A new system for risk stratification, that had emerged from the Fifth

Toronto Sepsis Roundtable, held in Toronto, Canada in October 2000 [28] was also adopted, the IRO system (insult, response, and organ dysfunction), which was now called PIRO (with the addition of predisposition) [29–32]. Although interesting and promising, this approach remained up to now virtually conceptual, with results of a first attempt to develop such a system in a small population published in 2004 [33].

In the last few years, our research group empirically tested, using a large multicenter, multinational database – the SAPS 3 database [34] – whether a modified definition of PIRO (using the concept of predisposition, infection and organ dysfunction/failure) could be useful for predicting mortality in patients with severe infection, sepsis and septic shock at ICU admission. In this cohort (comprising 16,784 patients from 303 ICUs), 3,505 patients already had an infection on ICU admission of which 2,628 had a length of stay in the ICU equal to or greater than 48 hours.

To test the PIRO concept, three different logical boxes were defined:

- Predisposition: The variables of the SAPS 3 Admission Score Boxes 1 and 2, which are not related to infection, were used. These include age, comorbidities, use of vasoactive drugs before ICU admission, intrahospital location before ICU admission, length of stay in the hospital before ICU admission, reason(s) for ICU admission, planned/unplanned ICU admission, surgical status at ICU admission and, if applicable, the anatomic site of surgery.
- Injury: For this box, all variables related to infection at ICU admission were used. These include acquisition of the infection, extension and site of infection, the presence of bacteremia and the microbial agents identified.
- Response: To identify the response to infection, we used the development of organ dysfunction and failure, measured as the highest SOFA score values for each organ system between 24 and 48 h after ICU admission.

These variables were selected according to their association with hospital mortality as described elsewhere and a multilevel model (logistic regression with random effects) was applied to the data, using patient characteristics as fixed effects and ICUs as a random effect, to estimate the impact of each of the analyzed variables on the outcome variable [35]. In the multivariate analysis, the variables that turned out to be significant were:

- Predisposition (Box 1): age; location from which the patient was admitted to the ICU; comorbidities; length of stay before ICU admission (days); and some reasons for ICU admission;
- Injury (Box 2): acquisition of infection; extension of infection; site of infection; and infective agent;
- Response (Box 3): dysfunction of the renal and coagulation systems; failure of the cardiovascular, respiratory, renal, coagulation and central nervous systems

Based on their contribution to outcome, a score sheet was developed (**Table 1**) and an equation relating the SAPS 3 PIRO score to the vital status at hospital discharge was created:

$$\text{logit} = -46.6757 + \ln(\text{PIRO}+76.7688) \times 9.8797$$

with the probability of hospital mortality being given by the equation:

$$\text{Probability of death} = \frac{e^{\text{logit}}}{1 + e^{\text{logit}}}$$

The prognostic performance of the developed model was tested by means of discrimination and calibration and found to be excellent, both in the overall population

Table 1. Score sheet for the computation of SAPS 3-PIRO. Adapted from [35] with permission.

BOX 1: Predisposition	**0**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**14**	**16**
Age, years	<40	>=40 <60				>= 60 <70			>=70 <75	>=75 <80	>=80
Location from which the pat. was admitted to the ICU		Same hospital									
Co-Morbidities				Cancer [1)]		Cirrhosis [2)]	AIDS [3)]				
Length of stay before ICU admission, days	<14		>=14 <28		>=28						
Reason(s) for ICU admission							Cardiac arrest [4)]				
BOX 2 : Infection	**0**	**4**	**5**		**7**	**8**	**9**	**10**	**11**	**14**	**16**
Acquisition		Nosocomial [5)]									
Extension		Other than localized [6)]									
Site			Respiratory [7)]								
Agent								Candida, Fungi [8)]			
BOX 3: Response	**0**	**4**	**5**		**7**	**8**	**9**	**10**	**11**	**14**	**16**
Organ dysfunction (OD) [9)]		Renal	Coagulation								
Organ failure (OF) [10),11)]			Cardiovasular Respiratory				CNS Coagulation Renal				

1) *Cancer* refers to the data definitions in Appendix C of the ESM [35]: Co-Morbidities: Metastatic Cancer, Haematological Cancer, Chemotherapy, Immunosupression other, Radiotherapy, Steroid treatment
2) *Cirrhosis* refers to the data definitions in Appendix C of the ESM [35]: Co-Morbidities: Cirrhosis.
3) *AIDS* refers to the data definitions in Appendix C of the ESM [35]: Co-Morbidities: AIDS
4) *Cardiac Arrest* refers to the data definitions in Appendix C of the ESM [35]: Reasons for ICU Admission: Cardiovascular – Cardiac Arrest.
5) *Nosocomial* refers to the data definitions in Appendix C of the ESM [35]: Acute infection at ICU admission – Acquisition: Hospital-acquired.
6) *Other than localized* refers to the data definitions in Appendix C of the ESM [35]: Acute infection at ICU admission – Localized infection with regional involvement, Dissiminated.
7) *Respiratory* refers to the data definition in Appendix C of the ESM [35]: Acute infection at ICU admission – Site: Lower respiratory tract: Pneumonia, Lung abscess, other.
8) *Candida, Fungi* refer to the data definitions in Appendix C of the ESM [35]: Acute infection at ICU admission – Agent and -Bacteremia: if any of the following was present in any of the fields: Candida albicans; Candida, spp, other; Fungi, other;
9) If the maximum SOFAvalue of dayl and day 2 is 1 or2
10) If the maximum SOFA value of dayl and day 2 is 3 or 4
11) With multiple items the points are additive.

and in specific subgroups of patients, as defined by the ACCP/SCCM classification of sepsis and septic shock [35].

It should be noted that in this system, as described in the original publication, the evaluation of the Response and the resultant Organ dysfunction/failure were collapsed. This happens because, in our understanding, the host response to the insult and the resulting organ dysfunction cannot be distinguished from each other based on clinical variables. Effectively there are no specific biomarkers available and ready for such use. Altogether, this resulted in the proposed three-level staging model consisting of predisposition, injury and response. We can anticipate that, as new biomarkers or panels of biomarkers become available in the future we might be able to differentiate true biological response from the physiological consequences of that response, i.e., the organ dysfunction and/or failure.

More recently, Francesca Rubulotta and co-workers published a similar attempt to derive a PIRO score from a retrospective analysis of two international databases of patients with severe sepsis and septic shock, the placebo-treated patients from a phase III clinical trial of patients with severe sepsis (PROWESS), and the global severe sepsis registry, PROmoting Global Research Excellence in Severe Sepsis (PROGRESS) [36]. The score considers the 4 dimensions of PIRO, assigning 0 to 4 points to each of the dimensions. To the best of our knowledge this system has not been used outside the original database and presents the same conceptual problem in distinguishing the response of the organism to the insult (infection) and the resultant organ dysfunction/failure, since different manifestations of the same physiopathological mechanism are considered under the two different constructs (e.g., tachycardia is considered a 'response' and 'hypotension' an organ dysfunction/failure, while both relate to the same phenomenon, i.e., vasodilation).

Should We Have One PIRO Or Many PIROs?

Jordi Rello and the Intensive Care Group from Tarragona have recently analyzed the problem of PIRO from a different perspective: Instead of lumping all causes of sepsis together, regardless of the site of infection, they decided to construct a PIRO for each major site of infection. This approach resulted in two different models: one for ventilator-associated pneumonia (the VAP-PIRO) [37] and the other for community acquired pneumonia (the CAP-PIRO) [38]. Both systems are very simple and share common characteristics:

- Developed in cohorts of patients with a single type of infection (respectively community-acquired pneumonia requiring ICU admission and ventilator associated pneumonia);
- Both are computed at 24 hours after ICU admission;
- Both use a simple scale comprising just a few variables (8 for CAP-PIRO and 4 for VAP-PIRO), derived by multivariate logistic regression with outcome at 28 days after ICU admission (CAP-PIRO) or vital status at ICU discharge (VAP-PIRO) used to selected the variables, from a list of disease-specific variables for each disease, resulting in different variables (and different weights for common variables) in the two models;
- Both divide the patients into a few levels of risk (4 for CAP-PIRO and 3 FOR VAP-PIRO);
- Neither provide the user with a quantitative estimate of vital status at hospital discharge.

These systems have the advantage of being easy to compute and more specific for the risk factors of CAP and VAP. The price paid is that they loose the ability to be applied to more heterogeneous cohorts with severe infection, sepsis and septic shock, including patients with other infections (e.g., intra-abdominal, central nervous system or urinary tract infections), that constitute a significant number of severe infections in the ICU [12, 35]. Moreover the development of these scores was done in small, national datasets and the extent of their utility and performance outside the development demographics is still unknown.

Should we use PIRO or MOF Scores?

The prevalence of severe sepsis and septic shock in the ICU seems to be increasing. This fact has been consistently reported in recently published studies [39–42]. This trend might partially be explained as a result of initiatives such as the Surviving Sepsis Campaign [43] which have increased physician awareness for early recognition and treatment of sepsis. However, an increasing incidence of sepsis was present well before these initiatives and, thus, other reasons, such as the changing demographics of the population (increasing age, comorbidities) and changing characteristics of the microorganisms (prevalence, resistance), are more likely responsible for this phenomenon.

Outcome from sepsis in terms of mortality is not only associated with the presence and amount of organ dysfunction/failure developed either before or after ICU admission [21, 42, 44, 45]. Other factors also seem to play an important role, for example the place of acquisition (nosocomial versus community-acquired) [42, 46] and characteristics of the infection itself (site of infection, microorganisms involved, or extension of the infection) [47, 48]. Consequently, to reduce the evaluation of severe infection and sepsis to the evaluation, quantification and time-course of MOF can be called a reductionistic approach which will lead to a loss of important information [21, 49, 50].

In a recently developed general outcome prediction model, pre-existing conditions (in other words, predisposition) were responsible for almost half of the explanatory power of the model [51]. In the specific model developed for severe infection and sepsis (SAPS 3-PIRO), this value also remained very high (44.8 %) [35]. Although the sampling space of both models is different, which prevents definitive comparisons between them [52], this finding provides evidence that exclusive use of physiological variables in this context is inappropriate: In both models (SAPS 3, SAPS 3-PIRO) the explanatory power of physiological data alone was low (27.4 % in the general model and 35.3 % in the sepsis model). For these reasons, we believe that future models should be based on an approach similar to the SAPS-PIRO. In addition, such attempts could be complemented by:

- The incorporation of genetic markers, based on DNA, able to quantify the risk of progression of the infection, to drive the choice of the most appropriate therapy to a given patient.
- A better distinction between risk factors for progression of infection and risk factors for death, since we know that there might be differences [48];
- A better distinction between general risk factors for sepsis and mortality to be used in all patient cohorts and specific risk factors for sepsis and mortality to be used in specific infections;
- The incorporation of biomarkers (or panels of biomarkers) to detect and measure the response;

- The incorporation in the evaluation of the response of markers to quantify the probability of the patient to respond to a given therapy (given the nature of the patient and the specificities of the infection), at a given point in the evaluation of the disease;
- An increase in the window for follow-up of the course of organ dysfunction/failure, allowing a better evaluation of the course of the disease, based mainly on the sequential evaluation of the presence and amount of organ systems failure.

Such an extended evaluation would allow an earlier evaluation of risk (that could drive the use of preventive or pre-emptive therapies). Moreover, specific therapies could be specifically targeted at the insult and adapted according to the pattern of response. Finally, a better use of organ support and replacement therapies in patients with severe infection, sepsis, and septic shock could be a result of this approach.

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XVII Critical Care Outreach

On the Response to Acutely Deteriorating Patients

S. Mukherjee and S.J. Brett

Introduction: The Deteriorating Patient

An aging population, increasingly complex surgical procedures and yet shorter inpatient stays has led to much a greater proportion of significantly ill patients within the in-patient population [1]. Such patients may benefit from input from critical care, hence the need for expansion of critical care beyond the traditional physical boundaries of high dependency and intensive care units [1]. Thus, in the United Kingdom the levels of care are now defined as follows [1].

- Level 0: Patients whose needs can be met through normal ward care in an acute hospital
- Level 1: Patients at risk of their condition deteriorating, or those recently relocated from higher levels of care, whose needs can be met on an acute ward with additional advice and support from the critical care team
- Level 2: Patents requiring more detailed observation or intervention including support for a single failing organ system or postoperative care and those 'stepping down' from higher levels of care
- Level 3: Patients requiring advanced respiratory support alone or basic respiratory support together with support of at least two organ systems. This level includes all complex patients requiring support for multi-organ failure.

Deterioration in a patient's condition can occur at any stage, although may be more likely during the onset of illness, during surgical or medical interventions, and during recovery from critical illness. The timely detection of such deterioration and the delivery of remedial measures remains a challenge

Sub-optimal Care

Outcome is a complex function of age, surgical or medical status, elective or emergency presentation, co morbidities, physiological reserve, nature of severity of acute illness, and quality of care. The quality of care and the early identification of severity of illness and effective management ought to be in the control of clinicians [2]. However, there is a substantial and consistent body of evidence suggesting that management of airway, breathing, circulation, oxygen therapy, and monitoring before admission to intensive care units (ICUs) has been sub-optimal [3]. A large proportion of patients are referred to intensive care late in the clinical course of their illness, many having suffered cardiac arrest [4]. Frustratingly, observation charts often show clear evidence of deterioration, which might have triggered earlier action [5].

The reasons for such sub-optimal care have been identified as serious deficiencies in communication between acute medical and critical care services, lack of awareness by medical staff of the worsening condition of their patients [6], failure to seek timely advice, and lack of knowledge and skills [3] of staff to recognize and react appropriately. A significant number of admissions to critical care could have been avoided by timely referral and intervention by critical care staff. One study estimated that this sub-optimal care may have contributed to one third of the deaths that occurred [3]. Acutely deteriorating patients experience a mismatch of resources to needs and hospitals have been encouraged to implement a response based system based on an afferent limb 'crisis detection', a 'response triggering' mechanism, and an *efferent limb*, a 'rapid response team' or similar [7]. Studies comparing events and outcomes with or without involvement of a 'Patient At Risk Team' showed early advice and active management may prevent the need for cardiopulmonary resuscitation (CPR) and may improve outcomes [8].

'Track and Trigger' Mechanisms

There is evidence to show that a majority of adverse events (deaths, cardiac arrests and unplanned ICU admission) is preceded by documented abnormal physiology, the commonest being decrease in Glasgow Coma Score, hypotension [4], and change in respiratory rate [8].

One might think early identification of patients at risk, both before admission and after discharge from the ICU, may facilitate early treatment and decrease mortality [9]. A NCEPOD (National Confidential Enquiry into Patient Outcome and Death) report (a nationwide audit from the UK) suggested that the majority (66 %) of patients who have been in hospital for more than 24 hours prior to ICU admission had exhibited physiological instability for more than 12 hours [5]. Others have shown a significant increase in mortality as the number of abnormal physiological variables increase [10].

In pre-critical care settings, physiological 'track and trigger' warning systems are used to identify patients who are at risk of deteriorating clinically. These are usually derived from routine vital sign observations and if implemented properly should be a tool to ensure early recognition of clinical worsening and the initiation of timely intervention from appropriately experienced medical staff. Such systems include periodic observation of pre-set physiological parameters and pre-determined response criteria. The types of track and trigger and response algorithm vary, and include, e.g., Patient at Risk (PAR) score [8], (Modified) Early Warning Score (MEWS) [11], Assessment Score for Sick patient Identification and Step-up in Treatment (ASSIST) [12], and locally devised scores.

Track and trigger systems may be classified as follows [13]:

- Single parameter system: Periodic observation of selected vital signs which are compared with a simple set of criteria with predefined thresholds, with a response algorithm being activated when any criterion is met
- Multiple parameter system: Response algorithm requires more than one criterion to be met or differs according to the number of criteria met
- Aggregate scoring system: Where weighted scores are assigned to physiological values and compared with predefined trigger thresholds
- Combination system: Involving single or multiple parameter systems in combination with aggregate weighted scoring systems

Single parameter systems have been used extensively in the Medical Emergency Team (MET) approach adopted in Australia [14]. In the UK, most hospitals favor using the weighted aggregate scoring system [13] and these are usually some form of modified early warning system. In the USA, the Rapid Response Team concept uses track and trigger systems as a key component of the Institute of Healthcare Improvement 100,000 Lives Campaign [15].

Being a single parameter system, the MET has been shown to be simpler and more reproducible than the ASSIST and the MEWS but does not enable monitoring of clinical progress [13]. MEWS is more complex, taking into account urine output and relative changes in blood pressure; ASSIST is a simplified version of MEWS with only four parameters and an age-constant; both ASSIST and MEWS allow monitoring of clinical progress, and are representative of the wide range of track and trigger systems in use [13].

Systematic reviews have shown that the variety of published track and trigger systems in use have little rigorous evidence of validity [16]. Sensitivities and positive predictive values were unacceptably low but they had acceptable specificity and negative predictive values. The low sensitivity may be partly due to the rapid deterioration of patients, infrequent non-standardized measurement of physiology and varying trigger thresholds. Sensitivities can be improved by reducing these thresholds but at the cost of specificity and potentially increased workload.

In the absence of level 1 evidence, those considering introduction of a track and trigger system may seek a mechanism that is tailored to their local needs [16]. It is important to bear in mind that track and trigger systems should only be used as an adjunct to clinical judgment and staff must be trained and supported to use them [13].

Role of Critical Care Outreach Services

A proposal to extend critical care outside the physical walls of the ICU resulted in the evolution of critical care 'outreach'. Outreach has three essential objectives [1]:

1. To avert or facilitate ICU admission by identifying deteriorating patients in a timely manner and intervene to ensure the best outcome.
2. To enable discharges by supporting the continued recovery of the discharged patient.
3. To share critical care skills with staff in the ward and impart appropriate training and awareness.

The graded response strategies for an identified deteriorating patient in medical, surgical and emergency wards would be as follows. First, initiation of a ward level response by increased frequency of physiological monitoring, second an urgent call to a team with primary medical responsibility for the patient, and third the involvement of a dedicated hospital team competent in acute medicine and critical care.

