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CONFERENCE REPORT

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Mechanisms of organ dysfunction in critical illness: report from a Round Table Conference held in Brussels

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Introduction

The most common cause of death in patients with sepsis or other forms of critical illness is deterioration in the function of multiple organs, now termed multiple organ dysfunction syndrome (MODS). Commonly affected organs include the lungs, liver, and kidneys, and the clinical manifestations of arterial hypoxemia, decreased pulmonary compliance, cholestatic jaundice, oliguria, and azotemia are familiar to all intensivists. Manifestations of central nervous system dysfunction, ranging from subtle alterations in mental status to frank coma, are also common in patients with sepsis. Derangements in gastrointestinal function, including loss of normal peristalsis (i.e., ileus) and enterocytic barrier function, are also common, albeit difficult to quantify, manifestations of MODS. Although a fatal outcome in patients with sepsis and septic shock is virtually always accompanied by MODS, the histopathology of fatal sepsis is remarkably bland. For example, histological sections of liver or kidney tissue from patients dying from sepsis or septic shock occasionally show evidence of focal necrosis or apoptosis ("programmed cell death"), but massive loss of parenchymal mass is rarely observed [1]. Thus the physiological basis for organ dysfunction in sepsis remains a puzzling problem.

To provide a "snapshot" of the state of the art of research into this fascinating problem a Roundtable Conference was recently held in Brussels to discuss and review "Mechanisms of Organ Dysfunction in Critical Illness." The Roundtable Conference was jointly sponsored the European Society of Intensive Care Medicine, the Society of Critical Care Medicine, and the American Thoracic Society. The list of participants included the following clinical and basic scientists from several European countries, Canada, and the United States: A.J. Bauer, T.G. Buchman, W.A. Buurman, G.P. Downey, T.W. Evans, M.P. Fink, A.P. Halestrap, C. Ince, P. Kochaneck, X.M. Laverve, M.A. Matthay, J.C. Marshall, B.A. Molitoris, R. Neviere, D. Payen, P. Radermacher, J. Saklatvala, P.T. Schumacker, W. Sibbald, A.S. Slutsky, C. Szabó, K.J. Tracey, R.J. Traystman, T. van der Poll, B. Vallet, J.-L. Vincent, and J.M. Weinberg

Mitochondrial dysfunction and "cytopathic hypoxia"

A derangement in cellular energy metabolism seems a likely proximate cause of cellular – and hence organ – dysfunction in critical illness. Adenosine triphosphate (ATP) is the "energy currency" for cells. The free energy for the hydrolysis reaction, ATP→ adenosine diphosphate (ATP) + inorganic phosphate (Pi) + hydrogen ion (H^+), is used to power various metabolic processes in cells, such as the activities of membrane-bound transporters and the synthesis and degradation of proteins. In most cells ATP production occurs primarily in the mitochondria through the process called oxidative phosphorylation. In this process, reducing equivalents, namely the reduced forms of nicotinamide adenine dinucleotide (NADH) and flavin adenine dinucleotide ($FADH_2$) are oxidized by molecular oxygen to their oxidized forms (i.e., NAD^+ and FAD, respectively). The energy released by this process is used to create a gradient of hydrogen ions across the inner mitochondrial membrane. As pro-

tons move down this gradient through a specialized enzyme complex, the F_0F_1ATPase, the energy stored in the gradient as an electrochemical potential is released and coupled to the formation of ATP from ADP, Pi, and H^+. The reducing equivalents, NADH and $FADH_2$, are produced through the catabolism of fuels produced during anaerobic glycolysis, the β-oxidation of fats, and the oxidation of acetyl-coenzyme A in the tricarboxylic acid cycle.

The normal functioning of this remarkable cellular machinery depends of course on the adequate availability of oxygen. However, the normal functioning of the mitochondrial ATP factory also depends upon many other factors, such as the availability of catalytic quantities of NADH/NAD^+, integrity of the various enzyme complexes that carry out electron transport, and appropriate maintenance of the protonic gradient across the inner mitochondrial membrane. Accordingly, energy metabolism might be deranged either on the basis of decreased delivery of oxygen to cells or an acquired intrinsic alteration in the functioning of mitochondria.

