

Commentary

Iatrogenesis, inflammation and organ injury: insights from a murine model

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See related research by O'Mahony *et al.*, <http://ccforum.com/content/10/5/R136>

Abstract

The complex biology of critical illness not only reflects the initial insult that brought the patient to the intensive care unit but also, and perhaps even more importantly, it reflects the consequences of the many clinical interventions initiated to support life during a time of lethal organ system insufficiency. The latter may amplify or modify the response to the former and are eminently amenable to modulation by changes in practice. However, they rarely figure in conceptual models of critical illness and are almost never accounted for in preclinical models of disease. In the preceding issue of *Critical Care*, O'Mahony and colleagues reported on an animal model in which sequential insults - low-dose endotoxin followed by mechanical ventilation - induce much greater remote organ injury than either insult alone. Although animal models are poor surrogates for clinical illness, studies such as these provide valuable platforms for probing the complex interactions between insult and therapy that give rise to the intricate biology of critical illness.

The multiple organ dysfunction syndrome - the common final pathway to death for the majority of critically ill patients who succumb in the intensive care unit - is an enormously complex and elusive process. Support of acute organ system insufficiency is the *raison d'être* of intensive care and is the embodiment of the remarkable successes of a relatively young discipline. However, organ system support itself can exacerbate the very injury it seeks to support, and despite apparently successful resuscitation and intensive care unit management of the critically ill, *de novo* organ dysfunction, remote to the site of the original insult, commonly evolves in the most seriously ill patients. The intricate interactions of an acute life-threatening insult with the profound homeostatic derangements that follow resuscitation, and the superimposed injury caused by the need for organ system support, are poorly understood; they are largely ignored in our attempts to replicate critical illness using animal models.

In the preceding issue of *Critical Care*, O'Mahony and colleagues [1], from the University of Washington, describe an elegant series of studies that probe the capacity of two relatively trivial insults to synergize to produce remote organ injury. The first of these insults is microbial (intra-peritoneal challenge with lipopolysaccharide) and the second is iatrogenic (mechanical ventilation at a conventional tidal volume). Their observations echo those of others [2,3], namely that the synergistic interaction of two subclinical insults can result in clinically important organ injury that is much more severe than might be predicted on the basis of either of the two component insults. This observation - colloquially termed the 'two-hit hypothesis' of multiple organ failure - represents an important refinement in our understanding of the way in which activation of innate immunity can produce the phenotypic alterations of critical illness. In study conducted by O'Mahony and colleagues, pulmonary exposure to endotoxin was without significant sequelae and mechanical ventilation alone had only a minimal impact in evoking an inflammatory response in the lung. However, the same mode of mechanical ventilation, applied to a lung that had previously been exposed to endotoxin, evoked a striking increase in lung chemokine production and release of interleukin-6, an increase in circulating levels of tumour necrosis factor (TNF), and histological evidence of renal and hepatic injury, even in the absence of significant local pulmonary injury.

The mechanism of remote organ injury in this model is unknown; its unravelling promises to provide important new insights into the mechanisms of acute organ injury. The authors did not measure blood pressure, and acknowledge that it is possible that renal and hepatic hypoperfusion are responsible for the injury documented, although the histological features were not characteristic of ischaemic injury. Others have documented a role for the proapoptotic

sFasL = soluble Fas ligand; TNF = tumour necrosis factor.

molecule soluble Fas ligand (sFasL) in remote organ injury associated with injurious strategies of mechanical ventilation in an animal model of acid-induced acute lung injury [4]. Although evidence of apoptosis was not detected in the study conducted by O'Mahony and colleagues, absence of the markers evaluated (cleaved caspase-3 and sFasL) does not entirely exclude the possibility that increased rates of apoptosis occur in this model. Indeed, TNF bears many similarities to sFasL, each engaging a receptor of the CD95 family of death receptors (TNFR1 and Fas, respectively), which are responsible for initiating apoptosis in response to signals from the environment [5]. Priming for an exaggerated procoagulant response, for altered microvascular reactivity, or for mitochondrial dysfunction all represent hypothetical mechanisms that are consistent with prevalent views on the pathogenesis of acute organ injury in sepsis [6-8].

However, study of the cellular mechanisms of altered responsiveness to sequential insults is also revealing that cellular pathways leading to inflammatory gene expression can become altered or reprogrammed. Powers and her colleagues [9], for example, recently reported that oxidant species generated during haemorrhagic shock stimulate the translocation of Toll-like receptor 4 to lipid rafts in the membrane of macrophages, and so render the cell more responsive to subsequent stimulation by lipopolysaccharide. Also, multiple lines of evidence show that complement activation or a variety of inflammatory stimuli can prime neutrophils for an augmented respiratory burst in response to microbial products such as zymosan or fMLP (formyl-met-leu-phe) [10]. The critical concept here is that one acute injurious insult can modify the cellular response to a second insult, and so either amplify or attenuate that cellular response. Critical illness can readily be conceptualized as a process of repetitive acute insults, starting, for example, with an acute life-threatening insult such as multiple trauma and haemorrhagic shock. It then evolves in response to a series of sequential and poorly understood insults including massive fluid resuscitation, mechanical ventilation, vasoactive therapy and nosocomial infection, and the ecological derangements induced by broad-spectrum antibiotic therapy.

Clearly, the work reported by O'Mahony and coworkers [1] is at best a crude approximation of this complex clinical process; acute illness cannot be reliably replicated with a single animal model [11]. Rather a model provides an investigator with an opportunity to probe one discrete dimension of a complex state, and so to gain mechanistic insights that are only poorly perceptible through the cacophony of interventions and responses that are present during the course of critical illness. However, it is intriguing that the pattern of acute renal and hepatic injury seen in the sequential hit model used by O'Mahony and coworkers reflects the pattern of organ dysfunction seen in the landmark ARDSNet study, attenuated by the use of a low tidal volume ventilatory strategy [12]. We look forward to the

mechanistic insights that their ongoing studies promise to provide.

Competing interests

The author declares that they have no competing interests.

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