A predominantly nurse led Critical Care Outreach Team (CCOT) runs in the UK, although often with physician or physiotherapist support. Alternative models have more integral physician membership, such as the Patient At Risk Team (PART) in the UK [8], METs [14] in Australia and Rapid Response teams in the USA [15]. Similar team services are now rapidly emerging across Europe. The first Consensus Conference [7] on METs, held in the USA in 2005, concluded that hospitals should implement the MET approach.

Two good quality cluster-randomized controlled trials (RCTs) with level 1+ evidence show conflicting outcomes of the outreach/response team concept. The MERIT study [17] by Hillman et al. was conducted in Australia using a MET with a single parameter track and trigger system; the study included 23 hospitals over a period of six months. These investigators showed a significant increase in call out to the MET after the introduction of the system, but no difference in the incidences of cardiac arrest, unplanned ICU admissions or unexpected deaths.

The other study [18], also a cluster-RCT, was set in an acute hospital in England using a nurse lead CCOT with a multiple parameter track and trigger system making up the PAR score [8]. The results showed significant reduction in hospital mortality with involvement of CCOT but a non-significant increase in hospital length of stay.

A prospective large cohort study [19] of adult patients was performed by Chan et al. in a tertiary hospital at Kansas City Missouri where standard activation criteria for a Rapid Response Team were used. The study did not show any reduction in hospital wide cardiac arrest or mortality rates after implementation of the Rapid Response Team. However, other work has indicated an improvement in survival to discharge from hospital and reduced readmission rates to critical care with the introduction of CCOT [20].

A large observational study by Gao et al. in England [21] showed a reduction in the number of patients undergoing CPR before admission to intensive care but no effect on unit mortality.

A systematic review by Esmonde et al. [22] and a subsequent Cochrane review [23] on the impact of outreach services highlighted similar issues of poor quality research and lack of evidence to support the outreach concept. Based on the fact that there are only two good quality RCTs available with conflicting outcomes, no strong recommendations can be made based on the available evidence. However, with the introduction of similar services in Sweden, Netherlands, Italy, Portugal, and the USA, further data regarding the impact of outreach services will become available for consideration. A broad range of process and outcome measures is recommended to evaluate the impact of outreach [7].

Educational Tools

There is some evidence that simple educational training tools imparted to a large number of front line staff empowers action [24]. The recognition of the fact that averting patient deterioration to cardiac arrest is as important as treating the cardiac arrest, has led to advances in resuscitation training which emphasize both recognition of impending cardiac arrest and its treatment. The Immediate Life Support (ILS) course [25] and the Acute Life-threatening Events-Recognition and Treatment (ALERT™) course [26] provide a wide range of healthcare professionals with the competence to recognize acutely ill patients before cardiac arrest, as well as the core resuscitation skills.

A six-year prospective audit [24] of 3,126 in-hospital emergency calls within a multi-site 1,200 bed London teaching hospital following the organization-wide adoption of the ILS course was conducted. The observation showed a reduction in the proportion of emergency calls for cardiac arrest ($p < 0.0001$; from 85 % in 2002 to 45 % in 2007) a corresponding increase in the proportion of 'pre-arrest' calls ($p < 0.0001$; from 15 % in 2002 to 55 % in 2007), a reduction in deaths at cardiac

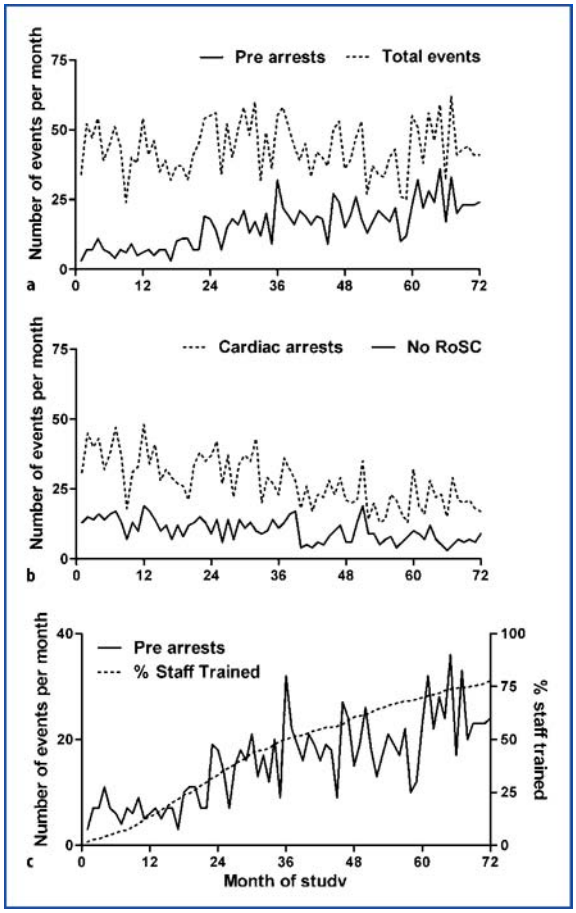

Fig. 1. Results from a six-year (January 2002 to December 2007) prospective audit of 3,126 in-hospital emergency calls in a London teaching hospital following the organization-wide adoption of the Immediate Life Support (ILS) course [24]. a) Monthly numbers of all in-patient emergency alert calls (dashed line) and pre-arrest calls (solid); b) Monthly numbers of in-patient cardiac arrests (dashed line, this includes events which were full cardiac arrests from the start and pre-arrest calls which proceeded to full cardiac arrests), and events during which a resuscitation attempt took place but without achieving return of spontaneous circulation (RoSC, solid); c) Monthly numbers of pre-arrest calls (solid line, left hand y-axis) plotted with the percentage of workforce who were ILS trained (dashed line, right hand y-axis). Modified from [24]

arrest ($p = 0.0002$), and an increased survival to hospital discharge from an emergency call from 28 % in 2004 to 39 % in 2007 (**Fig. 1**).

The above study [24] is an example of how a simple and widespread educational program, which is easy to implement, and is inexpensive with high uptake amongst healthcare professionals can influence behavior within the institution and reduce the number of in-hospital cardiac arrests and of unsuccessful CPR attempts. Although a positive study, identifying the critical nature of a patient's condition just proximal to a cardiac arrest still seems rather late and presents a clear opportunity for improvement; the key message seems to be around balancing complexity of concept with simplicity of introduction and retention. Perhaps for some things, broad but relatively shallow coverage is better than deep coverage which can be delivered to only a few.

Use of Technology as a Tool to 'Track and Trigger'

Continuous monitoring of cardiorespiratory variables by nursing staff at a central station or periodic bedside direct inspection potentially reflects an inefficient use of

human resources. Moreover, targeting a single variable anomaly may be inefficient and insensitive; early signs of patient compromise might be identified by combining multiple parameter changes [27]. Monitoring systems that integrate data from multiple physiologic sources may more efficiently identify patients at risk [28]. Although early warning scores can identify unstable patients earlier [29], such non-automated systems still require direct and intermittent data collection and calculation and are thus vulnerable to error. Although clinical judgment and experience cannot be substituted by automation, the use of technology in identifying 'at-risk' patients may confer accuracy and speed of early identification. With the advent of new technology, 'intelligent' systems, surveillance, and hand-held electronic devices are emerging; however, proper evaluation is required before widespread deployment as introduction of technology into a 'human factors' dominated environment may have unanticipated consequences.

A recent observational study [30] showed that the use of an automated monitoring system in a surgical step-down unit resulted in the mean time of identifying a MET triggering condition being 6.3 hours earlier than previously. A patient monitoring system called the Bio Sign IMS (Integrated Monitoring System) was used to produce a single parameter, called the Bio Sign Index, from five input vital signs (heart rate, respiratory rate, blood pressure, pulse oximetry [SpO_2] and temperature). The generated Bio Sign Index ranged from 0 (no abnormalities) to 10 (severe abnormalities in all variables). A Bio Sign Index of 3 or greater was deemed to reflect significant cardiorespiratory instability requiring medical attention [30]. A Bio Sign Index of 3 or greater can still occur even when no single vital sign parameter is outside the range of normal if their combined patterns are consistent with an instability pattern. Thus, continuous non-invasive monitoring augmented with integrated information from multiple variables provides a more sensitive and faster means to detect cardiorespiratory instability [31].

Human Factors

The establishment of apparently robust outreach and emergency response systems can have unanticipated consequences, usually related to human factors. One of the authors (SB) was an external expert at a review of some adverse episodes that occurred at a large well-organized teaching hospital, enquiring into some unanticipated deaths. In spite of apparently robust systems, a number of important contributory factors were identified:

1. The availability of outreach services encouraged over reliance on these systems and allowed poorly motivated on-call medical staff to duck their responsibility.
2. Outreach services do not have embedded diagnostic capacity, yet were relied on to respond and generate a management plan, a task for which they were ill equipped.
3. Out of hours there was a lack of clarity over who was responsible for the care of deteriorating patients when identified; this confusion leading to lack of 'ownership' of such patients.
4. The European Working Time Directive has mandated on-call systems associated with multiple shift handovers; these handovers, unless supervised by very senior staff, were an opportunity for information to be lost, and for a lack of continuity of plan and responsibility to creep in.

5. Research staff who had been recruited primarily for their research capacity via a casual mechanism and were poorly integrated into the clinical life of the hospital, had on-call responsibilities. They had a poor understanding of how to generate the rapid action often needed to avert impending critical illness or disaster.

The lesson here is that the introduction of outreach or emergency response systems is the equivalent of starting a complex intervention and one needs to be open-minded about the possibility of unanticipated consequences, and ensure that a thorough watch is kept for this. Senior night nursing staff are often good sources of information.

Conclusion

It seems odd that the introduction of early warning scores, outreach, rapid response teams, etc., has not produced unequivocal evidence of benefit – why? Perhaps the answers lie in a better understanding of how these concepts function when translated from paper to the clinical arena, and are challenged by the addition of humans, both patients and staff. It may be that ambitious plans do not work because of a tendency for diminishing returns for complexity and unanticipated negative consequences; both concepts hard to quantify.

Taken overall we would contend that there is evidence that system and human behavior can be changed to produce better outcomes for patients. However, we would further conclude that the introduction of system change and novel technological propositions are evaluated thoroughly before widespread adoption and investment, much the same as we would expect for new drugs or surgical procedures.

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Identifying Cardiorespiratory Insufficiency Outside the ICU

M.R. Pinsky and M. Hravnak

Introduction

The pressure to increase intensive care unit (ICU) bed availability continues to grow as the need to streamline patient throughput in acute care facilities intensifies across the world. Thus, patients with higher illness acuity levels are transferred from ICUs and into step-down units for continued monitoring via non-invasive monitoring tools. These non-invasive tools include electrocardiography, automated sphygmomanometer and pulse oximetry to give estimates of heart rate (HR) and respiratory rate (RR), blood pressure (BP) and peripheral arterial oxygen saturation (SpO_2), respectively.

However, it is not known if such step-down unit non-invasive monitoring and associated protocols identify cardiorespiratory instability accurately for a variety of reasons. First, it is not clear how often mandated continuous monitoring is actually applied in these patients. Although often ordered as continuous, non-invasive monitoring devices are rarely operational 24 hours a day even in dedicated monitoring units. Second, the incidence of clinically relevant cardiorespiratory instability in this population is unknown. Although acutely ill ICU patients often display cardiorespiratory dysfunction and indeed have this characteristic as a qualification for ICU admission, step-down unit patients are presumed to be more stable with only a tendency for instability; how much instability is unknown. Third, in those step-down unit patients who do develop cardiorespiratory instability requiring acute medical intervention, it is not clear if their instability occurs rapidly, as may occur with the expression of an arrhythmia, progressively, as may occur with respiratory failure, or episodically. These factors would affect the efficiency of step-down unit bedside monitoring to detect their occurrence. Finally, present monitoring uses individual hemodynamic variables and does not consider patterns of cardiorespiratory variable response usually present with specific types of disease, such as acute respiratory failure, heart failure or sepsis.

Clearly, identification of cardiorespiratory insufficiency in lesser acuity units, such as step-down units is problematic and potentially of great medical importance. Cardiorespiratory instability that is not recognized promptly and acted upon in order to prevent death constitutes failure-to-rescue [1]. The failure-to-rescue risk is lowered when instability is recognized quickly and treated aggressively [1]. Likewise, the failure-to-rescue risk increases when deleterious changes in patient status occur but are not recognized early or if the interventions chosen are not correct [2, 3].

The earlier that cardiorespiratory instability in acutely and critically ill patients is recognized and acted upon, the less negative is the impact on patient outcome. At the present time, single-channel vital sign monitoring is the standard for detecting

instability, identifying it as such appropriately, and then applying appropriate interventions in order to prevent failure-to-rescue [4]. For the purposes of this discussion, vital signs include HR, RR, BP, temperature and SpO_2, all of which can be monitored non-invasively using readily available bedside monitoring devices. Nevertheless, even when single parameter vital sign monitoring occurs continuously and with increasingly sophisticated levels of technology, failure-to-rescue can only be fully improved when clinicians utilize monitoring information to detect the change in status, process information from multiple sources to identify probable cause, select the appropriate intervention(s), and evaluate effectiveness [5].

Non-invasively acquired vital signs are usually displayed on bedside monitors. In many step-down units these vital signs are also forwarded to a central station, but are not generally overseen by dedicated personnel. These monitoring data are observed by nurses who usually manage caseloads of 4–6 patients. Thus, recognizing acute cardiorespiratory instability can be difficult, and marshaling the appropriate caregivers and equipment to support these patient situations even more so.

There are recent descriptions of a systematic rapid-intervention intensive-care based program (the Medical Emergency Team or MET), usually triggered by recognition of abnormalities in non-invasively acquired monitoring variables, to respond early in the course of instability in non-ICU patients. MET availability can prevent adverse events [6, 7]. However, MET functionality requires afferent activation, as staff must first perceive and then process the achievement of MET activation (triggering) criteria [8]. Thus, a primary aspect of the use of MET is that monitoring of patient instability is both accurate and acknowledged prior to severe cardiorespiratory insufficiency and associated end-organ sequelae. The subsequent efferent MET system is completely dependent on this sensing arm. Even when Rapid Response Systems and METs are utilized to support critically unstable patients, their utilization is totally dependent upon instability being first detected and recognized.

Existing Non-invasive Cardiovascular Monitoring is Ineffective at Identifying Instability In Step-down Units

We prospectively studied the degree to which non-invasive monitoring of single variables are used and identify cardiorespiratory insufficiency, as defined by activation of nursing care and/or MET activation [9]. We obtained data from 326 monitored patients representing all patients admitted to the step-down unit over an 8-week period. Defining monitoring hours as times when any electronic vital sign parameter was recorded singly or in combination, a total of 18,248 hours were captured. SpO_2 monitoring was absent in 30 % of the monitored hours, despite the care standard for continuous monitoring. We observed a lesser degree of missed variable monitoring for HR (4.8 %) and RR (7.9 %). We made several primary observations from our data set.

First, most step-down unit patients were stable for their entire step-down unit stay, and even those who had episodes of instability were stable most of the time. Fully 75 % of all monitored patients had no episodes of cardiorespiratory insufficiency. Of the 25 % of patients who demonstrated instability, the instability was episodic and often progressive, interposed with periods of normal vital signs and occasionally ending in cardiovascular collapse. Thus, the continuous monitoring of central station multi-patient outputs is an inefficient and ineffective way to identify cardiorespiratory insufficiency.

Second, in a continuous single-parameter monitored environment, cardiorespiratory instability was undetected and undertreated 83 % of the time. Fully half the severe cardiorespiratory events, as defined by blind retrospective review by a senior intensivist, were not identified nor acted upon despite single variable alarms being activated at the bedside. In essence, the alarms became part of the acoustic wallpaper and desensitized the nursing staff to act upon their activation.

Third, cardiorespiratory instability that reached MET activation thresholds occurred in different patterns. Clinically significant cardiorespiratory instability in a step-down unit frequently goes unnoticed, is generally a process that occurs over time, not an acute-onset event, and is multiparameter in nature. In our study, in those 7 patients in whom the MET was activated for cardiorespiratory reasons, the average time when they reached an instability above which an integrated monitoring system (IMS) alarm would have gone off was 6.3 hours before the activation occurred.

Although these data imply that having integrated monitoring system triggers that incorporate all vital signs available to nursing services may improve earlier recognition of patient instability, we did not address this point directly. Our study merely documented that an extreme potential for earlier recognition exists [9]. This point is characterized by the continuous vital sign display of one subject who eventually had MET activation for cardiorespiratory insufficiency (**Fig. 1**). In this example from our dataset, the patient starts out as being stable until 06:00 (A) when the RR gradually

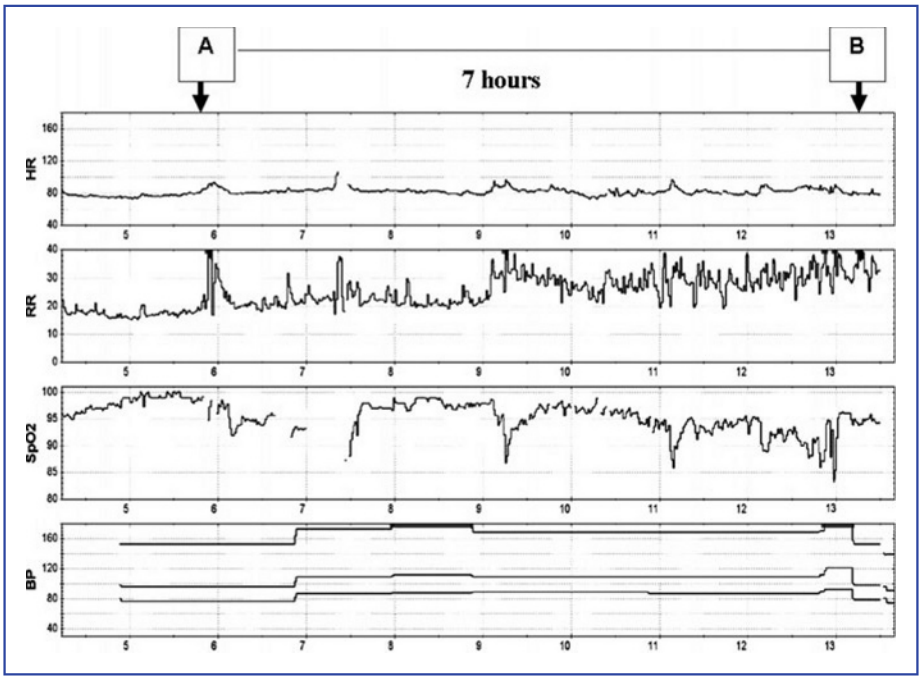

Fig. 1. Dynamic multi-parameter time series of heart rate (HR), respiratory rate (RR), pulse oximeter O_2 saturation (SpO_2) and blood pressure (BP) over a 10 hour interval in a patient experiencing repeated cardiorespiratory insufficiency, which was first observed at time point A but was not responded to by MET activation until time point B, fully 7 hours later.

increases. Progressively, RR trends upward, the SpO_2 gradually trends downward (with occasional dips), and the systolic BP remains high. The MET was not activated until 13:29 (B), or 7 hours after instability onset. This case illustrates that early instability is frequently characterized by subtle deviation of several vital signs simultaneously, and that the degree of noted abnormality waxes and wanes as patients attempt to apply compensatory mechanisms that cyclically correct and fail until the ability to compensate is exhausted and persistent severe instability ensues.