One potentially important form of mitochondrial dysfunction can be caused by the opening of a nonspecific pore in the mitochondrial inner membrane. This mitochondrial permeability transition pore (MPTP) is normally closed. However, under certain pathological conditions, such as during reperfusion after a period of ischemia or after exposure of the cell to various toxins, the MPTP opens, leading to dissipation of the mitochondrial protonic gradient ("mitochondrial depolarization") and hence disruption of ATP synthesis [2]. Although the MPTP was first described many years ago, major advances in our understanding of its importance were not made until the discovery that submicromolar concentrations of the immunosuppressive agent cyclosporin A inhibit opening of the pore [3]. Opening of the MPTP has been implicated in various forms of organ dysfunction, including hepatocyte damage due to exposure to tumor necrosis factor [4], myocardial reperfusion injury [5], and neuronal damage induced by glucose and oxygen deprivation [6]. Of considerable interest are data indicating that opening of the MPTP can be blocked by analogues of cyclosporin A that lack the immunosuppressive activity of the parent compound [6]. Even some unrelated agents, such as the cardioprotective compound carvedilol [7], may work by blocking opening of the MPTP. Pharmacological blockade of the MPTP may therefore become a viable therapeutic strategy in the management of critically ill patients.

Activation of the enzyme poly(ADP-ribose) polymerase (PARP), also sometimes called poly(ADP-ribose) synthetase, is another potential cause of "cytopathic hypoxia" (intrinsic derangement in cellular respiration) during critical illness [8]. Under normal conditions PARP is relatively inactive in cells. However, PARP is activated by the presence of single-strand breaks in nuclear DNA, which can be induced by various endogenously generated oxidants, such as peroxynitrite ($ONOO^-$) and hydrogen peroxide (H_2O_2) [9]. The natural substrate for PARP is NAD^+. When activated, PARP cleaves NAD^+ into ADP-ribose and nicotinamide. PARP then covalently attaches the ADP-ribose units to various nuclear proteins, forming in the process a branched homopolymer, poly-ADP-ribose. Simultaneously, poly-ADP-ribose is degraded by various nuclear enzymes, especially poly-ADP-ribose glycohydrolase [10]. Thus the coupled actions of PARP plus poly-ADP-ribose glycohydrolase are the biochemical equivalent of an "NADase." As a consequence the activation of PARP can lead to profound depletion of cellular levels of NAD and thereby to an "energy crisis" in cells [11, 12, 13]. Pharmacological inhibition of PARP has been shown to be beneficial in animal models of sepsis and/or multiple organ dysfunction [11, 14]. New, potent PARP inhibitors may represent a novel an important therapeutic approach for the management or prevention of organ system dysfunction in critical illness [15].

Ischemic injury to cells can lead to derangements in mitochondrial function even after normal tissue oxygenation is restored. Thus respiration by renal tubules subjected to an episode of hypoxia is inhibited during reoxygenation, predominantly because of dysfunction of the mitochondrial enzyme complex, complex I [16]. ATP depletion within the mitochondria may contribute irreversible damage to the organelle during episodes of tissue ischemia and cellular hypoxia. Accordingly, pharmacological maneuvers to (at least partially) preserve ATP content during hypoxia might promote cellular recovery during reoxygenation. Indeed, during ischemia and other insults that limit mitochondrial oxidative phosphorylation, ATP production by anaerobic glycolysis can prevent generalized cell injury and, via reverse operation of the inner membrane ATP synthase (F_0F_1-ATPase), maintain mitochondrial energization and prevent opening of MPTP [17, 18]. However, anaerobic glycolysis is eventually suppressed during myocardial ischemia and is inherently limited or absent in other cells such as neurons and kidney proximal tubular cells. Interestingly, anaerobic mitochondrial metabolism can generate ATP and maintain mitochondrial energization via at least two pathways: substrate-level phosphorylation during the conversion of α-ketoglutarate to succinate by α-ketoglutarate dehydrogenase, and electron transport in complexes I and II driven by reduction of fumarate to succinate coupled to the oxidation of reduced ubiquinone that is generated via NADH from citric acid cycle reducing equivalents [16, 19]. Anaerobic generation of ATP by mitochondria is promoted by providing cells with a combination of substrates, containing α-ketoglutarate and apartate, and the use of this substrate cocktail has been shown to support mitochondrial function in renal tubules subjected to a hypoxia/reoxygenation stress [16, 19].

