What Are the Relevant Molecular Routes in Septic Acute Kidney Injury?*

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In the absence of global hypoperfusion, septic acute kidney injury (AKI) is more likely to have a (glomerular) functional rather than an (tubular) injurious origin even though renal function may not fully recover in survivors (1). Indeed, the histopathology of septic AKI is characterized by subtle inflammatory changes and only focal tubular lesions with autophagy, apoptosis, or necrosis in humans (2–4). However, the molecular mechanisms in the pathogenesis of septic AKI remain largely unknown, whereas their understanding could help future diagnostic (e.g., biomarkers), preventive, and therapeutic interventions (5, 6). In particular, the respective roles of tissue (medullary) hypoxia and inflammation and resultant (sub)cellular changes are continued to be hotly debated. Furthermore, the up- and down-regulation of molecules require careful interpretation and correlation with function and anatomy since some molecules may reflect detrimental and others protective responses, and some may be associated with both, rendering the pathophysiology extremely complex, both at the glomerular and tubular level. Genetic or intervention studies, with deliberate blocking or expressing molecular routes, will ultimately reveal the role of the latter in the pathogenesis of AKI.

In this issue of *Critical Care Medicine*, Langenberg et al (7) studied some molecules thought to play a role in the pathogenesis and pathophysiology of septic AKI in sheep. They compared three groups of sheep: in one group septic AKI was induced by infusion with *Escherichia coli*, in the second group recovery after septic AKI was simulated by infusion with *E. coli*, followed by administration of IV gentamicin. A control group of sheep was killed without any intervention. In the septic sheep, there was a hyperdynamic circulation with increased global renal blood flow, in which, as in the systemic circulation (8), increased inducible nitric oxide synthetase (iNOS) activity and subsequently increased levels of nitric oxide (NO) may play a causative role (9). By contrast, the molecule may also contribute to (mitochondrial, tubular) damage of the kidneys in human septic shock (10). Selective or unselective blockade of NO synthesis in previous studies, however, did not improve renal dysfunction (9, 10). In the septic sheep evaluated by Langenberg et al (7), renal cortical messenger RNA (mRNA) expression of iNOS as well as endothelial and neuronal NOS was increased, but did not correlate with renal blood flow, leaving the role of various NOS isoforms in septic AKI obscure. The authors also evaluated by mRNA if hypoxia-inducible factor-1-α (HIF1-α) was activated and contributed to the development of apoptosis in sepsis, as indicated by cleaved caspase-3. In none of the prepared tissue samples, evidence for increased tubular apoptosis and necrosis was found, however, rendering the role of HIF1-α unclear. The authors propose a mechanism of NO-induced (and hypoxia independent) up-regulation of HIF1-α as an explanation for the increased cortical expression of the latter marker. However, only endothelial NOS correlated with HIF1-α expression. Interestingly, the model was also characterized by the absence of neutrophil infiltration and neutrophil gelatinase-associated lipocalin expression, unlike other (human) observations (3). Taken together, the role of the selected molecules studied does not fit into a clear picture of the functional alterations in septic AKI and may be in line with the absence of global hypoperfusion and ischemic damage only. The molecular routing for the fall in creatinine clearance (in spite of elevated blood flow), which may be caused by glomerular rather than tubular dysfunction, thus remains unclear, partly because specific glomerular alterations have not been studied in their septic sheep. Future research should focus on molecular mediators of the pathology and pathophysiology of AKI according to a conceptual framework and subsequently formulated hypotheses. In conclusion, the complex pathogenesis of septic AKI requires a careful sorting out of relevant mechanisms according to predominant features of renal dysfunction and injury. The molecules and routes currently studied (7) suggest that hypoperfusion does not play a major role but do not yet reveal any positive clues to explain the renal functional alterations in sepsis.

*See also p. e58.

Key Words: acute kidney injury; histology; nitric oxide synthase; pathophysiology; sepsis

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Does Blast Limb Trauma Constitute a Multisystem Critical Illness?*

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Blast injury is a traumatic injury mechanism seen with increasing frequency and severity during the global war on terror and has unfortunately had a concomitant rise in the civilian setting (1). The current paradigm of blast lung injury as an overpressure phenomenon primarily affecting hollow organs (ear, lung, and bowel) with resultant acute respiratory distress syndrome (ARDS) from capillary leak and fluid resuscitation explains rapid onset lung injury following injury (2). It has been suggested that acute lung injury (ALI) and ARDS of delayed onset without early signs of blast lung injury represent subclinical injury exacerbated by fluid resuscitation undertaken in the course of trauma management (1). However, this mechanism may not adequately account for delayed onset ALI. In fact, some authors have reported that it is far more common for survivors to not have a primary blast injury, as many of these victims will die at the scene. They report that a secondary blast injury from projectiles is far more common and goes so far as to categorize explosive injury as primarily penetrating trauma (3). Further categorizing lung injury as immediate (and likely the result of primary blast injury) or late onset (and likely the result of some other mechanism or a multiple insult mechanism) is made problematic by the retrospective nature of much of the literature regarding explosion-related injury. The increased morbidity and mortality of ALI and ARDS in trauma patients are well established, and the difficulty in categorizing the causes of lung injury in the blast victim inhibits efforts to mitigate these risks (4, 5). Physics and epidemiologic reviews of blast injury demonstrate that there are a myriad of injury patterns dependent on whether the explosion occurs in a closed or open environment, whether it is complicated by projectiles and fragmentation, and whether it occurs in a civilian or military environment (6–10). There is a lack of experimental models to match the variety and myriad nature of injuries resulting from explosion (3).

Hypothermia has demonstrated benefit in postcardiac arrest patients. Studies have investigated the use of hypothermia in other disease processes, such as stroke (11). The results have been promising, which has led to the application of hypothermia as a potential treatment modality in various trauma populations, such as spinal cord injury, hemorrhagic shock, traumatic brain injury, and burns (12). In animal studies at our institution, moderate systemic hypothermia has conveyed a local benefit in burn injury by decreasing burn depth, and genomic studies have implied that hypothermia may be able to provide a systemic benefit as well by decreasing inflammatory cytokines and promoting healing (13). These findings are in agreement with other animal studies that demonstrated that hypothermia attenuated distant organ injury (14).

Ning et al (15), whose article is featured in this issue of *Critical Care Medicine*, provide evidence that regional hypothermia applied to animals after blast limb trauma offers both local protection to the injured limb and systemic protection for the lungs. Similar findings were demonstrated in a study by Santora et al (14) who used regional hypothermia in an ischemia-perfusion injury model. These data show that hypothermia has the potential to convey both local and distant effects. Additionally, the investigation by Ning et al (15) provides two important novel contributions. One is a viable

***See also p. e68.**

Key Words: blast limb trauma; blast lung injury; burn progression; inflammation; therapeutic hypothermia

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