Instability onset is, therefore, gradual without a clear, prospectively defined onset point, and the subtle and multiparameter contributions can make treatment decisions, including a call for help, difficult, particularly in the hands of non-expert clinicians.

Integrated Monitoring Systems to Monitor the Monitors

A major challenge is to develop initiatives to improve the ability for nurse and physician clinicians to detect and treat patients with acute onset cardiorespiratory instability at a higher level of expertise, resulting in primary endpoints of increased frequency of return to stability and decreased duration of instability. The potential impact of such a process is great. The target community includes two groups. First, it includes all acutely and critically ill hospitalized patients. Second, it includes the front-line nurses and physicians responsible for the bedside care of such patients. According to the American Hospital Association, there are 945,199 total staffed beds in all USA registered hospitals, of which 90 % are non-ICU designated. Even though the standard of care for hospitalized patients increasingly calls for non-invasive monitoring with continuous but separate monitoring of vital signs, the development of unrecognized cardiorespiratory instability is still ubiquitous [10].

In our study described above in the step-down unit monitored environment, about 25 % of patients developed instability, but that instability may not be detected at an early stage in up to 85 % of those affected. Consequently, the potential of using standard step-down unit monitoring information to intervene early in the course of instability is not realized. In fact, patients on a step-down unit remain seriously unstable for an average of 6.3 hours before a call for emergency help is made [9].

In looking at our existing repository of clinical monitoring data, we have also observed, not surprisingly, that acute step-down unit cardiorespiratory instability seems to aggregate into a surprisingly parsimonious set of multiparameter presentation clusters described in **Table 1**. Importantly, these patterned responses should be useful in creating identification rules to define the etiology of cardiorespiratory insufficiency so that directed alerts and management protocols can be rapidly instituted.

Table 1. Patterns of acute changes in non-invasive monitoring variables during cardiorespiratory deterioration in a step-down unit

Pathophysiology	Heart rate	Respiratory rate	SpO_2	Blood pressure
Hypovolemia	↑	↑	↔	↓
Hypoxemia due to impaired O_2 uptake	↑	↑	↓	↔
Hypoxemia due to hypoventilation	↑	↓	↓	↔
Cardiac arrhythmia	↑&↓	↔	↔	↑&↓
Pain, agitation and delirium	↑	↑	↔	↑

SpO_2: pulse oximetry O_2 saturation

As listed above, the second community affected is that of nurses and physicians responsible for the bedside care of hospitalized patients. In the hospital setting, nurses are the first line of clinicians responsible for dynamic instability detection, recognition, and treatment. Thus, nurses are frequently the gatekeepers of in-patient access to instability support. In fact, in the non-ICU setting, physician contact with patients is generally limited to a daily visit, with physicians unlikely to see the patient again unless called for by the nurse. Failure-to-rescue has been linked to nurse staffing, experience and education [11].

Implications

Clearly, traditional monitoring of patients at risk for cardiorespiratory insufficiency outside the ICU appears to be ineffective at identifying it and even when alarms activate appropriately, nursing activation appears to be blunted in a clinically significant fashion [9]. Since non-ICU patients tend to be less unstable than their ICU counterparts, it is not surprising that fully 75 % of all step-down unit patients remained stable throughout their entire step-down unit stay whereas those who had clinically relevant instability events did so only infrequently (i.e., < 20 % of the time). Furthermore, instability is characterized by bouts of insufficiency interspaced by periods of relatively normal vital signs. These qualities collectively undermine the usefulness of continuous single parameter monitoring or even periodic bedside monitoring. Clearly, improved identification and use of more integrated monitoring systems with a low false positive alarm rate need to be studied as the next logical step toward improving patient care and decreasing failure-to-rescue events in the acute care setting [11].

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XVIII End-of-life Issues

XVIII

An Update on ICU Management of the Potential Organ Donor

XVIII

M.T. Keegan, K.E. Wood, and D.B. Coursin

Introduction

Solid organ transplantation was one of the great advances in medicine in the 20th century. Indications and demand for transplantation have, however, led to a chronic shortage of transplantable organs. Although donation rates have increased over the past decade, many patients die while waiting for a transplant [1]. In September 2009, there were 103,000 patients awaiting transplantation in the United States [2]. The development of artificial organs continues, but in the short to medium term the medical community will continue to rely on organs retrieved from recently-deceased patients. The majority of organs are procured from patients who have suffered a devastating neurologic injury and have progressed to brainstem death. In recent years, programs have been developed to allow organ donation after cardiac death, though such donors account for less than 10 % of all organs transplanted. Unfortunately, many individuals who satisfy criteria for becoming organ donors fail to donate, mainly because of lack of consent [3]. In others, a suboptimal number of organs are recovered. The greatest discrepancy between supply and demand exists for lungs and only 7 – 22 % of multiple-organ donors are deemed suitable to become lung donors. 'Non-conversion' occurs for two main reasons: In 10 – 20 % of cases, the patient succumbs to somatic death (i.e., cardiac arrest) after brainstem death but before organs can be retrieved [4]; in other cases, organs are deemed unsuitable for donation because of their condition. 'Optimization' of such organs has been the focus of initiatives by organ procurement organizations. The Organ Donation and Transplantation Breakthrough Collaborative, the latest initiative of the United States Health Resources and Service Administration, seeks to meet the goals of 3.75 organs transplanted per donor and a 75 % conversion rate for all potential organ donors.

Role of the Intensivist

In the United States, management of the patient after brain stem death, but before organ donation, has traditionally fallen to organ procurement organization donor coordinators. Such donor coordinators often have many years' experience in nursing or other allied health disciplines, though are usually not physicians. Intensivists have tended to stop caring for patients after declaration of brainstem death, committed as they are to caring for other, still living, intensive care unit (ICU) patients. Recently, attempts have been made to engage critical care practitioners in the care of such recently-deceased patients who may have significant and progressive extra-cranial organ dysfunction [5]. Often, intensivists are simply being asked to use their resusci-

tative skills to continue to provide care to a patient who they cared for before declaration of brainstem death. Each donor is the potential source of organs for seven patients on transplant waiting lists. When managing donors, evidence-based care should be applied to allow donor stabilization, optimize organ condition, and fulfill the wishes of the patient and/or family to donate.

Physiologic Changes Associated with Brainstem Death

Brainstem death represents the culmination of progressive rostral to caudal ischemia [6, 7]. Mass effect secondary to intracranial hemorrhage or traumatic brain injury (TBI) leads to worsening cerebral ischemia, venous congestion, and brain swelling. The brainstem is forced through the foramen magnum with subsequent sequential ischemia and infarction. Pontine ischemia leads to a mixed vagal and sympathetic stimulation, resulting in the Cushing response (bradycardia, hypertension, and an irregular breathing pattern) and associated myocardial dysfunction [6]. When ischemia reaches the vagal and cardiomotor nuclei in the lower medulla, unopposed sympathetic stimulation occurs. This 'autonomic storm' probably reflects an attempt to preserve cerebral perfusion pressure (CPP), and causes a significant increase in vascular resistance. An imbalance between myocardial oxygen demand and supply may lead to electrocardiogram (EKG) changes, conduction abnormalities, arrhythmias, and even anatomical heart damage. Loss of spinal sympathetic pathways causes a total sympathectomy, with associated systemic vasodilatation and bradycardia [8]. Demonstration of a clinically relevant association between primary graft dysfunction in the heart, lungs, and kidneys from the same donor suggests a global process is at work and treatment of autonomic storm may increase the number of available cardiac grafts.

Szabo and colleagues have examined the mechanisms of hemodynamic instability and cardiac dysfunction in brain death using *ex vivo* and *in vivo* models [9]. Both neural and humoral factors are responsible for the initial Cushing response, the combination leading to a maximal response. Alterations in preload and afterload also contribute to decreased coronary blood flow and impaired myocardial contractility. In addition, brainstem death can impair coronary endothelial function and loss of vasomotor tone after brain death may lead to 'downregulation' of myocardial contractility. Such impairment of contractility, due to load effects rather than myocardial damage, may be reversible [9].

Protocols for Management of the Potential Organ Donor

Lack of standardization of donor management has been blamed for failure to retrieve as many organs as possible. Consequently, protocols for management of patients after brain death have been developed and implemented by organ procurement organizations. Controversy still exists regarding optimum donor management. Management focused on retrieval of one particular organ may conflict with management directed at another organ. However, optimum hemodynamic management is beneficial to all organs, and, for example, a higher procurement rate and better renal graft function is seen when kidneys are procured in association with the heart, rather than in isolation [10].

Professional organizations have developed recommendations for donor management, although some of these refer specifically to individual organs [11–15]. A con-

sensus conference on maximizing the use of organs recovered from the cadaver donor was held in Crystal City, Virginia, USA in 2001 [16]. A number of reviews on management of the potential organ donor are also available [7, 17–19].

Previously, because of fear of cardiac arrest and loss of all organs, there was a tendency to rush patients to the operating room for organ retrieval soon after brainstem death had been declared and consent for donation obtained. It has been increasingly recognized, however, that a window of time exists after brain death during which maneuvers to improve function of a given organ may allow retrieval of organs which had been deemed 'unsuitable' for donation. Lytle and colleagues documented the progression of organ dysfunction in 182 adult critically ill patients who subsequently met criteria for brainstem death [20]. Daily Sequential Organ Failure Assessment (SOFA) scores were used to assess the degree of organ dysfunction and did not significantly change over the course of the ICU stay. After brainstem death was declared, 67.6 % of patients donated one or more organs. The median time from ICU admission to declaration of brainstem death was 18.8 hours (interquartile range 10.3 to 45.0) and, in those who donated organs, the time from declaration of brainstem death to organ retrieval was 11.8 hours (9.5 to 17.6). The stability of SOFA score over time, even after brainstem death, has implications for the timing of organ retrieval and suggests that time for donor optimization exists.

Management of Individual Organ Systems

Cardiovascular

The procurement of transplantable organs is dependent on maintenance of hemodynamic stability and optimal perfusion. This may be challenging when brain stem infarction causes death of the vasomotor centers and loss of autoregulation. Decrease in systemic vascular resistance (SVR), increase in capillary permeability, and intravascular volume depletion (perhaps worsened by pre-mortem administration of diuretics for cerebral protection) may be accompanied by direct or indirect myocardial depression. Initial hypotension may be present in up to 80 % of donors, and sustained hypotension may occur in 20 % of donors, despite vasoactive drug support [7]. Evaluation of donor hypotension is detailed in **Figure 1**. Cardiac arrest is more common in hypotensive donors. Restoration of blood pressure typically requires volume administration and use of vasopressors. The central venous pressure (CVP) should be continuously monitored. Optimization of intravascular volume should be achieved to restore blood pressure and organ perfusion and minimize the use of vasopressors which may lead to organ ischemia. Both crystalloids (lactated Ringer's solution or half-normal saline with sodium bicarbonate added) and colloids may be used. In potential lung donors, colloid solutions are recommended to minimize the development of pulmonary edema [16]. Correction of hypernatremia (see below) may require the use of hypotonic solutions, but such fluids should be introduced only after the initial volume expansion. Hydroxyethyl starch should be avoided as it may cause renal tubular damage and impair early renal graft function [21].

Although volume resuscitation is required to optimize perfusion of organs such as the kidneys, if the lungs are to be procured, many authorities recommend that CVP be kept "as low as possible", as a minimally positive fluid balance is associated with higher rates of lung procurement. Early assessment of the potential recoverabil-

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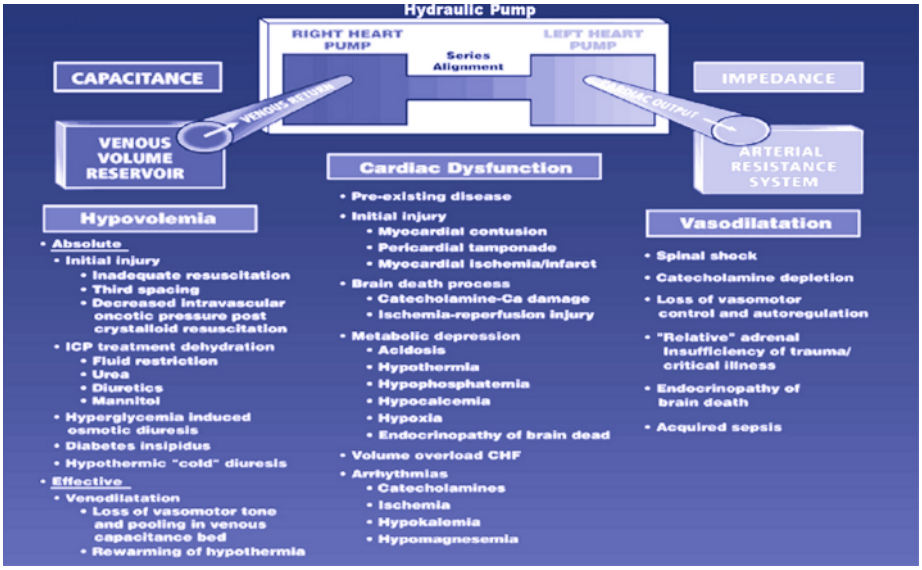

Fig. 1. Evaluation of hypotension in the potential organ donor. From [19] with permission

ity of the lungs may aid fluid management, as a more liberal fluid strategy is appropriate when contraindications to lung donation are evident [7].

Cardiovascular goals include mean arterial pressure (MAP) 60 – 70 mmHg, urine output 1 – 3 ml/kg/h, CVP 6 – 10 mmHg, and heart rate 60 – 120 beats/minute. Hemoglobin concentration should be maintained at > 10 g/dl [7, 15, 18]. Vasopressor medications recommended to achieve these parameters include dopamine, norepinephrine, and vasopressin. Dopamine has long been used in donor management and goals can usually be achieved with a dose of 5 – 10 μg/kg/min. The requirement for higher doses should prompt the addition of adjunctive agents. Inotropic agents may also be required, and typically dobutamine or epinephrine is chosen. The evidence for use of a specific vasopressor or inotrope is relatively weak. Combination therapy may avoid excessively high doses of a single agent with strong vasoconstrictor effects. Although high doses of vasopressors may cause ischemia and worsen transplant outcome, the clinical data are conflicting [22, 23]. Hormonal therapies (see below), however, do improve hemodynamics [24].

Assessment of cardiac structure and function is mandatory if retrieval of the heart is contemplated, and also aids in selection of inotropic or vasopressor medications. Trans-thoracic echocardiography is used most commonly, although a transesophageal echocardiogram is used on occasion. Timing of echocardiography is important. Anemia, metabolic abnormalities and excessive dosing of inotropes should be corrected before echocardiography if possible and cardiac donation should not be excluded solely on the basis of the initial echocardiogram. Left ventricular dysfunction may be due to 'stunning' after neurologic injury, and may recover, especially in young patients. Dobutamine stress echocardiography has also been used as part of 'aggressive' donor management strategies to delineate potentially reversible myocardial dysfunction [25]. If the ejection fraction is less than 45 %, and/or if hemodynamic instability persists despite apparently adequate volume replacement then placement of a pulmonary artery catheter (PAC) should be

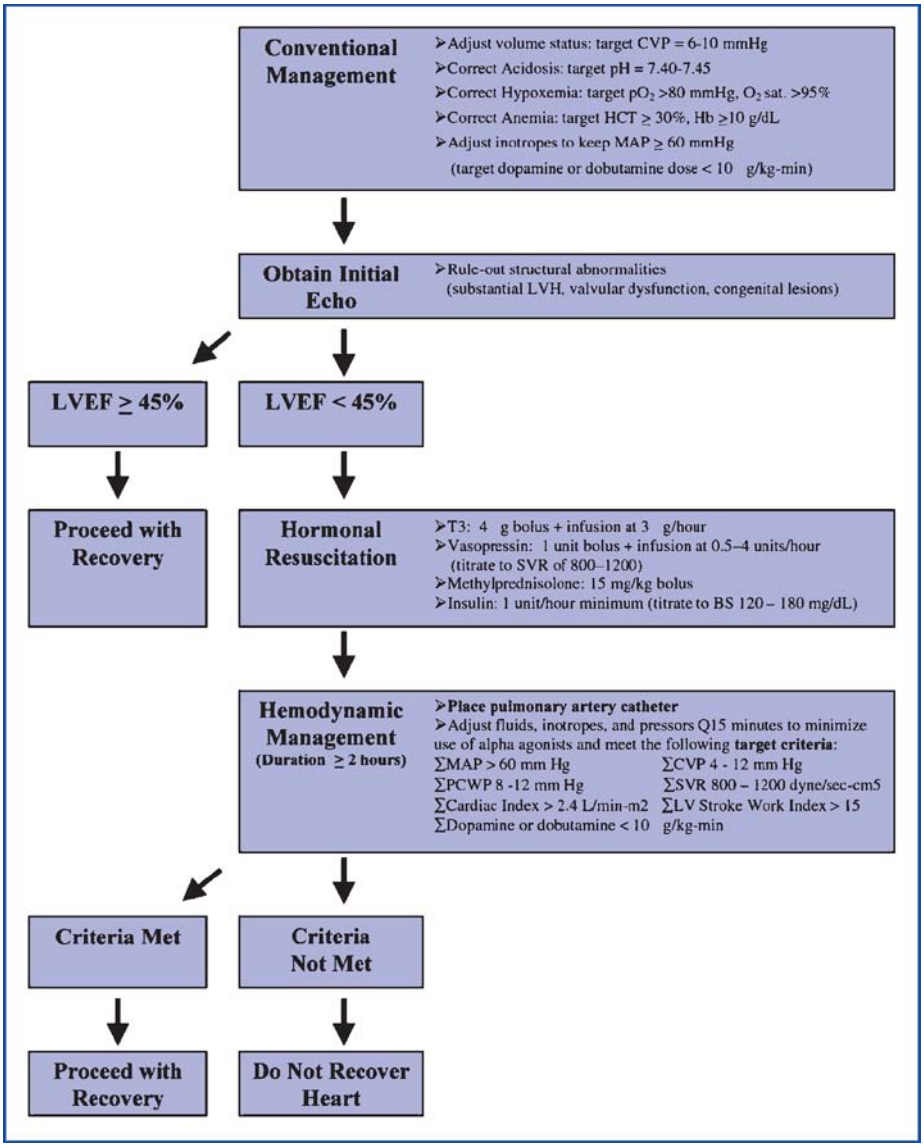

Fig. 2. Crystal City recommendations for cardiac donor management. CVP: central venous pressure; Hb: hemoglobin; MAP: mean arterial pressure; LVH: left ventricular hypertrophy; SVR: systemic vascular resistance. From [16] with permission.

considered. Hemodynamic targets include a pulmonary artery occlusion pressure (PAOP) of 8 – 12 mmHg, cardiac index ≥ 2.4 l/min/m^2, and SVR 800 – 1200 dynes/sec/cm^5 [6]. Central venous oxygen saturation ($ScvO_2$) and mixed venous oxygen saturations (SvO_2) have not been formally studied in patients after brainstem death. If used they should be maintained at values typically used for the resuscitation of patients with shock due to other causes. Accordingly, $ScvO_2$ > 70 % and SvO_2 > 65 %

are desirable [15, 18]. Cardiac arrhythmias are common in the brain-dead potential donor and may be due to conduction system necrosis [26]. Standard anti-arrhythmic medications are appropriate for treatment, although bradyarrhythmias due to vagal stimuli secondary to brain stem compression should be treated with isoproterenol or epinephrine rather than atropine, to which they are often refractory [7, 26]. A scheme for optimization of hearts for recovery is detailed in **Figure 2**.