It is becoming increasingly apparent that mitochondria play hugely important roles in cellular physiology in ways that are only indirectly related to the function of these organelles as factories for producing ATP. For example, during hypoxia mitochondria tend to "leak" partially reduced forms of molecular oxygen, so-called "free radicals," and these potent oxidants can initiate proinflammatory signal transduction pathway, including activation of the transcription factor nuclear factor-κB, important in the regulation of tumor necrosis factor expression [20].

Leukocytes, cell signaling mechanisms, and alterations in capillary perfusion

Leukocyte trafficking and senescence, and cytokine-mediated cell signaling play important roles in mediating the microcirculatory dysfunction that characterizes clinical sepsis. Chemokine-induced neutrophil migration from the pulmonary vasculature into the alveoli involves neutrophils transiting the endothelium, the interstitial matrix, and tight junctions between adjacent alveolar epithelial cells. Neutrophils therefore can damage the normal alveolar fluid-clearance mechanism and thus promote alveolar flooding in conditions association with pulmonary inflammation and acute lung injury [21]. Moreover, the efficiency of this alveolar clearance system is, at least in experimental models, influenced in part by sheer forces. Thus in experimental models the application of lower tidal volumes is associated with improved solute and ion clearance [22]. Clinical studies confirm that the ability of the alveoli to remove ions and solutes holds prognostic significance in patients with established acute respiratory distress syndrome [23]. Inflammatory stimuli induce species-specific phenotypic changes in pulmonary vascular smooth muscle, leading to the expression of enzyme systems producing vasomotor substances including endothelins, which appear to induce smooth muscle cell proliferation. The clinical importance of pulmonary vascular remodeling in acute respiratory distress syndrome has yet to be explored in any detail, but prostacyclin analogues appear to inhibit this endothelin-mediated effect [24].

Apoptosis (programmed cell death) of neutrophils can be triggered via both cell surface receptors and the release of cytochrome *c* by mitochondria [25]. These processes are tightly regulated by inhibitors of apoptosis proteins and caspases [26]. Caspases can have both pro- and antiapoptotic actions, and their therapeutic manipulation to affect inflammatory processes is theoretically highly attractive. Neutrophils are also a potent source of proinflammatory cytokines, principal among which are tumor necrosis factor and interleukin 1. Their effects appear to be regulated in part by the coexpression of anti-inflammatory cytokines, including interleukin 10. Recently published work suggests that interleukin 10 is critically important in determining the lethality of sepsis in mice. For example, when subjected to a septic challenge, mice with a genetic inability to produce interleukin 10 have a markedly higher death rate and incidence of organ failure than wild-type controls [27].

The way in which inflammatory processes lead to various manifestations of endothelial dysfunction, including alterations in cell adhesion, coagulation, and vasomotor regulation, is gradually becoming clearer. Some in vivo studies using intravital techniques have suggested that the density of perfused capillaries is altered in sepsis such that some microvascular units are hyperperfused, possibly leading to apparent shunt flow, whereas other units are underperfused (or even "stopped-up" entirely) due to the presence of aggregates of red cells and/or leukocytes [28, 29]. Other studies, however, suggest that sepsis-induced organ dysfunction can occur even in the absence of alterations in microvascular perfusion [30].

The extent to which changes in microvascular perfusion lead directly to organ system failure was the subject of persistent debate, the strands of which permeated discussions following all presentations. Thus, although capillary hyper- and hypoperfusion can now be visualized in a number of microvascular beds clinically and in animal models, it does not appear to be invariably associated with organ system failure and death. Indeed, the extent to which multiorgan system failure can be attributed solely to microcirculatory abnormalities continues to be hotly contested by those who feel that cellular dysfunction, possibly at a mitochondrial level, is more likely responsible. Ongoing clinical studies using powerful techniques such as orthogonal polarization spectral imaging, which permit visualization of the microcirculation in patients, should prove to be very informative in this regard [31, 32].

