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Kidney Attack in Sepsis: The Role of Haemodynamics

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For decades, textbooks have suggested that renal hypoperfusion and tissue ischemia are the primary pathogenic event in sepsis-induced acute kidney injury (S-AKI). Although paradigms are actively changing, there is still a shortage of data clarifying the pathogenic role of renal circulation in the development of S-AKI.

The kidney is a common 'victim organ' of sepsis. A number of pathological processes have been postulated for S-AKI, including alterations of renal global and microvascular (both glomerular and peritubular) haemodynamics and changes in immunological, inflammatory and bioenergetic pathways. However, the causative contribution of each to kidney dysfunction in sepsis remains enigmatic. This is particularly true for the role of renal circulatory alterations, which is still a subject of inflammatory debate (Wan et al. 2008; Prowle et al. 2012). The fuel for this fire lies in the fact that almost all our knowledge is derived from various animal models with rather limited clinical relevance, because online recording of renal haemodynamics, oxygenation, and a clear-cut detection of evolving pathology is lacking for the human kidney during the development of S-AKI. It has been postulated for almost 60 years that AKI in sepsis is largely an ischaemic form of AKI and that renal vasoconstriction is the first and major pathogenetic event there (Schrier 2004). This might certainly be valid for prolonged unresuscitated sepsis. By contrast, only relatively recently, an Australian group of researchers challenged this old-fashioned view, and showed in a sheep model that renal vasoconstriction is not necessarily a prerequisite for AKI to develop during resuscitated, hyperdynamic sepsis (Langenberg et al. 2006; 2007). They demonstrated that AKI can develop despite significant renal vasodilatation and increased renal artery blood flow and the paradigm of renal hyperaemia in S-AKI has been introduced (Wan et al. 2008). The persisting controversy regarding the role of renal haemodynamics in sepsis has nicely been illustrated by an extensive review of available human and experimental evidence performed in 2005 (Langenberg et al. 2005). The analysis documented that

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renal blood flow reported mostly in experimental studies is markedly heterogeneous (decreased, increased or unchanged), and that cardiac output appears to be the dominant predictor of both renal blood flow and renal vascular resistance in sepsis. It should be stressed, however, that the majority of studies reporting a reduction in renal blood flow were derived from short-term and mostly hypodynamic models characterised by a reduced cardiac output, which clearly limit the inference that could be drawn. Nevertheless, even after eight years since publication, we still do not know the dynamic behaviour of renal circulation during S-AKI, in particular due to the lack of reliable methods allowing continuous renal blood flow measurement in critically ill patients.

Generally speaking, we have two contradictory concepts in renal circulatory responses in sepsis: the theory of renal ischaemia despite systemic vasodilatation and the concept of renal hyperaemia with the renal circulation participating in sepsis-induced vasoplegia and low systemic vascular resistance. Physiologically, both renal vasoconstrictive and vasodilatory profile is compatible with a reduction in glomerular filtration as a result of reduced glomerular filtration pressure. Note, however, that AKI affects 40-50% of all septic patients (Zarjou and Agarwal 2011). Hence, the relevant question arises whether renal circulation behaves differently in patients developing AKI as opposed to those without AKI. To address this issue, we studied the dynamic renal circulatory changes using two porcine models of severe sepsis (peritonitis and IV infusion of live *Pseudomonas aeruginosa*) (Benes et al. 2012). This modelling allowed us to generate two distinct groups of septic animals, those with and without the development of S-AKI, thereby enabling us to isolate and study both haemodynamic and non-haemodynamic factors discriminating AKI from non-AKI. We observed that 50% of all animals developed S-AKI despite comparable septic insult and totally identical supportive treatment. Interestingly, despite identical systemic haemodynamic profiles characterised by well-maintained cardiac output and systemic vasodilatation, a different renal circulatory pattern was observed in AKI and non-AKI subjects. Whereas a consistent link between well-maintained cardiac output and preserved renal blood flow was documented in septic animals that remained AKI-free, the animals complicated by the development of S-AKI showed progressively increased renal vascular resistance accompanied by reduced renal blood flow suggesting an apparent renal vasoconstriction.