Pulmonary

The rate of recovery of lungs for donation has been disappointingly low. In 2005, only 35 % of patients on the United Network for Organ Sharing (UNOS) lung transplant waiting list received transplants and 10 % died while waiting [18]. Half of the listed patients waited two years for a transplant. However, the implementation of standardized respiratory management of potential organ donors has resulted in an increased retrieval rate for lungs without jeopardizing the procurement of other organs and in 2008, 71 % of patients on the waiting list were transplanted [27]. Van Reamdonck et al. and Botha and colleagues have recently summarized issues in lung donor selection and management [28, 29].

Pulmonary dysfunction after brain injury may be related to aspiration, hemo- and/or pneumothorax, infection, and neurogenic pulmonary edema. Animal models have reported that up to 72 % of the effective circulating volume may be stored in the pulmonary vasculature during brain death [30]. Patients with brain damage exhibit abnormal respiratory mechanics even on admission to the ICU and deterioration in oxygenation and decrease in compliance may occur progressively thereafter [31]. It has also been recognized that brainstem death initiates a marked systemic inflammatory response, analogous to that seen in sepsis and after cardiopulmonary bypass (CPB), and that such inflammation may generate a pulmonary inflammatory surge, the extent of which has been demonstrated to correlate with recipient graft function [32, 33]. The use of high tidal volumes in such a situation risks the generation of further acute lung inflammation and worsening of a pre-existing lung injury. Primary graft failure in the lung transplant recipient is likely related to events following brain death, and procedures involved in procuring and implanting the new organ.

Reversible causes of hypoxemia, which may make lungs unsuitable for donation, include atelectasis and volume overload. Frequent suctioning, bronchoscopy and diuresis, in addition to ventilatory strategies which favor recruitment, are recommended. A PAC, targeting a PAOP of 8 – 12 mmHg, may be used to balance perfusion of potentially transplantable organs while minimizing extravascular lung water (EVLW). The ventilatory strategy recommended for potential lung donors by the Crystal City Consensus Conference is similar to the strategy recommended for brain-injured patients, employing the use of high tidal volumes to maintain high PaO_2 and low normal $PaCO_2$ and low levels of positive end-expiratory pressure (PEEP) [16]. This strategy conflicts with the standard of care in patients with the acute respiratory distress syndrome (ARDS). Nonetheless, the transplant community persists with the high tidal volume strategy, and has, in fact, demonstrated increased procurement of lungs when a standardized protocol, which includes high tidal volume, is used [34].

The San Antonio Lung Transplant (SALT) donor management protocol used standardized donor management, an educational program, and changes in the selection criteria for lung donation. Lungs procured per eligible donor increased from 11.5 %

to 22.5 % with concomitant increase in transplants without adverse effects on recipient outcomes [35]. In Australia, Gabbay and colleagues used multiple maneuvers, including adjustment of ventilatory settings and PEEP, to convert lungs previously deemed unsuitable for donation because of PaO_2/FiO_2 ratios less than 300, into transplantable organs, without adversely affecting recipient outcomes [34]. Similar findings were reported by the California Organ Bank.

The donor management guidelines of the UNOS in the USA, Papworth Hospital in the UK, and Leuven University Hospital in Belgium each recommend potential donor lung tidal volumes of 15 ml/kg (10 – 15 ml in the case of UNOS) and PEEP of 5 cmH_2O. The Canadian Guidelines' recommended tidal volume of 8 – 10 ml/kg is a compromise between high and low tidal volume strategies. These guidelines also recommend maintenance of peak inspiratory pressure $\leq$ 30 cmH_2O and PEEP at 5 cmH_2O, but allow for recruitment maneuvers with PEEP up to 15 cmH_2O and sustained inflations to peak pressures of 30 cmH_2O. Spanish guidelines also recommend 8 – 10 ml/kg tidal volumes [11].

Antibiotic therapy should be administered on the basis of Gram stains of respiratory secretions [7]. Steroids are administered as a component of many donor management protocols, presumably to decrease inflammation and EVLW [36]. Albuterol has been used to augment the clearance of pulmonary edema, although the most recent data from the ARDSNet group do not support the use of beta-agonists in patients with acute lung injury.

Endocrine

Hypothalamic-pituitary-adrenal insufficiency occurs in 30 – 50 % of patients after traumatic and non-traumatic brain injury and there is a high prevalence after brainstem death [37]. Recent guidelines advocate the use of a standard hormonal resuscitation package in potential organ donors. The Crystal City Consensus Conference recommended that four-drug hormonal resuscitation (tri-iodothyronine [T3], vasopressin, methylprednisolone and insulin) be an integral component of the UNOS Donor Management Protocol. Methylprednisolone (15/mg kg bolus), T3 (4 μg bolus, then an infusion at 3 μg/hour), arginine vasopressin (1 unit bolus, then 0.5 – 4 units/hour) and insulin (infused at a minimum of 1 unit/hour, titrating blood glucose to 120 – 180 mg/dl) are proposed [15]. Combination hormonal treatment of brain-dead donors results in an increased number of organs transplanted and recipients from hormone treated donors are less likely to die and less likely to have early graft dysfunction.

T3 influences cardiac output by affecting tissue oxygen consumption (thermogenesis), vascular resistance, blood volume, cardiac contractility, and heart rate. The utility of thyroid hormone supplementation in the potential organ donor is supported by most clinical data, although conflicting data have also been published [38]. Although T3 is relatively more expensive than T4, its potential advantages have led to its endorsement as a key component of donor management protocols. Corticosteroids are used to attenuate the effects of inflammatory cytokines generated as a result of brain death. In addition to the potential advantages when used in lung donors, steroids have been demonstrated to improve graft survival after renal and cardiac transplantation.

Central diabetes insipidus is the most common endocrinopathy in the brain-dead donor because of inadequate antidiuretic hormone production from the posterior pituitary. Hypovolemia and hypernatremia may be severe and are usually only par-

tially corrected by administration of 5 % dextrose and/or free water flushes via the nasogastric tube. In many cases, urine output is so high that administration of vasopressin is required. A dose of 0.5 – 0.6 units/h reduces urine output to acceptable levels. A second benefit of vasopressin is increased SVR and a potential catecholamine-sparing effect.

Patients who have suffered severe intracranial insults are usually managed with insulin infusions to ensure glycemic control. Successful procurement and use of the donor pancreas for transplantation may be aided by glycemic control in the donor, to minimize the adverse effects of donor hyperglycemia on pancreatic beta-cells [39].

Renal and Gastrointestinal

Successful retrieval and transplantation of kidneys, livers, and intestines is dependent on optimal perfusion of the donor and the management strategies detailed above are appropriate. Allograft function after transplantation may be influenced by donor management. Although the use of dopamine as a renal protective agent in the general critical care population is inappropriate, Schnuelle and colleagues demonstrated in a European multicenter trial that donor pretreatment with low-dose dopamine reduced the need for dialysis after kidney transplantation [40]. In addition, failure to treat hypernatremia in the donor has been linked with graft loss after liver transplantation [41].

Coagulopathy and Hypothermia

Traumatized or necrotic brain tissue releases a variety of antithrombotic substances, which, coupled with dilutional coagulopathy from volume resuscitation and transfusion as well as the potential impact of acidosis and hypothermia, can lead to marked coagulopathy in the donor. Replacement of coagulation factors should proceed along conventional lines. Hypothermia occurs due to a combination of factors including loss of hypothalamic thermoregulation, an inability to shiver and properly vasoconstrict, as well as infusion of relatively hypothermic fluids and blood products. Hypothermia causes vasoconstriction, arrhythmias, and myocardial dysfunction, among other deleterious effects. Prevention is easier than treatment, and involves heating and humidification of inhaled gases, warming of infused fluids, and use of forced air warming devices.

Donation after Cardiac Death

Improvements in medical care and developments in public safety laws have resulted in a decrease in the number of patients developing brain death. Some patients with devastating neurologic injury who have previously expressed a wish to donate are unable to do so because they have not progressed to brainstem death. This may cause significant distress among patients' relatives, and of course, deprives those in need of potentially transplantable organs. In response, protocols for donation of organs soon after somatic death have been developed. Such practice has been called "non-heart beating donation", though it is more commonly known as "donation after cardiac death". The Maastricht group has identified four well-established categories of patients from whom organs may be procured. Patients most suitable for

the 'controlled' donation required in donation after cardiac death are those in Maastricht category 3 (patients in the emergency department with a non-survivable injury or those in ICUs in whom death is inevitable and who are awaiting cardiac arrest) [42]. Those individuals in Maastricht category 4 (cardiac arrest in a brain-dead potential donor) may also be suitable for donation after cardiac death, depending on how far the donation process has proceeded before cardiac arrest occurs.

Donation after cardiac death donors have increased in number. In the USA, donation after cardiac death increased from 452 in 2005 to 538 in 2006 [1]. The American Society of Transplant Surgeons (ASTS) has published practice guidelines for organ procurement and transplantation in the donation after cardiac death setting [43]. They point out that donation after cardiac death should not be viewed as an equally acceptable alternative to donation after brainstem death because donation after cardiac death, on average, yields fewer organs and the organs recovered are of lower quality. The Joint Commission has mandated that centers which receive organs for transplantation have a policy for donation after cardiac death in place and this will probably further increase the number of donation after cardiac death organs available. National organizations have published guidelines in support of donation after cardiac death. A USA national conference on the use of donation after cardiac death was convened in 2005 to assess the increasing experience of donation after cardiac death and to discuss the ethics of the practice [44]. Separate work groups discussed the determination of death by cardiopulmonary criteria, the prediction of donation after cardiac death candidacy following withdrawal of life support, protocols for donation after cardiac death organ recovery and successful transplantation, methods to initiate and increase the practice of donation after cardiac death, and allocation of organs for transplantation. Furthermore, a discussion of media interest and the public perception of this controversial subject was deemed necessary.

Organ donation has traditionally been guided by the 'dead donor rule', meaning that organs are not procured until irreversible cessation of cardiac or brainstem functions has occurred. The definition of irreversible is open to interpretation, however, and there has been much ethical debate on the practice [45]. Nonetheless, the performance of donation after cardiac death has been supported by many organizations, including the Ethics Committee of the American College of Critical Care Medicine/Society of Critical Care Medicine [46].

In reality, only a limited number of organs are potentially recoverable for donation after cardiac death, the kidneys and liver being most suitable. Although the incidence of delayed graft function is significantly higher with kidneys from donation after cardiac death donors when compared with brain-dead donors, there is no difference in long-term outcome [47].

The logistics of donation after cardiac death vary from center to center. Formal protocols should be in place and of paramount importance is respect for the dying patient (potential donor) and their family. Identification of potential donors may be aided by local recommendations, which mandate that patients in whom withdrawal of support is being contemplated or in whom an apparently non-survivable (neurologic) injury has occurred are reported to the responsible organ procurement organization. Although this allows a preliminary assessment of the potential suitability for donation, it is vital that any discussions of withdrawal of support are made by the medical team caring for the patient in conjunction with the patient's family, independent of discussions or decisions regarding organ donation. Only after a decision to withdraw support has been made should an approach to the family regarding organ donation be made. Such requests for consideration of organ donation are best

made by an individual trained in the process. If consent for donation is obtained, expeditious testing must occur to identify whether or not the patient is a suitable donor candidate and to identify potential organ recipients. Protocols for maintenance of patient comfort during withdrawal of life support, typically involving the use of benzodiazepines and opiates, should be implemented.

The location for withdrawal of life support varies. Withdrawal in the ICU allows the continuation of usual care practices in the patient's current environment. However, once death has been declared, there is a need to move quickly to the operating room to minimize warm ischemia time, the duration of which is inversely related to organ quality. Alternatively, withdrawal may take place in the operating room, with the patient's ICU nurse and critical care physician in attendance to provide comfort measures before, during, and after cessation of vasopressor support and termination of mechanical ventilation. Family members should have the opportunity to come to the operating room for withdrawal of support if desired. Ideally, surgical preparation and draping of the patient should be performed before the family enters the operating room, and then the surgical field covered with towels or a blanket. Once pulselessness is noted, the family are respectfully but expeditiously ushered out of the operating room. Preparation of the family is key. They should be aware of the need to leave once pulselessness has been declared, and, in general, will be motivated to allow successful donation and will comply with such requests to leave.

Declaration of death should be by a senior physician who is not involved in the transplant process. The intensivist caring for the patient may be the physician who declares death. The duration of pulselessness required before death can be declared has been a matter of some debate, but many institutions follow the Institute of Medicine recommendation of 5 minutes. Asystole is not required, as agonal rhythms may persist for a considerable period of time after cessation of respiratory effort and onset of pulselessness.

The use of agents such as phentolamine and heparin administered pre-mortem to preserve viability of organs is controversial. Although these agents may theoretically hasten the patient's death, in practice this is very uncommon, and administration of such agents is allowed by some centers depending on whether the donor has previously articulated a wish to donate. Even more controversial practices used in some centers include declaration of death after only 2 minutes of pulselessness (potentially within the time during which 'autoresuscitation' may occur), and pre-mortem placement of vascular access devices to allow flushing of organs with iced solutions to decrease warm ischemia time.

If a patient does not die within a certain period of time after withdrawal of support (typically 60–90 minutes), organ donation should be abandoned, and the patient should be returned to the ICU where the dying process can continue. Use of predictive scores to identify patients likely to succumb within the time allowable may decrease the chance of non-donation.

Conclusion

The advent of modern surgical and preservation techniques, improved multimodal immunosuppressants, and educational programs to facilitate identification of potential donors has resulted in improved outcomes in transplant patients. Despite these advances, the number of potential organ recipients continues to far outstrip the number of available donor organs. To help address this shortage, international

efforts continue to standardize and improve the identification and management of the potential organ donor. These efforts include careful pre-procurement assessment of individual organs, particularly heart and lung; judicious management of fluids to optimize perfusion while limiting cardiac and pulmonary compromise; and specific attention to maintenance of intravascular volume, cardiovascular function, and electrolyte, glucose, thermal coagulation, and acid-base homeostasis.

The 'best' approach to fluid management, use of vasoactive support, mechanical ventilation, and hormonal replacement therapy continues to be investigated. Recent literature has identified that 'marginal' organs, particularly heart and lung, can be successfully transplanted when an aggressive evaluation and management scheme is applied.

Although controversies remain and the numbers of transplants are limited, the role of donation after cardiac death in modern transplantation continues to evolve. Individual institutional plans for management of donation after cardiac death should be established based on recent international recommendations.

Intensive care practitioners play an integral part in the identification of the potential organ donor. The intensivist's role in the management of these patients is unique and often challenging. The ICU physician first and foremost has responsibility to the potential donor and his/her family. Open communication by the intensivist with organ procurement organization staff and transplant surgeons combined with appropriate management guidance during the pre-procurement period is crucial to continued optimization of the potential donor and successful transplantation.

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XVIII

End-of-life Care in the ICU: Commonalities and Differences between North America and Europe

Y.-L.C. Nguyen, F.B. Mayr, and D.C. Angus

Introduction

Advances in medical science and health care have gradually changed the nature of dying. Death no longer is likely to be the sudden result of infection or injury, but instead occurs slowly, in old age, and at the end of a period of life-limiting or chronic illness. This shift has created new challenges for critical care medicine. In this chapter, we provide a brief overview about critical care utilization at the end-of-life and the most important challenges we face. We discuss these challenges from an American and European perspective, as end-of-life decisions vary substantially between these two continents.

Discrepancy between Preferred and Actual Place of Death

Facilitating a patient's death in his or her preferred location (such as home or hospital) is an important quality indicator of end-of-life care, reflecting the fundamental notion that good care empowers patients and families to control the decision-making process. Surveys of the general population show that people overwhelmingly prefer to die at home [1, 2]. For some patients, this preference is unconditional, while for others it depends on circumstances such as the ability to control pain or to minimize the burden on loved ones [3, 4].