Inappropriately high tidal volumes applied to the lung can also lead to the generation and dispersal of inflammatory cytokines into the pulmonary and systemic circulations, with important implications for distant organ function [33, 34]. However, inappropriate sheer stresses applied to the lung in this fashion may also lead to neutrophil apoptosis in kidney cells through the effects of transmitted pressures rather than systemic inflammation. Moreover, the rhythmic application of sheer to isolated cells systems in culture can result in mitochondrial activation, activation of nuclear factor-κB, and increased expression of proinflammatory substances that might explain many of the vascular abnormalities described above.

The kidney and gastrointestinal tract

Acute renal failure is a common clinical event affecting 2–5% of hospitalized patients and up to 10–30% of those

in intensive care units [35]. Renal ischemia is one of the most important antecedent factors in acute renal failure, reported to be causative in 50% of cases [35]. Until recently necrosis was believed to be the major form of cell death involved in acute renal failure. This belief gave birth to a commonly used, but nonetheless misleading, synonym for acute renal failure: acute tubular necrosis. When cells undergo necrosis, the cells swell and lose their membrane integrity. As a consequence there is leakage of intracellular compounds into the extracellular milieu. This leakage of intracellular material into surrounding tissue is believed to initiate the ischemia/reperfusion-induced inflammatory response, which is considered to be a major cause of the resultant tissue damage and organ dysfunction. Recently, however, apoptosis has been implicated in the pathophysiology of renal injury secondary to ischemia/reperfusion. Apoptosis is a highly conserved biological process essential in maintaining normal homeostasis. As noted above, apoptosis is characterized by activation of caspases, the intracellular execution enzymes of apoptotic cell death. Activated caspases cleave a wide range of intracellular substrates, ultimately leading to formation of apoptotic bodies that can be ingested by neighboring cells or macrophages without provoking an inflammatory response. Evidence for the occurrence of apoptotic cell death in ischemia/reperfusion injury was originally reported by Schumer et al. [36] in 1992, who demonstrated apoptotic cell death upon reperfusion after renal ischemia in the rat. Since then evidence has accumulated that apoptosis is not just an epiphenomenon of ischemia/reperfusion injury, but that it plays a functional role in the pathogenesis of renal ischemia/reperfusion injury [37, 38]. Accordingly, pharmacological inhibition of caspase activation, and hence apoptosis, someday may prove to be a clinically relevant strategy to prevent the development of acute renal failure in patients with critical illness.

The proper functioning of many different cell types, including renal and intestinal epithelial cells, depends on the maintenance of normal cytoskeletal organization. The protein actin forms the foundation for the cytoskeleton. The actin-based cytoskeleton is a dynamic structure requiring continuous actin assembly and disassembly. This assembly-disassembly process is regulated by a variety of intracellular mechanisms that include regulatory proteins such as the rho family GTPases and actin effector proteins such as actin-depolymerizing factor (depolymerizes F-actin in a pH-dependent fashion and sequesters G-actin), capping protein (caps the barbed end and stabilizes F-actin), and gelsolin (severs F-actin in a Ca^{2+} dependent fashion, caps and stabilizes F-actin, and nucleates actin filaments) [39]. Activation of actin depolymerizing factor by dephosphorylation may play a central role in mediating the cytoskeletal alterations induced by ischemia/reperfusion injury or other forms of cellular stress. The actin depolymerizing factor/cofilin (AC) family of proteins locate to apical membrane blebs shed from proximal tubule cells into the lumen during ischemia. This family of ubiquitous intracellular proteins plays an essential role in many actin regulated cellular processes such as the establishment of cellular polarity, cytokinesis, phagocytosis, motility, and fluid phase endocytosis. The primary function of AC proteins is their ability to act as "dynamizing factors" by greatly increasing actin filament turnover rates [40, 41, 42, 43]. Although the activity of AC proteins can be affected by several mechanisms, the primary mode of regulation is through phosphorylation of the amino terminal serine [44, 45, 46]. Phosphorylation of AC proteins inhibits their binding to actin and results in inactivation. Dephosphorylation of AC can be induced in response to a variety of cell stimuli, including ATP depletion.

