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Sepsis-induced acute kidney injury—is there a lack of energy?

Received: 31 December 2011

Accepted: 1 January 2012

Published online: 3 February 2012

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This editorial refers to the article available at:
doi:[10.1007/s00134-012-2487-2](https://doi.org/10.1007/s00134-012-2487-2).

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Acute kidney injury (AKI) is a common complication among critically ill patients and an important cause of mortality and morbidity. It affects approximately up to two-thirds of patients treated in intensive care units [1] and is closely associated with both short- and long-term mortality [2, 3]. The systemic inflammatory response to an infectious insult, i.e. sepsis, is the most frequent cause of AKI [4], and septic patients developing severe renal failure suffer, despite advanced vital organ support, a high risk of dying [5].

A common conception, supported by the results of animal experiments, is that septic AKI is due to an ischemic insult to the kidneys. The massive vasodilation caused by the release of vasodilators, mainly nitric oxide, results in hypotension and baroreceptor unloading. As a reflex response, renal sympathetic nerve activity increases and together with elevated levels of potent renal vasoconstrictors, such as angiotensin II, adenosine and endothelin, this severely impairs renal blood flow (RBF), subsequently leading to hypoxic injury and acute tubular necrosis [6–8]. Based on this theory, current clinical

practice aims at restoring renal oxygen supply to treat or prevent AKI from developing. However, little is known about the changes that occur in RBF during sepsis in humans. In the only study performed in septic patients with AKI in which a reliable method of measuring RBF was used [9], blood flow to the kidneys varied considerably between individuals: the majority of septic patients actually had a RBF within normal limits, albeit some patients with reduced glomerular filtration rate did present with a marked reduction in renal perfusion. Furthermore, human AKI caused by sepsis is not only associated with acute tubular necrosis but also with pronounced inflammation and apoptosis, as demonstrated by the examination of renal biopsies from diseased patients diagnosed with septic shock and anuria [10]. The concept that septic AKI is predominantly an inflammatory disorder is supported by the finding that inhibition of Toll-like receptor 4, the most important activator of the innate immune response in Gram-negative sepsis, is significantly more effective in preventing AKI in experimental sepsis than the optimization of cardiovascular function with intravenous fluid and norepinephrine [11].

Recently, the research group of Rinaldo Bellomo and Clive May has presented a series of interesting and well-executed investigations in conscious sheep made septic by an intravenous *Escherichia coli* infusion. These animals develop hyperdynamic, hypotensive sepsis with drastically impaired urine output and creatinine clearance, but with *increased* RBF [12]. This finding indicates that AKI may develop despite adequate total RBF, questioning the view that renal failure in sepsis is due to ischemia. However, oxygen supply/demand mismatch within organs, microcirculatory dysfunction or disrupted mitochondrial oxygen utilization have been described in sepsis and may still impair cellular energy production, despite normal or increased blood flow [13].

In this issue of *Intensive Care Medicine*, May et al. [14] present new interesting data on renal ATP production

in anesthetized sheep during sepsis induced by an infusion of live *E. coli*. Prior to the experiments the animals were surgically prepared with a transit-time flow-probe around the left renal artery to measure RBF and with a custom-made phosphorus coil surrounding the left kidney. The latter was used in an elegant approach to obtain repeated non-invasive ATP measurements by mass resonance (MR) spectroscopy. By measuring the ^{31}P -MR spectra every 15 min from a 10-cm-thick slice of the kidney, the authors were able to calculate the global renal ATP levels. The key finding of the study is that 4 h of sepsis, resulting in hypotension and reduced RBF, did not reduce renal ATP levels. In an earlier study, these authors demonstrated that intravenous infusion of angiotensin II, a potent vasoconstrictor, in conscious septic sheep reduces the RBF to baseline levels and concomitantly increases creatinine clearance and urine output [15]. In their current study, angiotensin II was titrated to restore mean arterial pressure, which reduced RBF to very low levels. Still, the ATP levels remained unchanged. These results indicate that the diminished renal oxygen supply was compensated for by increased oxygen extraction or that the energy consumption in the kidney was acutely reduced, most likely impairing tubular function.

The experiments by May et al. [14] presented in the current issue are performed in a large-animal model using a validated technique for estimating ATP levels. Obviously, the sheep had to be anesthetized to facilitate placement in the MR-scanner and to prevent movement during the measurements. However, the use of anesthesia did introduce some limitations to the study. The animals developed what appeared to be a hypodynamic septic response, associated with reduced RBF. This is in contrast to the earlier results published by this group in which the

RBF increased and, consequently, makes direct comparisons between studies difficult. The reduction in RBF by sepsis per se also complicated the treatment with angiotensin II since additional vasoconstriction did not normalize the RBF, as seen previously in conscious septic sheep, but rather caused further reduction to levels not compatible with normal renal function. In addition, isoflurane anesthesia is known to aggravate renal dysfunction caused by *E. coli* lipopolysaccharide in sheep [16]. The technical circumstances preventing continuous urine collection also made detailed estimation of renal function impossible. Global renal oxygen consumption in patients with non-septic AKI is not different from that of controls, but the oxygen utilization for reabsorbing sodium, the most energy-consuming process in the kidney, is significantly increased [17]. Thus, although there may be no absolute lack of cellular energy during AKI, the ATP consumed may be used more or less efficiently.

In summary, this important study by May et al. [14] suggests that septic AKI does not necessarily have to be associated with major renal energy depletion. Acute tubular necrosis develops from the aggregated effects of the many cellular reactions activated by a severe lack of usable energy. Hence, this investigation emphasizes the concept that sepsis-induced AKI may be the result of a more complex chain of events than merely inadequate renal blood supply resulting in hypoxia and premature cell death. The study also confirms that we are still a long way from deciphering the mystery of why renal function is so severely affected in sepsis.

Acknowledgments Robert Frithiof is supported by funds from the Swedish Research Council (grant 521-2011-2843).

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