Although the majority of patients prefer to die at home, data suggest that the reality is the opposite: Most Americans die in an institutional setting. As of 2001, nearly 50 % of deaths due to chronic illness occurred in acute care facilities, compared to 20 % of deaths at home or in nursing homes [5]. In Europe, home deaths have decreased over the past 30 years from roughly 35 % to 20 %. The proportion of people dying in hospital is higher compared to the USA and varies between 37 % and 60 %, depending on country [6, 7].

A recent population-based study comparing intensive care unit (ICU) use in England and the USA estimated that 50.3 % of deaths in England occur in an acute hospital setting compared to 36.6 % in the USA [8]. The higher percentage of deaths in acute hospitals in England compared with the USA is surprising, given the overall lower expenditure on healthcare in the UK, as well as a similar number of hospital beds per capita compared with the USA [9]. One possible explanation is the increasing use of skilled nursing, and also out-of-hospital hospice care in the USA.

Use of Critical Care Services during Terminal Hospitalization

In 1999, Angus et al. conducted a population-based study on the use of intensive care at the end-of-life in the USA [10]. Based on discharge data from six states, these authors projected that more than half a million Americans die after receiving ICU care. Mean ICU length of stay was 8.0 days, and almost half of the decedents spent their entire hospital episode in the ICU.

Critical care services during terminal hospitalization are considerably lower in Europe than the USA. Wunsch et al. showed that only 10.1 % of hospital deaths involved intensive care services in England versus 47.1 % in the USA [8]. This difference is particularly striking in patients 85 years and older, with only 1.3 % of all decedents receiving intensive care in England compared to 11.0 % in the USA.

Health Care Costs during Terminal Hospitalization

A disproportionate share of health care expenditure is incurred at the end-of-life. Thirty percent of Medicare expenditures are attributable to the 5 % of beneficiaries who die each year. Roughly one-third of expenditure in the last year of life is spent in the last month, and most of these costs result from life-sustaining care (e.g., mechanical ventilation and resuscitation [11]. Terminal hospitalizations account for ~7.5 % of all inpatient costs per year, and the majority of these costs are due to use of ICU services [10].

Data on health expenditures during terminal hospitalizations in Europe are scarce. A Dutch study found that about 10 % of annual health care expenditure was associated with health care use of persons in their last year. Average costs for younger decedents were higher than for those who died at higher ages predominantly due to a higher use of intensive care services [12].

Variation in End-of-life Intensive Care Use

End-of-life treatment intensity not only varies between countries (e.g., England vs USA), but also across different hospital referral regions within the USA [13]. These differences are largely attributable to differences in the quantity of medical services provided rather than to the quality of care [14]. Structural hospital characteristics such as location, for-profit status and bed-size do not explain the entire variation in end-of-life treatment intensity. Hence, many believe that individual hospital 'microclimates' exist [15], and that certain aspects of a microclimate (e.g., caregiver interaction) are associated with quality of care and outcomes. Indeed, a physician's perception of patient preferences and prediction of a low likelihood of survival in the ICU and a high likelihood of poor cognitive function for the patient are among the strongest determinants of withdrawal of mechanical ventilation in critically ill patients [16].

Similarly, decisions to forego life-sustaining treatments vary across different European countries. For example, the ETHICUS study showed that decisions to withdraw treatment were less common in southern European countries, where cardiopulmonary resuscitation (CPR) was more often used and ICU stays were longer than in northern countries [17]. These differences have been attributed in part to different case-mix, differences in culture and religion, differences in physician values

and practices, as well as variability in the ongoing evolution of end-of-life practices [17, 18].

End-of-life Decision-making Process

During the mid-20th century polio epidemic, when the first ICUs were built in Europe and in North America, the common request to critical care professionals, "do your best", was often interpreted as "use all your skills to save lives". The development of new life supporting technologies facilitated maintenance of 'unnatural' life. Therapeutic decisions were often made without taking into account underlying disease severity, the predicted reversibility of acute or chronic disease, predicted residual impairments, or the expected future quality of life. ICU admissions of patients with a questionable prognosis were common. An American survey conducted in 1988 highlighted that 40 % of respondents would admit patients with a chronic vegetative state or a patient with metastatic carcinoma and a superposed life-threatening event [19]. A European survey conducted in 1996 showed that three-quarters of intensivists regularly admitted patients with no hope of survival although only a third of respondents felt that such a decision was justified [20]. Recent American guidelines recommend that ICU admission should be restricted to patients who are likely to benefit from ICU care without defining exact triage criteria [21].

The management of end-of-life care in the ICU is a relatively new phenomenon. The SUPPORT study (Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments) conducted 20 years ago in the USA also showed that discussions related to end-of-life were uncommon among seriously ill hospitalized patients while unwanted life sustaining treatments and insufficient palliative care were frequent [22]. Over the last decade, North American and European professional societies have agreed that, in particular circumstances when the treatments provided do not accomplish their intended role, undertaking decisions to forgo life sustaining therapies and starting palliative care is ethical. Nowadays, the majority of deaths occurring in the ICU are preceded by decisions to forgo life-sustaining therapies [23, 24]. The proposal to initiate end-of-life discussions is often undertaken by the physicians and there is an association between the presence of end-of-life discussions and the quality of care delivered [25, 26].

The process of end-of-life decision-making may be defined by the discussions between caregivers, patients and patients' families (when the patients are incapacitated) on whether life-sustaining treatments should be either withheld or withdrawn and palliative care started. The discussions may take place in the general ward, the emergency department or the ICU. Less than 5 % of ICU patients are able to participate in the end-of-life discussion. Therefore, to preserve patient autonomy, current guidelines of professional societies recommend shared decision-making with patient surrogates (family members or close friend). The following section describes cultural variations in the end-of-life decision-making process between North America and Europe (**Table 1**).

An American Perspective

Broadly speaking, expectations of the North American population are strongly impregnated by a culture of autonomy and self-determination. Data on the specific

Table 1. Broad themes governing end-of-life decision-making in North America and Europe.

	North America	Europe
Expectations		
Surrogates	Majority want to participate in the decision-making process	Mixed views regarding desire to participate in the decision-making process
Caregivers	Majority perceive family has major decision-making role	Majority want to involve families in the decision-making process, though there may be regional differences
Legislation		
Patients	Decisional role	Decisional role
Surrogates	Decisional role	Decisional or consultative role
Physicians	Consultative role	Decisional or consultative role
Reports of unintended consequences	Poor satisfaction	Poor satisfaction
	Anxiety-depression symptoms increased when surrogates did not share in the decision making process	Anxiety-depression symptoms increased when surrogates shared in the decision-making process
	Conflicts	Post-traumatic stress disorder Conflicts Burn-out syndrome

expectations of conscious ICU patients regarding end-of-life preferences are lacking, but are likely to be related to underlying cultural values. Data from seriously ill patients are consistent with a desire for autonomy. For example, the majority of those who had not discussed their end-of-life preferences with their physicians were willing to do so [27]. It is also likely that the preferred role in the decision-making process is not consensual. In a monocentric survey among patients with end-stage chronic diseases, Heyland et al. found that 40 % of respondents wanted to make the final decision, 32 % wanted to share the responsibility of the final decision with their physician, 19 % wanted the physician to make the final decision, and 10 % did not have any opinion [27]. This survey also revealed that although only 15 % of the physicians did not feel able to define the preferred role of the patient in decision-making, they correctly judged patients' preferences in fewer than in one in five cases.

The majority of family members of patients dying in the ICU want to participate in the decision-making process but there is no consensus on their preferred role [28, 29]. In a Canadian study of 256 substitute decision makers for ICU patients, 33 % of the respondents wanted to make the final decision (active role), 43 % wanted to share the responsibility of the final decision with their physician, and 24 % wanted the physician to make the final decision (passive role) [30]. Around 70 % of the respondents reported that their current role was congruent with their preferences and that their satisfaction with end-of-life care was high. In an American study where 48 relatives of ICU patients were interviewed, 58 % reported preferring to share responsibility with the doctor, 25 % reported preferring an active role, and 17 % reported preferring a passive role [29]. There was an association between the level of education and decision-making preferences: Attending college was associated with a preferred shared or active role. The investigators did not find any association between age, sex, ethnicity, religion or relationship to the patient and decision-making preferences. White et al. examined the attitude of surrogate decision-makers towards receiving a physician's recommendation during end-of-life care discussions

[31]. The investigators interviewed 169 surrogates and found that 56 % preferred to receive a recommendation, 42 % preferred to not receive a recommendation, and 2 % found both approaches acceptable. The main reason underlying the refusal of a recommendation was that the respondents believed that giving a recommendation was not part of the role of the physician.

The current recommendations for end-of-life care in the ICU from the American College of Critical Care Medicine encourage physicians to ask patients and families about their preferred role in the decision-making process before giving any recommendation [32]. Two observational studies conducted before the publication of the guidelines showed that family's preferences on the decision-making process were never or rarely discussed [33, 34]. White et al. also found that half of the physicians requested by the surrogates to provide a recommendation refused to do it, justifying that it was not part of their role.

These observational data highlight the difficulties in standardizing the end-of-life decision-making process. The preferred role of the patient or the surrogate in the decision-making process is not consensual, which makes each physician-family conference unique. Of note, to meet a family's needs, the physician may need to adapt to a certain role, an action for which the physician may lack the skills or may feel uncomfortable performing, particularly when physician values disagree with the patient's or family's expectations.

A European Perspective

Broadly speaking, many European cultures tolerate a more parental role for authority figures, such as physicians. Likely as a consequence, a majority of medical decisions has traditionally been made primarily by physicians. In a French study conducted across 113 ICUs, Ferrand et al. showed that all decisions to withhold or withdraw life-sustaining treatments were made either by the medical staff or by the medical and nursing staff [24]. In a European survey, Vincent showed that end-of-life decisions were made entirely by the attending intensivist in Italy, Greece, and Portugal, and by the ICU team in the UK and Switzerland [20]. Other data support the notion that the participation of nurses in end-of-life discussions is more common in northern and central Europe than in southern Europe [35]. The rare involvement of the patient or the family in the decision-making process was also found in France [24, 36].

Survey data, however, can be misleading, and there is often a discrepancy between what intensivists believe and what they do. In France, Azoulay et al. showed that 91 % of intensivists believed that families should participate in the decision-making process but only 39 % involved families [37]. Knowledge of the willingness of the patients to limit their care was uncommon and the concept of advance directives was sometimes unfamiliar to intensivists [24, 26, 38]. Little importance was accorded either to a patient's wishes or perception of his or her quality of life [36]. Also, information from the patient or his/her family on the decision taken was infrequent. Nearly one in four competent patients and one in three families available were not informed about the decision taken [24]. Furthermore, intensivists frequently did not believe that transparency of end-of-life medical decisions, such as thorough documentation in the medical record, was required. A European survey also found that physicians were more likely to claim transparency was important in end-of-life decisions than to conduct the decisions with transparency [20]. There was also a large variation across countries in the rate of transparent decisions for do-not-resuscitate orders (from 8 % in Italy to 91 % in The Netherlands) [20].

Perhaps not surprisingly, the principles and components of advance directives, patient surrogacy, and an informed and shared decision-making process, all features of greater self-autonomy, have been introduced more slowly and more recently in Europe than in North America. However, data suggest the concepts are engendering wide, though perhaps inconsistent, support. A survey among the French population conducted at the beginning of the twenty-first century showed that 90 % of the respondents were willing to have a surrogate to represent them in the decision-making process if they become incapacitated [37]. Another French survey, conducted at the same time, evaluated the position of critical care professionals and ICU patient family members on the process of shared decision-making [39]. The results showed that the majority of physicians and non-physicians believed that participation of families should be considered in the decision-making process. On the other hand, less than half of family members wanted to share in the decision-making process.

Over the last decade, legislation on advance directives, surrogate designation, and the process of decision-making, whether the patient is incapacitated or not, has been voted into law in several western European countries [40]. There is consensus on the decisional capacity of the patient when he/she is capacitated. However, there is no consensus regarding when the patient becomes incapacitated. The power of advance directives differs across countries. Some countries, including Belgium, Denmark, England, the Netherlands, Spain, and Switzerland, recognize the validity of the decisional power of advance directives while others, most notably France, consider advance directives as consultative. The designation and role of surrogates also vary; Spain and Denmark require a written document by the patient while others, including Germany, Belgium, and Switzerland, require confirmation by a judge [41]. The role of the surrogate may be either decisional (e.g., Belgium, Denmark, England, Germany, Spain, and Switzerland) or consultative (e.g., France and the Netherlands).

Thus, European legislation on end-of-life decisions is very recent and current data on the end-of-life decision-making processes are missing. There is now a common trend in Europe to give more autonomy to the patient or surrogates, but there are still variations across countries particularly on the surrogate's role. These variations may be explained either by a persistent pure paternalistic tradition or a volunteer of non-maleficence, protecting surrogates from unintended consequences associated with end-of-life decision-making.

Unintended Consequences of End-of-life Decision-making

There are unintended consequences of ICU end-of-life decision-making on both families and ICU providers. Although a recent Canadian survey showed that the majority of families of ICU patients were satisfied with the end-of-life care provided, this study also highlighted that 15 % of the respondents felt they were not in control of the care provided to their loved one, 11 % believed that life was prolonged unnecessarily, and 9 % reported that the patient was uncomfortable in the last few hours [30]. Adequate communication (amount, quality and timing of the information provided) and a congruent role in the decision-making process with their preferred role were predictors of being satisfied. The evaluation of the satisfaction in 26 Swiss-German ICUs highlighted that the item "support during decision-making" had a poor satisfaction rating [42].

Conflicts between family members and medical staff are common in end-of-life discussions [43, 44]. Abbott et al. [43] reported that the majority of the conflicts

were generated by perceptions of inadequate communication or unprofessional, disrespectful behavior by physicians and nurses. Azoulay et al. [44] reported that the main source of ICU team-family conflicts occurred when family or patient preferences were disregarded, when end-of-life decisions were made too late or too early, and when there was a poor level of communication during the decision-making process [44].

Many studies showed that family members of ICU patients suffer from anxiety and symptoms of depression [29, 37, 45]. A French study showed that 3 months after an ICU experience, one third of family members suffered from post-traumatic stress disorder, which was associated with higher rates of anxiety and depression and decreased quality of life. The incidence of post-traumatic stress disorder among ICU patient families was higher when the death of the patient occurred after a decision to forgo life-sustaining therapies or when they participated in an end-of-life shared decision-making process [46]. On the other hand, an American study showed that a passive role of surrogates in the decision-making process was associated with a higher risk of anxiety and depression symptoms [29]. In studies of work stress, high numbers of end-of-life decision-making processes are risk factors for burn-out syndrome [47].

Thus, the current practice of end-of-life decision-making in North America and in Europe carries important stress and strain for all involved. The process is inherently stressful, but it is likely that there are opportunities to improve the quality of the decision-making, including better training of clinicians to enhance their communication skills. Lautrette et al. showed that pro-active communication and a brochure for relatives of patients dying in the ICU reduced the burden of grief [48]. Rosenzweig et al. showed that a patient communication simulation laboratory helped nurse students to improve their confidence and perceived efficacy in communication in difficult acute care situations [49]. Hopefully, better quality decision-making will lead to improved family satisfaction, to a decreased risk of post-traumatic stress disorder symptoms among surrogates, and to reduced burn-out among caregivers.

Conclusion

The aging of the population in developed countries is going to create an increasing demand for critical care resources. Recent changes in European and American recommendations on end-of-life care reflect a societal desire to redistribute the rights and duties between patients, surrogates and caregivers in this major ethical issue. Increasing the quality of the end-of-life decision-making process is essential to improve quality of end-of-life care and to decrease unintended consequences (poor satisfaction, conflicts, anxiety-depression symptoms, burn-out syndrome symptoms). The end-of-life decision-making process varies across continents in terms of expectations but also in terms of the role (decisional or consultative) of the physician or the surrogate. To date, both approaches are less than perfect and associated with undesirable adverse effects. Additional research is needed to evaluate whether current practices meet patients' and family members' needs and to identify interventions to improve the quality of end-of-life care.

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XIX Patient Care

Do Sleep Disorders have an Impact on Outcome in ICU Patients?

XIX

J. Mantz, C. Paugam-Burtz, and S. Hamada

Introduction

The intensive care unit (ICU) setting represents a hostile environment for mechanically ventilated patients. Although considerable efforts have been undertaken to continuously improve the outcomes of ICU patients, overall morbidity and mortality have not been dramatically reduced during the past 20 years. The role of factors that have previously been considered as having a negligible impact on outcome needs to be revisited. Several lines of evidence suggest that sleep is qualitatively and quantitatively severely disturbed in ICU mechanically ventilated patients. Hence, sleep disturbances, as estimated using sleep-quality questionnaires, affect a very high percentage of patients, and persist for many days, even for several weeks or months in some cases, after anesthesia and intensive care. Sleep disorders may play an unexpectedly important role in decreasing host defenses and in worsening patient outcome. The importance of sleep disorders in the ICU has been recently emphasized in elegant reviews on the topic [1, 2]. In the present chapter, we will focus on the possible impact of these disorders on outcomes in ICU patients, and suggest possible ways to improve sleep quality in the ICU.

Anesthesia/sedation and Sleep are not Identical, but may Share Common Mechanisms

The sleep-wake cycle represents a vital physiological function that depends on the modulatory activity of neuronal networks originating from cortical and subcortical areas. Synchronization of the sleep-wake cycle to the dark-light cycle involves an internal clock located in the suprachiasmatic hypothalamic area, which controls the secretion of melatonin, a sleep-promoting hormone. The typical pattern of a sleep cycle in healthy individuals consists of successive stages of increasingly deep slow wave sleep interrupted by brief episodes of rapid eye movement (REM) sleep [3]. This cycle of approximately 90 min duration occurs 5–6 times per night. Interestingly, the proportion of REM sleep increases in the second part of the night [4]. The electroencephalogram (EEG) pattern of the different stages of sleep has been extensively described: Non-REM sleep is characterized by slow cortical waves of great magnitude, which reflect the progressive involvement of the thalamic pacemaker triggered by the inhibition of peripheral sensory afferents to the reticular nucleus of the thalamus. There is a shift from a predominantly alpha rhythm to theta and delta rhythms from stage 1 to 4 of non-REM sleep. REM sleep corresponds to a cortical desynchronization pattern on the EEG, which is close to that of an awake individual (beta rhythm).