Because patients can be fed parenterally, the gut was until fairly recently viewed as a "quiescent" organ during critical illness [47]. However, there now is good evidence that marked derangements in gut barrier function portend a bad outcome, at least for certain groups of critically ill patients [48, 49]. Moreover, several clinical studies support the view that providing enteral nutrition to critically ill patients improves outcome [50, 51]. Thus understanding the basis for both gut barrier dysfunction and the loss of normal peristalsis (i.e., the development of ileus) in critical illness assumes considerable importance.

Alterations in intestinal barrier function in critical illness appear to be caused by multiple factors, including induction of the inducible isoform of nitric oxide ($NO\cdot$) synthase and overproduction of $NO\cdot$ [52, 53], cytoskeletal alterations, derangements in cellular respiration [54], and, possibly, increased epithelial apoptosis [1, 55]. Recently obtained data strongly suggest that induction of PARP is a key factor. Ileus, signifying the impairment of coordinated propulsive intestinal peristalsis, remains a well documented and virtually inevitable consequence of open abdominal surgery, sepsis, and shock. Although the pathophysiology of ileus in critical illness remains incompletely understood, accumulating data support the view that infiltration of the muscular coats of the bowel by neutrophils and activation of resident macrophages, plays a crucial role [56, 57].

Brain and nervous system

Progress in the successful application of novel therapies in the treatment of severe traumatic brain injury in humans has been disappointing. Currently treatment is limited to field stabilization and supportive neurointensive care, the application of clinically accepted strategies to control intracranial hypertension, and surgical resection of mass lesions. A number of novel therapies have shown promise in contemporary experimental models of

severe traumatic brain injury, but none has been successfully translated to clinical use via a randomized controlled clinical trial demonstrating a beneficial effect on outcome. Examples of important failures include the trials of two agents targeting oxidative injury, tirilazad [58] and superoxide dismutase [59], and one targeting excitotoxicity, Selfotel [60]. Similarly dismal results have been obtained in clinical studies of new agents for the management of stroke [61, 62, 63]. Recent preclinical studies, however, suggest that pharmacological inhibition of PARP may prove to be very promising for this indication [64].

A very promising strategy to treat cerebral ischemia has recently emerged, focusing upon blocking the deleterious effects of a small molecule, 3-aminopropanal, which appears to be important in cause of neuronal damage in stroke [65]. 3-Aminopropanal is a metabolic product of the degradation of the polyamines spermine and spermidine by polyamine oxidase. Levels of spermine and spermidine fall during cerebral ischemia, and polyamine oxidase activity increases, resulting in increased production of 3-aminopropanal. 3-Aminopropanal is a potent cytotoxin that causes neuronal necrosis and glial cell apoptosis [65]. 3-Aminopropanal modified proteins can be detected in the cerebrospinal fluid of patients with stroke or head injury (Connolly and Ivanova, unpublished data). Administration of experimental therapeutics that either inhibit polyamine oxidase activity or react directly with 3-aminopropanal prevent brain damage in animals with cerebral ischemia or brain trauma [66, 67, 68].

It is increasingly apparent that the brain and neuroendocrine systems play hugely important roles in determining the responses of the whole organism to trauma and proinflammatory stimuli. For example, it has recently been shown that efferent signals transmitted through the vagal nerve dramatically down-regulate systemic cardiovascular and immunological responses to an injection of lipopolysaccharide in mice [69]. Moreover, evidence is accumulating that a key feature of critical illness in humans is a decrease in the variability of heart rate, a finding that suggests a loss of the normal neuroendocrine linkages between the heart and other organs [70, 71, 72]. Of course, intensivists recognize that changes in mental status, ranging from subtle abnormalities in cognition to agitation to frank coma, are common findings in critically ill patients. Whether these alterations in mental status and/or a loosening of the neuroendocrine linkages between organ systems is adaptive or maladaptive responses remains to be determined.

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