Figure 1. Different global renal hemodynamic phenotypes: cause or consequence of S-AKI?

These results allow for several important considerations. First, renal circulation behaves differently in sepsis with AKI as opposed to sepsis alone. Second, renal haemodynamics in septic subjects developing AKI cannot reliably be predicted from systemic haemodynamics. Finally, septic AKI may be accompanied by an uncoupling between systemic and renal vascular resistance, supporting the existence of the phenomenon of selective renal vasoconstriction even in a well-resuscitated large animal model with sepsis-induced systemic vasodilatation. It should be noted, however, that a wide inter-individual variability in renal vascular resistance was observed in S-AKI animals, ranging from highly increased to unchanged or even slightly reduced. Such a variability might question a causative link between renal global circulatory changes and kidney dysfunction, at least in early, well-resuscitated, and normotensive large mammals sepsis. Regardless of causation, our results suggest that S-AKI can occur within the setting of two different renal haemodynamic phenotypes: vasodilatory and vasoconstrictive (see Figure 1) (Lipcsey and Bellomo 2011), i.e. that both haemodynamic paradigms exist. The fact that renal circulatory changes appear to be independent from systemic haemodynamics implies that S-AKI develops as a consequence of kidney-specific pathophysiology. The underlying mechanisms that determine which phenotype predominates remain unknown. Theoretically, the type of infection, stage, and severity of sepsis or even genetically driven imbalance in vasomotor control and yet undefined disharmony of glomerular vascular balancing mediators may dictate the renal haemodynamic phenotype. These relationships are amenable to direct investigation.

New data on the renal haemodynamics in S-AKI has emerged from a recent clinical study by Prowle et al. (2012). The authors assessed renal blood flow using cine phase-contrast magnetic resonance imaging in ten adult patients with established S-AKI. In this cohort of patients, median renal blood flow was significantly lower compared to the renal blood flow in healthy individuals. Moreover, despite a wide range of cardiac output, renal blood flow was consistently reduced as a fraction of cardiac output (less than half normal). Finally, a majority of patients had markedly increased renal vascular resistance when compared to healthy volunteers. Collectively, these data suggest that renal vasoconstriction might be a feature of established S-AKI, independent from systemic haemodynamics. Although larger studies with serial measurements are necessary to inform us about the exact fate and the role of renal blood flow in sepsis and AKI, this study is undoubtedly a welcome step further.

It is essential not only to understand the complex behaviour of global kidney perfusion, but also its intrarenal distribution as well as changes in local microvascular blood flow. Certainly, the damage to the renal microcirculation and resulting tissue hypoxia may constitute early critical steps in the development of S-AKI. However, lack of techniques enabling direct visualisation of the unique architecture of the kidney microcirculation both in the cortex and medulla and exact real-time measurements of oxygen tension in the corresponding areas represent the main impediments to the study of intrarenal oxygenation in man (Matejovic 2011). Nonetheless, several experimental studies have provided evidence for the causative role of peritubular microvascular injury in S-AKI (Mayeux and MacMillan-Crow 2012). Age is one of the factors that may markedly influence not only the pattern of global renal haemodynamic profile (Seely et al. 2011), but also the vulnerability of renal microvasculature to the inflammatory stimuli (Wulfert et al. 2012). Recent experimental research has also reinforced interest in glomerular pathobiology during S-AKI. Xu et al. suggested an important role of TNF- α -mediated degradation of the glomerular endothelial surface layer and loss of glomerular endothelial fenestration in the development of S-AKI in mice (Xu et al. 2013). Another attractive, yet speculative, concept of glomerular bypass shunts permitting renal arterial blood to bypass the process of filtration has recently been discussed (Bellomo 2013).

Conclusions

In conclusion, there is still an ongoing debate whether or not the global renal haemodynamic alterations (regardless of the phenotype) are a primary pathogenic factor or if they are just a consequence rather than a cause of renal injury. Over time, as information accumulates and our understanding increases, a gradual shift from 'haemodynamically-based' theories to more complex approaches has occurred in recent years. Undoubtedly, further intensive mechanistic studies and solid reproducible research are warranted.

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