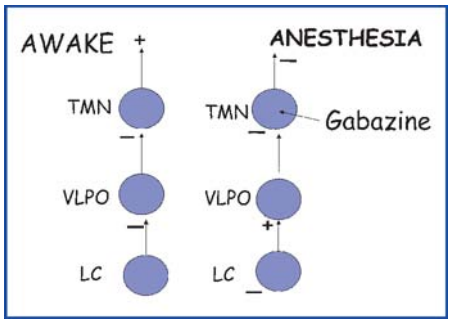

Fig. 1. Dexmedetomidine induces anesthesia via modulation of neuronal pathways belonging to non-rapid eye movement (REM) sleep network. Gabazine (GABA-A receptor antagonist) injected *in situ* into the tuberomamillary nucleus (TMN) reverses anesthesia induced by dexmedetomidine. LC = locus ceruleus; VLPO = Ventroposterolateral nucleus of the thalamus

Sedatives and analgesics are widely given to ICU patients to improve tolerance to the ICU environment. An intriguing question relative to the mechanisms whereby these agents produce loss of consciousness is whether anesthetic/sedative-induced hypnosis mimics, at least in part, natural sleep; for example, EEG patterns achieved by propofol share common features with natural sleep (slow wave activity mimicking slow wave sleep). A large body of recent work has shed light on the understanding of the molecular and cellular targets of anesthetic actions in the central nervous system (CNS). Hypnosis, immobility and amnesia are mediated by a restricted number of ligand- and/or voltage-gated ionic channels, some of which are coupled to key neurotransmitter receptors. Anesthetic/sedative agents, such as propofol and benzodiazepines, enhance the activity of these receptors/channels, mediating gamma-aminobutyric acid (GABA)-A receptor inhibitory neurotransmission in the CNS. In addition, most anesthetics decrease the activity of excitatory glutamate- and acetylcholine-mediated neurotransmission [5]. Neocortical circuitry appears crucial in the induction of hypnosis by anesthetics because of the presence of GABA-A receptors in most of these areas. Anesthetics may disrupt the balance in some neuronal networks involved in the generation of non-REM sleep to produce their effects; this is particularly the case for the locus ceruleus-hypothalamic-cortical circuit. Disruption of this balance may occur by shutting off the activity of the noradrenergic neurons via stimulation of the alpha$_2$-adrenoceptors of the locus ceruleus, as is the case for dexmedetomidine, or at the tuberomamillary nucleus for anesthetics that behave as GABA-A receptor agonists [5–8] (**Fig. 1**). De-afferentation of brain arousal systems is also observed during non-REM sleep, leading to thalamocortical slow oscillations (1 Hz). Several lines of evidence support the idea that the integration of cortical information is lost during non-REM sleep, as has been also shown, in a series of elegant brain imaging experiments, to occur during anesthesia [9]. Alteration in the cortical integration of information may occur before the activity of subcortical structures, such as the subthalamic nucleus, has been shut off by anesthetics [10]. Although there is evidence that physiological non-REM sleep and sedation/anesthesia may involve the activation of common neuronal pathways, pharmacological sedation cannot be considered identical to natural sleep.

Exploring Sleep in ICU Patients

Several methods are available to explore sleep at the bedside. Polysomnography is the gold standard for measuring sleep. Appropriate recording requires monitoring of

at least three EEG signals, two electro-oculography signals, and a submental electromyography (EMG) signal. [1] In addition, signals such as airflow, pulse oximetry, electrocardiogram (EKG) and thoraco-abdominal movements are also recorded. The measurement of noise and light is optional. While polysomnography is easily achievable in volunteers or patients in the context of a specialized unit, its applicability to ICU patients remains a challenge. One main reason is the difficulty of obtaining reliable EEG recordings due to interference from ICU monitoring equipment. Interestingly, small recording devices are now available and should simplify the measurement of sleep in ICU patients. An important methodological point is the necessity of 24-h as well as 8-h recording periods, because of the presence of uncoupling of the normal day-night cycle in ICU patients, which favors daytime sleep. Also, measuring sleep in ICU patients reveals a significant number of abnormalities in the patterns observed, compared with volunteers. Pharmacological sedation and the alteration of consciousness or the presence of pre-existing disease represent potential causative factors. Therefore, sleep scoring in ICU patients most likely requires adaptation of the usual rules to this particular subpopulation.

Actigraphy may provide a simple, easy-to-use method, which has proved reliable in assessing wake-sleep cycles in ICU patients. Nevertheless, it simply measures the movements of a limb and does not record raw EEG data. For example, it generally underestimates sleep onset latency because many individuals are awake and inactive for a period of time before sleep patterns are detectable on EEG [11]. Specific factors due to a patient's status (neuromyopathy, motor deficit) may also limit the accuracy of actigraphy to reflect sleep in the ICU. Therefore, data obtained with actigraphy should be interpreted with caution in this critically ill patient population [12]. The value of measuring sleep with other devices that use EEG recordings, such as the bispectral index, has yet to be proven.

Finally, a simple, realistic, but subjective measurement of sleep in ICU patients consists of interviewing patients at a distance from their ICU stay using specific questionnaires, such as the Richards-Campbell Sleep questionnaire. This consists of a 5-item visual analog scale that aims at measuring the quality of sleep as perceived by the patient [13]. This approach should be considered for ICU patients because the ICU environment, severity of illness, and polymedication make it extremely difficult to identify independent predictors of altered sleep architecture in this patient population.

Characteristics of Sleep Alteration in ICU Patients

Sleep is severely disturbed in ICU mechanically ventilated patients [1, 2, 13]. Sleep deprivation is one of the most painful events reported by ICU patients after discharge [14, 15]. Of note is the fact that persistent sleep disturbances have been reported in a significant number of ICU patients several weeks after discharge. Whether sleep disturbances impact on patient outcomes by increasing ICU morbidity or even, possibly, mortality remains to be determined. However, there is indirect experimental and clinical evidence that this may be the case, and that sleep disorders may contribute to increased weaning time from the ventilator or favor the occurrence of post-ICU cognitive dysfunction. The results of sleep studies in ICU patients must be interpreted with caution because of methodological limitations. Study limitations include a restricted number of enrolled patients and the diversity of methods used to quantify sleep disturbances, together with limitations inherent

ICU environment
Frequent nursing and care
Permanent exposure to light
Permanent exposure to noise
Forced loss of physical activity
Severity of disease
Sepsis
Mechanical ventilation (pressure support ventilatory mode)
Sedatives and analgesics (propofol, benzodiazepines, opioids)
Antiepileptics, adrenergic agents

Table 1. Factors interfering with sleep in the ICU.

to these methods. Polysomnographic recordings indicate that sleep disruption, sleep stage changes, and sleep architecture organization are severely altered in mechanically ventilated ICU patients. The proportion of stage 1 non-REM sleep, which accounts for < 5 % of total sleep time in healthy individuals, represents up to 60 % of sleep in ICU patients. Conflicting results have been obtained from studies, probably because specific patient subpopulations may exhibit different sleep disturbances (surgical vs non-surgical, severity scores on admission, etc.) [1]. For example, REM sleep is markedly reduced, even suppressed, during the night following surgery.

Sleep fragmentation represents another unique feature in mechanically ventilated ICU patients. Indeed, it has been shown that multiple episodes of awakening occur during a single night in these patients, leading to frequent sleep interruptions [1]. Interestingly, the circadian rhythm, assessed by the onset of melatonin secretion, was altered in a majority of ICU patients. Whether there is a direct relationship between sleep alteration and profound changes in the circadian rhythm remains, however, to be investigated.

The understanding of sleep disturbances in the ICU is an exciting area in which there are more questions than answers to date: For example, whether the severity of illness impacts on sleep quality is not known. One study found that patients with acute myocardial infarction exhibited severe alterations in sleep architecture (increased arousal, decreased REM sleep) despite controlling for common environmental sleep-disrupting factors [16]. Recent studies have identified specific factors related to the ICU that interfere with natural sleep (**Table 1**).

ICU Environment

The ICU environment may be perceived as a hostile situation with the potential to compromise patients' rest and periods of sleep time. Noise, including frequent alarm sounds, continuous light in most ICUs, and 24-h patient care represent important environmental factors that prevent sleep restoration. However, a causal relationship between the level of noise and frequent awakening/arousal remains difficult to establish, particularly because of the great number of episodes of awakening per patient (sleep fragmentation). Loss of physical activity may also favor sleep disruption. This was suggested by the results of one study in volunteers staying in bed in an ICU environment who experienced disturbances of the sleep-wake cycle and slept most of the time during the day [14]. Severity of disease has also been suggested to influence sleep patterns in ICU patients. In a study by Gabor et al. [14], patients hospitalized in the ICU had shorter sleep times and reduced slow wave sleep duration than healthy volunteers staying in the ICU at the same time.

Mechanical Ventilation

Several lines of evidence support that mechanical ventilation with positive pressure is associated with frequent arousals, but the mechanisms by which it disturbs sleep in ICU patients remain poorly understood. One particularly interesting but unresolved issue is the discrepancy between the beneficial effects of mechanical ventilation with continuous positive airway pressure (CPAP) in improving sleep in patients with sleep apnea syndrome and the detrimental effects of mechanical ventilation with positive pressure on sleep quality in ICU patients. An interesting hypothesis is that when the pressure support mode is used, the level of support used during the day may be excessive during sleep, leading to passive hyperventilation and frequent arousals. This hypothesis has been confirmed by the results of several studies [17–20].

The effects of assist control ventilation and pressure support ventilation on sleep fragmentation have been examined in one study in healthy volunteers [17], in which the pressure support mode was associated with increases in the number of central apneas and subsequent sleep fragmentation in comparison with assist control ventilation. The role of patient-ventilator asynchrony was recently investigated in a randomized crossover trial in which ICU patients were randomly allocated to receive pressure support or proportional assist ventilation during the first night, and *vice versa* during the second night [18]. There was a significant reduction in the number of arousals per night with the proportional assist ventilatory mode (16 [range 2–74] vs 9 [range 1–41], $p = 0.02$). In addition, sleep quality was better with the proportional assist ventilatory mode, with significantly fewer arousals and awakening episodes per hour, and greater slow wave and REM sleep than with the pressure support ventilatory mode. During the night, the partial pressure of CO_2 in the arterial blood ($PaCO_2$) was found to be higher with the proportional assist ventilatory mode because of lower tidal volumes and minute ventilation. Finally, patient-ventilator asynchronies were also lower and correlated with the number of arousals per hour. A third study performed on mechanically ventilated ICU patients with acute or chronic respiratory failure confirmed and extended these findings [19]. In another study, the effect of proportional assist ventilation with superimposed automated adjustment of flow and volume assist (PAV+) on sleep quality in mechanically ventilated patients was compared with that of the pressure support ventilatory mode. PAV+ did not adversely affect quality of sleep despite frequent and short end-inspiratory occlusions [20].

Taken together, these data strongly suggest that mechanical ventilation has an impact on sleep disturbance, and provide an interesting hypothesis by which to improve sleep quality in ICU patients.

Drugs

Critically ill patients receive a significant amount of drugs, many of which interfere with sleep [21]. Although the impact of each drug on sleep architecture could be satisfactorily assessed in volunteer experiments, this is not realistic in the complex environment of the severely ill polymedicated ICU patient. Several key points need, however, to be discussed. Pharmacological sedation is often required to achieve security and comfort for ICU patients, and to adapt them to the ventilator. Sedatives such as propofol or benzodiazepines induce a reduction in the metabolic rate, hypotonia, and a decrease in vigilance, a pattern that can be observed in physiological

sleep. However, physiological sleep can be reversed by external stimuli. The relationship between anesthesia/sedation, circadian rhythm, and sleep disorders is complex and remains incompletely understood to date. For example, sleep deprivation potentiates anesthesia and prolongs the recovery delay in rodents [22]. A 20-min infusion of propofol in patients undergoing colonoscopy increases diurnal rest without changing nocturnal sleep in the days following anesthesia [23, 24]. Elegant experiments performed both in rodents and in patients support the idea that anesthesia/sedation resets circadian timing and may act as a synchronizing cue for the circadian clock [25]. Therefore, a nocturnal increase in sedation dosage may not necessarily improve quality of sleep in ICU patients. Whether continuous versus daily interrupted sedation differentially affects sleep quality in the ICU has not been addressed to date. Moreover, withdrawal syndrome may be observed upon the cessation of intravenous sedation and analgesia in mechanically ventilated ICU patients. The impact of this syndrome and, more generally, agitation episodes on sleep restoration in the ICU remains unknown.

Many other agents interfere with natural sleep in volunteers, but the relevance of these findings to the polymedicated sedated critically ill patient remains to be determined [1, 2]. Opioids, a commonly used analgesic medication in the ICU, reduce both slow wave and REM sleep. It has been suggested that catecholamines such as epinephrine, which are also frequently administered to ICU patients, may enhance propofol-induced sedation scores. Therefore, it cannot be excluded that catecholamines may also have an impact on sleep restoration.

Impact of Sleep Disturbance on Patient Outcome

Whether sleep disturbances impact on patient outcomes by increasing ICU morbidity or, possibly, even mortality remains to be determined. However, there is indirect experimental and clinical evidence that this may be the case, and that sleep disorders may contribute to altered weaning from the ventilator or favor the occurrence of post-ICU cognitive dysfunction. The consequences of sleep deprivation have been primarily studied in volunteers. Although they may also apply to ICU patients, the effects of sleep deprivation/disorganization on morbidity and mortality have not been extensively studied in this specific patient subpopulation and the results of studies in healthy volunteers require cautious extrapolation to the ICU population.
A large body of experimental work supports the idea that sleep deprivation leads to cachexia, septicemia and even death. Alterations in immune functions caused by sleep deprivation may account in part for these findings: Sleep deprivation results in antioxidant activities [2]. In human volunteers, sleep restriction alters the immune functions of peripheral blood white cells and natural killer cells *in vitro*. A significant link has also been demonstrated between sleep, circadian rhythms, and hormones or pro-inflammatory cytokines, suggesting that, potentially, sleep deprivation may alter the host defense against sepsis. For example, lipopolysaccharide administration induces sleep disorganization, depending on the dose delivered. Sleep deprivation produces a negative nitrogen balance, which may affect respiratory muscle mechanics [1, 2]. While these effects have no consequences in volunteers, it can be speculated that they may significantly increase the duration of weaning from the ventilator in ICU patients.

Delirium is a frequent adverse event observed in mechanically ventilated, sedated ICU patients [26]. Robust clinical data indicate that delirium is a predictor of mor-

tality at 6 months in the ICU. Whether sleep deprivation may cause delirium in ICU patients remains a matter of debate. It is tempting to speculate that there is a link between the cognitive dysfunction experienced by patients after an ICU stay and sleep disturbances. Severe cognitive alterations have been reported at distance from an ICU stay in ICU survivors. Essential cognitive domains, such as working memory and attention, are highly sensitive to sleep deprivation. Whether post-traumatic stress disorders after the ICU stay may be promoted by sleep disturbances during the stay is also an interesting working hypothesis, which remains to be addressed.

Therapeutic Interventions to Preserve/improve Sleep (Table 2)

Focusing on the preservation/improvement of sleep in ICU patients will represent a major change in the healthcare of ICU patients over the coming years. Although not definitely proven, the detrimental role of sleep disturbance on the outcomes of ICU patients should be taken into consideration. Targeting sleep preservation in ICU patients requires a multimodal strategy that includes minimal environmental disturbance, optimized ventilatory mode, and use of sleep-promoting sedatives. Achieving patient comfort, including the preservation of sleep, while at the same time being able to perform rapid interventions, are difficult factors to reconcile. Nevertheless, all attempts should be made to find a good compromise between patient safety and tranquility.

Table 2. Therapeutic interventions that limit the consequences of sleep disturbances in ICU patients

Avoid oversedation
Attenuate noise and light
Limit nursing interventions when feasible
Change to assist-control or proportional assist ventilatory modes at night
Use selected pharmacologic interventions

Attenuation of Noise and Light

The attenuation of noise is recommended. While the alarm tone is difficult to avoid for safety reasons, particular attention should be paid to loud conversations carried out by the medical and nursing staff in the ICU. The role of light attenuation during the night, or better, the synchronization of light with the nycthemeral cycle, should be emphasized, since it contributes to the preservation of the cycle of melatonin secretion [27]. Although of limited efficacy, the use of earplugs and eye-masks has been shown to improve sleep perception in a cohort of ICU patients; however, the number of awakenings remained unchanged [28]. Control of noise and light intensity in the unit requires education of the nursing staff by convinced intensivists. The use of clocks may also be useful with patients to help restore their perception of the nycthemeral cycle. Attention should be paid, however, to the fact that not all clocks differentiate between am and pm periods. However, some types of 'noise' can be beneficial. In one carefully controlled, randomized, double-blind, placebo-controlled study, a decrease in sedative requirements was required during the playing of a piece of music by Mozart [29]. The explanation for this proposed by the authors, was a reduction in the secretion of pro-inflammatory cytokines, particularly interleukin (IL)-6, via the influence of the hypothalamo-pituitary-adrenomedulla axis on the non-specific immune system. In some specific postsurgical patients, music listening was associated with an improvement in sleep quality.

Limiting Interventions

Limiting nurse interventions during the night to those strictly necessary should also be encouraged in less severely ill patients. Unnecessary blood samplings scheduled for the night should be postponed until the next morning.

Changing to Assist-control or Proportional Assist Ventilatory Modes

The amount of data showing the adverse effect of patient-ventilator dyssynchrony on sleep quality supports efforts in this direction. In patients ventilated under a pressure support mode by day, a shift to assist-control or proportional assist ventilatory modes at night should certainly be considered in order to reduce the number of central apneas. An interesting suggestion is to individually monitor the $PaCO_2$ threshold for central apnea in each patient.

Use of Pharmacological Interventions

Pharmacological interventions aimed at facilitating sleep preservation in ICU patients will certainly represent a key factor in the near future. The infusion or enhancement of doses of propofol and midazolam during the night may improve sleep perception. However, as discussed previously, pharmacological sedation does not equate to physiological sleep, and may even induce significant disturbances in sleep architecture. In addition, the prevention of delirium requires avoidance of excessive regimens of continuous intravenous sedation. Melatonin supplementation may be helpful in some patient subpopulations, such as medical patients with chronic obstructive pulmonary disease (COPD).

Interestingly, a growing body of evidence supports the idea that the use of dexmedetomidine as a sedative in ICU patients could be of major interest with respect to the preservation of sleep, and more generally, cognitive brain functions. Dexmedetomidine is a selective $alpha_2$-adrenoceptor agonist that exhibits unique properties among the sedatives available for ICU sedation: It is a sedative and an analgesic, and preserves the ventilatory drive while exhibiting potent sympatholytic effects, producing reductions in heart rate and blood pressure. Because of these latter actions, its use in patients with severely compromised left ventricular function of high-degree bundle block is not recommended. The sedative pattern of dexmedetomidine is unique in that continuous infusion ensures adequate sedation levels, as judged by intensivists in charge of the patient, and preserves rousability. Dexmedetomidine exhibits neuroprotective properties against experimental ischemic injury [30]. Interestingly, there is clinical evidence that the EEG pattern associated with dexmedetomidine sedation mimics that of non-REM sleep [31]. This unique property makes this agent an excellent candidate to attenuate sleep disturbance in the ICU and the putative consequences of an ICU stay on long-term cognitive functions. Two major recent clinical trials – SEDCOM (Safety and Efficacy of Dexmedetomidine Compared With Midazolam) and MENDS (Maximizing Efficacy of Targeted Sedation and Reducing Neurological Dysfunction) [32, 33] – demonstrated superiority of dexmedetomidine over lorazepam in preserving brain function in mechanically ventilated ICU patients. In both trials, dexmedetomine-sedated patients experienced significantly more delirium-free and coma-free days in the ICU than those receiving lorazepam. No effect on survival was found; however, there was a trend towards improved survival in the sepsis subgroup of patients in favor of dexmedetomidine in

the MENDS trial. Although no measurement of sleep was performed during these trials, it can be speculated that the beneficial effects of dexmedetomidine towards the preservation of sleep may have contributed to the improved brain function in ICU patients.

Conclusion

ICU sedation is at the onset of a fascinating era. Some physiological functions, such as sleep, have been disregarded for years, but are now becoming a major topic of interest for ICU patients. Whether sleep disturbance represents a predictor for worsened outcome or is simply a surrogate marker of the severity of disease cannot yet be delineated. Nevertheless, a large body of evidence suggests that sleep disorders negatively impact on outcome in the critically ill. Interestingly, sources of sleep disturbances arise from healthcare inside the ICU, including drugs, environment, mechanical ventilation, sedation. This should prompt intensivists to revisit their practice by considering preservation of sleep in ICU patients as an important, and not surrogate, target. In any case, this topic opens up an exciting path for future outcome-targeted clinical research in intensive care.

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Communication in Crisis: The Importance of 'Verbal Dexterity'

XIX

P.G. Brindley

"Meant is not said,
Said is not heard,
Heard is not understood,
Understood is not done" [1]

Introduction

Human factors are the number-one reason for commercial jet planes to crash. Furthermore, of all possible human factors, communication is the number one offender [1–3]. Evidence suggests exactly the same for acute care medicine [4–12]. However, in contrast to aviation, medical curricula focus on factual knowledge and procedural dexterity but rarely address ingrained culture or its effect upon communication [4–11]. The airline industry felt compelled, as lives, and profits, were at stake [2]. With medical errors believed to cause almost 100,000 deaths annually in the USA, and representing the eight leading cause of preventable death [13–14], we ought to be similarly motivated. This chapter hopes to offer practical strategies so that our 'verbal dexterity' can match our procedural dexterity. This will be done primarily by translating lessons from the flight deck to the bedside. After all, if other high-risk industries such as aviation can do so, then at least as much should be expected of acute care medicine.

The Importance of Communication and Culture

The typical fatality rate for major first-world airlines is approximately one per 4 million flights [2, 3]; in the 1990s, the fatality rate for Korean Air was more than 17 times higher [2]. Other airlines considered suspending partnerships, and nations considered revoking landing privileges. Today it is an award-winning airline with an exemplary safety record. Aviation has offered many lessons for acute care medicine [10–12], but the first from Korean Air was that neither inexperience nor poor equipment were to blame. Korean Air did not succeed until it acknowledged the importance of communication, and specifically how it is influenced by culture [2]. If we accept the parallels between high-risk industries such as aviation and critical care medicine then we should also have the maturity to implement its lessons. Some medical specialty boards have now decreed that trainees and practitioners be proficient communicators. However, this laudable goal is difficult to capture using traditional educational methods [16]. Furthermore, these are difficult skills to master, as they require a change in interpersonal dynamics, organizational culture, and communication norms. This means that we need to be innovative. Practical strategies already exist and will be outlined below. How Korean Air, and others, transformed their culture and communication is therefore worth dissecting.

Airway, Breathing, *Communication*: The New ABCs of Crisis Management

Flight investigators concluded that cultural factors such as speech patterns, authority gradients, and the inability to handle ambiguity, were some of the most common contributors to plane crashes [2, 17–18]. Airlines from cultures that typically rely most upon rigid rules, regardless of circumstances, also experience the greatest number of crashes [17, 18]. Similarly, crashes are more likely for cultures with the greatest reluctance to question authority [17, 18]. Most pilots and aviation regulatory boards now support 'horizontal authority' [2, 17, 18]. Notably, physicians and hospitals typically still do not [10]. Similarly, pilots think it is appropriate to select trainees based upon their ability to deal with ambiguity and to function in teams. Medicine typically still focuses upon written grades, individual aptitude, or research productivity.

Several languages (including Korean) require different word choices and sentence structure based upon the hierarchy of the speaker and the recipient [2, 19]; this can complicate simple communication. This can also perpetuate unhelpful authority gradients. As such, most airlines use English in the cockpit. The message for medicine is categorically not that any one language is superior to another, but rather that 'verbal dexterity' means using speech that is appropriate to the situation. For example, we accept the importance of communication when dealing with families and colleagues. However, unlike aviation, medicine has yet to widely accept (or actively teach) its importance in more acute situations. Furthermore, in aviation, communication is taught to both supervisors and subordinates. This way, supervisors can appreciate that questioning their authority is not intended to be threatening, at the same time that subordinates understand how best to question.

"Say what you Mean, and Mean what you Say"

Some languages (again, Korean is a prime example) are 'receiver orientated' [19]. This means it is up to the listener to make sense of what is being said. Again, nobody is arguing for all medical care to be conducted in English, nor is anyone arguing that one language is inherently better than any other. Instead, the lesson is that a 'receiver orientated' style only works when the listener is capable of close attention, or if time exists to unravel the meaning. It does not work in a cockpit on a stormy night, or with an exhausted pilot. It is not likely to work in a crowded resuscitation bay, or with a tired physician. In contrast, western languages are typically 'transmitter orientated' [19], meaning it is the responsibility of the speaker to communicate clearly and unambiguously. This means that there is an expectation that the speaker will make the effort to be understood, and that if they fail then it is the speaker's shortcoming – not the listener's.

Cognitive psychologists talk of the 'framing effect', which suggests that different decisions may be made depending upon how information is presented [20]. For medicine, the message is that good resuscitators are also good communicators. For the revamped Korean Airlines it meant that flight crews were expected only to use 'transmitter orientated' language [2]. There is no reason why we should tolerate any less from critical care staff. However, we can learn far more from the misfortunes of the former Korean Air. This includes not just what should be said (i.e., verbal communication) but also *how* it should be delivered (i.e., paraverbal communication) (**Table 1**).

Table 1. Potential acute care communication strategies.

Communication Strategy	Medical example
Combating mitigating language	*"Get me a surgeon"* *"Intubate the patient now"*
'Flying by voice'	*"We still have no pulse* *...what are we missing?".*
Graded assertiveness	Command: *"Do this now"*; Statement: *"We need to do the following"*; Shared suggestion: *"you and I should..."*; Query: *"what do you think we should do";* Preference*: "I think it would be wise"*; Hint: *"should things look like this".*
Focus on advocacy	*"Patient is hypotensive...we need help"*
Divide comments into one of four categories	Aggressive (*"what the hell happened"*); Submissive (*"I'm sorry to bother you"*); Cooperative ("I could use your help"); Assertive *("this is what I think").*
Repeat back method	*"okay, so that's 3mg of epinephrine"*
SBAR	Situation*: "I wish to sign over a patient"*; Background: *"He's a 35 year old trauma"*; Assessment: *"He's at risk for infection"*; Recommendation: *"Obtain cultures".*
Step back method	*"Stop chest compressions, while I reassess the heart rhythm"*
Below-ten	*"I want your opinion... do you have time to listen?"*
Closed-loop communication	*"Intubate the patient...and tell me when its done"*

SBAR: Situation-Background-Assessment-Recommendation

Mitigating Speech: "No ifs, and, or Buts"

'Mitigating speech' refers to language that 'de-emphasizes' or 'sugarcoats'. We mitigate speech to be polite, deferential, or when embarrassed or unsure. Again, Korean, as a language, is characteristic for its use of mitigating language [2, 19]. However, mitigating language appears to be a common feature prior to airline crashes, regardless of the airline or cockpit language. A review of hundreds of hours of medical simulation recordings also found mitigating language to be a common feature of inadequate medical crisis management [21].

In situations where time permits, mitigating language may be harmless. In fact, it may even be preferable if the primary goal is team building rather than acute intervention (e.g., "excuse me, but, when you get a moment, would you mind helping me with this patient?"). However, in a cockpit during non-routine flights it has been shown to be potentially deadly [2]. Presumably the same could be true during resuscitation of an unstable patient. In these circumstances, time-pressure, or the need to coordinate multiple tasks, means that communication should be brief and task-focused. It also means that team members must learn to be less concerned with offending, or being offended.

Combating 'mitigation' became one of the great crusades of aviation, just as it should now become one of medicine's. Overly cautious, or overly mitigating, language is inappropriate during crises in the same way that overly brusque language

is inappropriate when the goal is team-building (see below). This is why, during crises, we need to replace comments such as "perhaps we need a surgeon" or "we should think about intubating", with "get me a surgeon" and "intubate the patient now". Communication during crises should still be polite, but it must be unequivocal. With this in mind, Crew Resource Management (CRM) was developed to teach junior aircrew to communicate clearly and assertively. Dr David Gaba and others modified the lessons from aviation to create medicine's CRM, where the initials now stand for *Crisis* Resource Management [10, 11]. Regardless, as specialists in critical care we should also be specialists in critical communication. Our task as educators should be to disseminate these lessons, and to advocate for space in the medical curriculum. In the meantime, our first goal should be simply to get subordinates to speak up.

Silence is not always Golden

A common feature of poorly coordinated resuscitations is how little is said (e.g., a typical complaint during post-resuscitation debriefs is that it was unclear who was in charge). Similarly, the flight black-box recorder is often silent in the minutes before a crash [2]. Pilots are therefore taught to 'fly by voice', to announce what they intend to do. This strategy invites confirmation or correction from others. Similarly, healthcare personnel should learn to 'resuscitate by voice'. A simple example during cardiopulmonary resuscitation would be: "we're ten minutes into this resuscitation and still have no pulse...what are we missing?". Alternatively, if a healthcare worker announces, "I am going to give medicine X" it encourages a 'double-check' where others can prevent this action if that patient has a contraindication or an allergy. However, as we try to achieve the cultural change that encourages subordinates to speak up, we also need to teach how to be appropriately assertive. Once again, strategies can be borrowed from aviation.

Graded Assertiveness: Getting the Message Across

When teaching 'graded assertiveness' [20], pilots are taught about six basic command types from the most to least direct: Command ("do this now"); statement ("I think we need to do the following"); shared suggestion: ("you and I should do the following"); query ("what do you think we should do"); preference: ("I think it would be wise") and hint ("should things look like this"). Studying Korean Air showed that captains used more commands as they had little concern with being blunt [2]. The major problem was that first officers would overwhelmingly choose a more mitigating style, and frequently did no more than hint. Moreover, when initial hints were ignored, subordinates would not modify their comments beyond a hint [2]. In other words, they failed to escalate their assertiveness.

Another practical strategy is to communicate using a five step approach that focuses on advocacy [20]. The following includes aviation examples, and medical corollaries:

1. Attention getter: Address the individual (e.g., *"Excuse me, Captain/Doctor"*)
2. State your concern: Use clear language and include your own worry (e.g., *"We're low on fuel/the patient is becoming increasingly hypotensive"*)

3. State the problem as you see it (e.g., *"I don't think we have enough fuel to take evasive action/I think we need to get help, now"*)
4. State a solution (e.g., *"Let's re-route to another airport/I'll phone ICU to arrange transfer"*)
5. Obtain agreement (e.g., *"Does that sound good to you, Captain/Doctor?"*)

Another strategy to better understand which communication is likely to help, versus which is likely to hinder, is to conceptualize comments as belonging to one of four categories: Aggressive (e.g., "what the hell happened"); submissive (e.g., "I'm sorry to bother you"); cooperative (e.g., "I could use your help"); or assertive (e.g., "this is what I think"). Obviously, in reality, communication is far more nuanced. For example, the intent of each of the above comments can be altered without changing any words, but simply by changing the volume, or the emphasis on particular words, or by altering body language. However, this compartmentalized approach does explain how overly aggressive *and* overly submissive language changes the interaction from one focused on task to one focused on power. Both overly aggressive and overly passive speech are, therefore, usually inappropriate because neither is patient-focused. Cooperative language is preferable, but, again, things are more nuanced. Cooperative language is best suited when there are minimal authority gradients or during a planned handing-over of control. In contrast, and particularly in acute care, practitioners often need to take over control. As such a more assertive style is needed, and as long as the interaction remains patient-focused, it is appropriate.

Questioning Authority and Handing Over Responsibility: Underappreciated Skills

In order to allow team members to question plans without being disruptive, skillful communicators are careful to frame disagreements as being about ideas not people. Equally, if information or instructions seem incorrect or ill advised, we can use the 'Repeat Back Method' [20]. This means repeating to confirm mutual understanding (e.g., a nurse repeats an order from a physician... "okay, so that's three mg of epinephrine"). Similarly, the 'Read Back Method' [20] is used when transcribing a verbal order or information (e.g., the nurse reads back a telephone order before hanging up).

SBAR communication originated with the military and involves structuring communication into Situation–Background–Assessment–Recommendation [22]. This approach has been widely promoted for transferring care. It can also be used when obtaining a second opinion or formal consult. An example would include:

Situation: *"this is Dr X, I wish to sign over a patient"*.
Background: *"he's a 35 year old trauma victim from last week"*;
Assessment: *"he is surgically fixed, but is at risk for infection"*.
Recommendation: *"I would suggest cultures if febrile"*.

Another communication strategy is the 'Call Out' [20]. This means 'speaking up' to other team members whether completing a task (e.g., "I am increasing the oxygen flow rate"); making an important observation (e.g., "the blood pressure has dropped"); or when something appears to be wrong (e.g., "he's going back into ventricular fibrillation"). Similarly, the 'Step Back Method' [20] means verbally forcing a 'time-out' to reflect on the course of events (e.g., "stop chest compressions, I want to reassess the heart rhythm"), to reassess prior assumptions (e.g., "stop, is that still

ventricular fibrillation?"), or to question the efficacy of the action plan (e.g., "please stop what you are doing. I need you to listen to me").

XIX

Practicing Verbal Dexterity

The 'golden hours of resuscitation' are so called because actions taken during the initial hours play a major role in outcome, whether from coronary syndrome, stroke, trauma, or sepsis. In other words, resuscitation *delayed* really can be thought of as resuscitation *denied*. Unfortunately, these 'golden hours' frequently occur away from major hospitals. As a result, initial stabilization and therapy, triage, and transportation, is all typically coordinated verbally. Our experience is that trainees rarely get practice but are expected to assume this role immediately upon graduation [23].

We have incorporated simulated calls from the critical care line into the education of Canadian trainees in critical care medicine [23]. Regardless of how simulation training is performed what matters most is that there is an immersive experiential, reflective learning, and emotional investment [10, 11]. Our research has shown that telephone simulation is one way to capture the benefits of high fidelity simulation, but without the cost or logistics associated with complex expensive full body simulators [23]. In fact, despite the apparent simplicity (after all, all that is needed is two telephones in two separate rooms), evaluations routinely conclude that telephone simulation is more realistic than full body simulation [23]. This is likely because participants no longer have to suspend disbelief to the extent required with plastic mannequins unable to fully mimic the complexity of a real patient.

Senior trainees are simply paged during a normal workday by our triage phone line. A facilitator then assumes the role of a referring physician in a distant town. Relevant staff members are notified of this exercise, and asked to act as they would during a normal workday. For example, local emergency physicians and internists are notified that they may be brought into the call if the trainee decides, for example, to bring the patient through the emergency department, or for further workup, or if no bed is currently available in the intensive care unit (ICU). Calls are then recorded to aid debriefing. These simulated calls allow us to ascertain how well trainees obtain focused histories, offer practical advice appropriate to the skill set and resources of the referring physician, and even how they deal with complex ethical issues (e.g., what to do if a family wants to override a patient's wishes, or how aggressively to treat a terminally ill patient for whom no philosophical discussions have occurred). In other words, we can test not only acute care communication skills, but also how they are applied in a realistic setting [23].

Managing Interruptions and Distractions

Flight investigators have identified that cockpit interruptions are so concerning that they are now addressed in the Standard Operating Procedures for the Airbus [24]. These rules and regulations promote the 'sterile cockpit rule' to minimize distractions – especially when the plane is below ten-thousand feet [24]. Commercial airliners are only below ten thousand feet for three reasons: Take-off, landing...or crashing! This means that *no* non-operational talk is allowed 'below ten'.

The freedom to 'chat' is important for team building, or stress relief, but not during impending crises. Translated to the medical world, the 'sterile cockpit rule'

explains why the anesthetist should resist idle chatter while a surgeon is operating. It also explains why the surgeon should keep the operating room quiet during induction or awakening. It explains the appropriateness of confirming that another person is free to attend to your concern (e.g., "I want your opinion on a complex patient, do you have time to listen?"). Regardless of whether medical personnel ultimately use the actual words 'below ten' (e.g., "I'll have to get back to you, I'm currently 'below ten'"), this concept could reduce the reluctance of team leaders to request that team members focus their comments. It could also reduce offense from those asked to be silent.

Communication really Ought to have Three Cs

The 'three Cs of communication' means using Clear instructions, Citing names, and most importantly, Closing the loop [2, 10–11, 22, 25]. This third component, closing the loop, means reinforcing instructions by eliciting feedback (e.g., "John, please intubate the patient, and tell me when it's done"). Closed-loop communication is widely taught in aviation (e.g., "Roger, control tower, I am ready to take-off, do you copy?"). Our research of acute medical communication showed insufficient closed-loop communication, with gradual, but still inadequate, improvement following simulations [21, 25]. Physicians inconsistently communicated what they were doing or why. Furthermore, when they did communicate it was often only to other physicians rather than to the entire team. Our nurses, and respiratory therapists, also tended not to share what they had done or request future direction (e.g. "I have increased the oxygen level"; or "the fluid is in, would you like more?"). There were also lengthy delays between when they first identified a patient concern, and when this was shared with the team.

In order to improve closed loop communication, we performed additional simulations, but now with the physician leader blindfolded [25]. We found marked and immediate improvements. Physicians elicited more help and were more likely to confirm that instructions had been carried out. Other team members were more likely to communicate when tasks were completed, and volunteered changes in vital signs sooner. We speculate that this simple intervention encouraged behavior modification by creating an environment that prevented learners from relying upon pre-existing communication norms. Debriefing also confirmed that this simple, cost-free, addition to medical simulation was well received. The analogy can be made that in early, undifferentiated, shock, we are all essentially 'blind' to what is going on. We also demonstrated that this strategy is useful for trainees working in a language other than their mother tongue [25]. Blindfolding forced the participant to focus on their communication skills (with the goal of increasing the physician's self-confidence). It also provided useful feedback to supervisors. It is now an expectation of senior trainees to perform at least one blindfolded simulated-resuscitation.

Conclusion

Worldwide, fewer planes crash when the co-pilot is flying [2]. At the beginning of this manuscript that might have seemed contradictory, after all, the senior pilot has more experience. However, once we accept the importance of culture and communication it makes sense. Planes are probably safer with subordinates at the wheel

because the senior pilot is unafraid to speak up and the subordinate is more empowered [2, 12]. Furthermore, two people, rather than one, fly the plane. The medical corollary is that a second opinion is obtained. Regardless, each looks out for danger, each tries to determine the best way to respond, and each offers clarification and correction for the other.

Enhancing communication means encouraging a new culture that permits the respectful questioning of authority. Ultimately, verbal dexterity may be one of the most important skills in acute care medicine. Accordingly, we should regard the voice-box as one of the most important pieces of 'medical equipment'. Regardless, if communication is such a major determinant of safe patient care then there really is no excuse but to address medicine's 'missing curriculum' [26]. I cannot speak clearer than that.

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Patient Safety and Acute Care Medicine: Lessons for the Future, Insights from the Past

XIX

P.G. Brindley

"All truth passes through three stages:
First it is ridiculed,
Second it is violently opposed,
Third it is accepted as self-evident [1]."

Arthur Schopenhauer 1788 – 1860

Introduction

It is estimated that approximately 40,000 – 100,000 Americans die annually from medical errors [2]. Thousands more suffer harm from medical errors. Still others are exposed to errors, but are lucky enough to suffer no obvious harm [3]. In fact, medical errors are now the eighth leading cause of death in the USA; data are no less alarming from other nations [4]. Regardless of the exact figures, it seems that patient safety is far from adequate. Crudely put, if medicine were a patient, we physicians would say it is time to admit there is a problem. We would expect urgent action, and we would welcome any ideas, rather than tolerate further delays. This chapter hopes to provide a call-to-arms, but most importantly a range of ideas, both new and old, to achieve the sort of care that our patients deserve.

'The Missing Curriculum' [3]

Albert Einstein stated that: "you can never solve a problem by using the same thinking that created it" [5]. As such, the first step is to emphasize that medical errors are rarely merely negligence, sloppiness, incompetence, or poor motivation. Instead, we should accept that healthcare is amongst the world's most complex social systems [3]. Coupled with the complexity of medical diagnosis, and the need to make decisions despite time pressure and incomplete information, the shocking patient safety figures make more sense. Perhaps the complexity of the task ahead is also a little clearer.

The slogan states "Safety is no accident" [3]; stated another way, errors in healthcare are rarely random, unpredictable events. Some errors may ultimately be rooted in our organizations and perpetuated by our traditions. Like many complex systems, medicine has a double-headed Janus [6], where these traditions are both our greatest asset and our keenest shortfall. For example, the laudable tradition of self-reliance and patient-ownership means that physicians usually stay until the work is done, and diligently follow patients from admission to discharge. However, downsides include the dangerous effects of fatigue, and a reluctance to permit input from others. It has also created a system where we appreciate that errors occur, just not at a personal level! Centuries of pedagogy also mean we have been slow to implement innovative methods of training. For example, despite functioning in multi-professional teams that require nuanced coordination and communication skills, these skills are rarely deliberately taught, or sought after from applicants [7]. Our traditions also mean that while medical graduates are versed in the science of medicine,

Table 1. Insights for acute care medicine from diverse sources

Example	Insight
Engineering	Most errors are neither random nor unpredictable Benefits of Standard Operating Procedures Usefulness of second-opinions; fail-safes; time-outs Benefits of a systems approach to error and education Apply the Swiss-cheese model to understanding error
Cognitive Psychology	Benefits and detriments of: Gestalt, Law of Prägnanz, premature closure; availability and anchoring heuristics
Human/Machine Interface	Humans excel at pattern-recognition; Computers excel at calculation and vigilance The best system mitigates shortcomings
Chess	Need to concurrently manage multiple threats Two patterns of attention: Focus of predator; gaze of prey Benefits of risk-free simulation

and acquire skills to look after individual patients, few are trained to tackle systemic safety issues, or to understand how humans work in large groups or complex systems. One way to do so is to be open to innovative ideas, regardless of their source (**Table 1**). Another is to change the very way we regard our work.

Engineering and Acute Care Medicine

A favorite debate is whether medicine is more 'science' or 'art'. However, safe patient care could instead be understood as 'engineering'. After all, engineering means "applying the best current technical, scientific, and other knowledge to design and implement structures, machines, devices, systems, and processes to safely realize an objective" [8]. Commercial aviation is far from perfect, and there are differences between scheduled flights and unscheduled medical crises. However, aviation has achieved a log reduction in fatalities. This has been largely accomplished by applying engineering principles. In fact, there is now 1 fatal crash per 4.5 million take offs, and the most dangerous part of many a pilot's day is the airport commute, rather than the subsequent flight [9]. The same cannot be said for patients entering a hospital. An engineering approach would also mandate Standard Operating Procedures (such as protocols and check lists) and implement redundancies (such as double-checks, fail-safes, and time-outs). Engineering theory also means accepting that the complexity of the system exceeds the ability of any one individual. This means encouraging second-opinions and practicing teamwork [3]. Engineering also means accepting continuous updates, and utilizing the best current information, even if imperfect (i.e., "a good solution now is better than a perfect solution later"). In contrast, with our current medical model, imperfect research offers an excuse not to change. With an engineering model, near misses also represent an opportunity to improve the system, especially if freely discussed, and especially if all are permitted to contribute and learn. An open approach fosters a sense of responsibility and empowerment, rather than resignation.

The goal of aviation is safe, efficient, and predictable travel from point A to B. There is no reason why medicine should not similarly promote safe, efficient, and

predictable care from A to D (admission to discharge). Aviation passengers do not mind if pilots divide their task into take-off, flight, and landing. It does patients no disservice if healthcare workers similarly divide hospital care into input, throughout, and output. Furthermore, seeing ourselves as 'product safety engineers' redefines our role to that of coordinating the safe transit of a patient through the system, rather than making us responsible for making every minor decision, or performing every minor treatment.

Engineering and Error Prevention

Using the engineering model, errors are better conceptualized using a system model [7, 10]. For example, in a typical commercial airline crash, there might be a technical problem, but this alone is rarely enough to cause a crash. The crew might also be tired, such that decision-making skills erode, and things are missed that would otherwise not be. The plane might be behind schedule, adding stress and a reluctance to invest the extra time for safety. In addition, many crews have not flown together, so are unfamiliar with each other's style. The sum total of these minor stresses is a team that is 'maxed out', with nothing left if adversity strikes. Most of the time they will be lucky. Some of the time they will not.

An old proverb states that "failing to plan" is "planning to fail" [11]. This is why engineers and pilots also talk about enhancing situational awareness [12, 13]. This is because identifying a discrepancy between what is happening and what should be happening is often the first indication of an error. Enhanced situational awareness promotes a proactive, rather than reactive, approach. Pilots talk about "flying ahead of the plane", because they realize optimal crisis management begins before a crisis erupts. Regardless, defenses against error include personnel, technology, training, and administration [3, 7]. However, most important is culture: The collective attitudes, beliefs, and values [3]. Ideally, the combined layers of defense are impermeable. In reality, there are weaknesses and the layers are – to borrow another analogy from engineering – like slices of Swiss-cheese that contain holes. Fortunately, because there are multiple layers, single errors (i.e., a single hole) do not normally cause a bad outcome. In contrast when mishaps occur, the holes have lined up, at least momentarily [3]. This is why a minor technical problem, fatigue, or time pressure alone, would rarely cause a disaster, but when combined they can. In fact, when errors are dissected (whether following plane crashes, power station meltdowns, or medical mishaps) it is typical to find three or more minor issues resulting in one major error [3].

When an adverse event occurs, a system-approach means that corrective efforts should focus less on *who*, and more on *how* did it happen, *why* did the defenses fail, and *what* can be done to prevent it happening in future. This contrasts with the traditional medical approach where the focus is on assigning responsibility (so called 'name, blame, shame'). Traditional efforts to reduce error, however well intentioned, emphasize discipline, and retraining, but ignore the context in which the error occurred [3]. This is also why they are less likely to prevent recurrence [12, 13].

Understanding the Basics of Human Error

The most common reason for commercial aviation to crash is human error [9, 12 – 14]. The same appears to be true in acute care medicine [2, 3, 12 – 14]. Engineer-

ing therefore incorporates more than just mechanical know-how. A comprehensive strategy also means teaching situational awareness, improved communication, appropriate task distribution, and optimal teamwork [12–14]. This skill set, collectively known as Crew Resource Management, is widely taught in aviation. In contrast, medicine's Crisis Resource Management is rarely included in the standard medical curriculum [12–14]. Physicians, like engineers, should also be taught the basics of why errors occur if we are ever to mitigate them. What follows is a very basic introduction to the field of cognitive psychology.

The 'Gestalt effect' is the tendency to recognize objects or patterns instead of, for example, only seeing lines or curves [15, 16]. To pattern-recognize is an essential part of our ability, and one of our greatest sources of insight [12, 14]. The ability to see connections between seemingly disparate information enables our cleverest diagnoses, and most innovative thought. A simple example of pattern-recognition is the way we are able to recognize that an aging male with chest discomfort, breathlessness, and arm pain likely has an acute coronary syndrome. Early clinical training is all about pattern-recognition. Later on, we gain sufficient experience to pattern recognize automatically, almost without thinking. Unfortunately, as with any action that involves decision-making with minimal thinking, errors can occur [17].

Pattern-recognition is essential for efficient and expeditious medical care, but it requires that we prioritize some pieces of information, while downplaying others. In other words, when we look 'here', we risk missing 'there'. Most medical practitioners are familiar with the benefits of Occam's Razor [18], where we appropriately assume the most common explanation to be correct. However, we are less familiar with the detriments of the Law of Prägnanz, where we also subconsciously organize information into the simplest form possible [15, 17]. We also search for patterns in order to avoid the extra effort required for complex thought or calculation. Moreover, we subconsciously process information to maintain a sense of order and a feeling of competence. We downplay contrary evidence, and are reluctant to pursue alternatives (also known as 'premature closure') [16, 17]. We may even judge the likelihood by how easily the idea sprang to mind (the so called 'availability heuristic') [17, 19, 20]. We then tend to stick with our initial assumptions (the so called 'anchoring heuristic') [17, 19, 20]. This means that we tend to favor diagnoses that we are comfortable treating, overlook more serious possibilities, and even favor the excuse that it is "not my problem" [17]. Overall, an engineering approach means building systems to mitigate cognitive errors rather than assuming they result from mere arrogance, stupidity, or sloth. For example, cockpits are now deliberately configured to have two people operating them. This encourages a system where each checks the other and offers a second input. We have yet to consider the design of acute care areas in similar terms. In the meantime, there is no reason why we could not start by modifying medical education and training.

Educating for Safety

Learning from others could also change how we educate [7, 10]. For example, rather than relying upon teachers to simply cover their favorite topics, with minimal attention to relevance, curricula would be more deliberately matched to the goal of safer care. Routine audits would establish major problem areas (i.e., common shortfalls or steps that require particular precision or the co-ordination of many people). Results would then be widely shared, rather than being the purview of a select few. A curric-

ulum would 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) [10]. The process then begins again. 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 the modern hospital [7, 10]. Accordingly, educators become important agents of change, and as highly valued as good researchers or clinicians.

Maximizing the Best of Human and Machine

As outlined above, modern hospital care mandates an understanding of human factors and of technology. Therefore, understanding this interface is vital. The 1997 chess match between world champion Garry Kasparov and IBM's Deep Blue offers intriguing insights [21]. Kasparov (an example of the human mind) won the first game and Deep Blue (an example of technology) won the second. This proves that both are capable of impressive performance. However, it is more important to look at their respective skills and weaknesses. For example, Deep Blue was capable of evaluating 200 million positions per second, whereas Kasparov could only evaluate a handful and overlooked certain moves when overly focused. As outlined above, the inability to pick up on clues in medicine is known as a fixation error, and is a major source of error, even for experienced practitioners [12, 13].

The computer, Deep Blue, never fatigued, or succumbed to emotions. Kasparov had to be nourished and rested. Deep Blue also possessed a superior opening and end-game. Kasparov could think abstractly and plan long-term strategies. Using pattern recognition, Kasparov recognized fragments from previous games in order to choose the most appropriate few things upon which to focus. When Kasparov won, he did so by maximizing the middle game, namely where there are too many pieces (variables) on the chessboard for computers to calculate all possibilities. When Deep Blue won it was through consistency, aided by impeccable memory [21].

Humans excel at pattern recognition. In contrast, we are often poor at recognizing, or responding to, gradual deterioration. When stressed we are particularly prone to tunnel-vision (ignoring additional clues due to excessive focus) [12, 13, 17]. We are also weak at calculation (11 x 24 = ?). Computers are worse at pattern-recognition, but excel with calculation and vigilance. The lesson for healthcare from Kasparov versus Deep Blue is that healthcare should leverage each in their area of strength: Humans to recognize constellations of symptoms, and computers to monitor vital-signs and activate a response to gradual changes or concerning trends.

Additional insights include how Kasparov and Deep Blue's programmers learnt to mitigate their respective weaknesses. For example, Kasparov used computer chess engines to objectively analyze positions. Deep Blue's programmers teamed up with chess masters who recommended certain strategic moves, based upon their collective experience. It could be argued that both man and machine were actually 'cyborgs': Functional hybrids of each other [22]. Regardless, another lesson from Kasparov and Deep Blue's programmers is that harnessing the best of the human-technology hybrid created more than the sum of its parts [21, 22]. Similarly, we should learn that it is not a battle of human independence versus technological dominance, but the search for synergies in order to achieve excellence. Maximizing the best of the human and the technology is the real victory. Hopefully the patient will be the ultimate victor.

Other Lessons from the Chessboard

Engineering and aviation are well known for their use of simulation as a key strategy to improve safety. However, the game of chess is probably amongst the oldest examples of simulation, and was likely developed to hone military skills [23]. Chess has, therefore, been touted by proponents to emphasize that simulation is well-established, not an untested departure [23]. It is also remarkable how this archetype of simulation has other prescient lessons for acute care medicine, even 6,000 years on.

The ability to manage concurrent threats is essential in chess and in medicine. Interestingly, it is also essential for animals throughout nature. Two classic types of attention exist [24]. The first is the predator's focused-gaze. Whether this means a predator moving in for the kill, a chess player quickly capturing an opponent's queen, or a physician resuscitating a patient, there is a need to attend to only the most pressing issues, ignore less important stimuli...and to hopefully know the difference. The second type of attention is less discriminate vigilance. This is illustrated by the generalized watchful vigilance of prey, the caution shown during chess's opening moves, or the ability to attend to many non-acute issues during routine medical moments, such as daily rounds. In this case, there is a need to be more open to clues, to watch how others react, and to make a more measured response. Presumably good chess players, trusted acute care clinicians, and even wild animals that live to old age, possess both styles; success also means having the versatility to switch between the two.

The fact that 'play' is so widespread in both humans and animals suggests an important role – otherwise natural selection would have selected against it as a waste of scarce energy. Harmless games, like chess, may be beneficial precisely because they might result in 'less harm'. They allow practice in an environment where mistakes can be made with minimal consequences for those involved. This is presumably why play is so common in nature, and also why many medical societies now strongly endorse medical simulation [3, 7]. However, again compared to other high-risk professions, medicine lags far behind [25]. Medical simulation is not yet a routine or mandated part of medical training or ongoing practice. Increasingly the question is not why should we simulate, but rather why do we not?

Conclusion

If we really are serious about designing safer patient care for the future, then we should be open to lessons from all possible sources. As a result, the modest intent of this review was to offer insights from the profession of engineering, the field of cognitive psychology, and even from games such as chess. The conclusion should be obvious – diverse ideas already exist and, therefore, medicine need not 'reinvent the wheel'. However, the question, yet to be answered, is whether as a profession we have the insight, the will, or the humility. So far, no other high-risk industry has waited, or expected the level of unequivocal proof, before making changes [25]. That change is needed should indeed be "self-evident" [1]. Whether the increasing call for change will be "ridiculed" or "violently opposed" [1] represents the next stage in the evolution of acute care medicine and patient safety.

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