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The kidney in acute renal failure: innocent bystander, victim or still a suspect?

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Despite great progress in critical care, acute renal failure (ARF) is a frequent and fatal complication contributing significantly to morbidity and mortality among critically ill patients [1]. The incidence of ARF in intensive care units ranges from 3 to 25% depending on the criteria applied, underlining the problem of more than 30 definitions. Today the two widely accepted classification systems are the RIFLE criteria and the staging system for acute kidney injury (AKI) as established by the Acute Dialysis Quality Initiative (ADQI) and the Acute Kidney Injury Network (AKIN), respectively [2, 3]. Regardless of modern renal replacement therapies and promising pre-clinical and clinical treatment trials, ARF-related hospital mortality ranges between 25 and 80% [2–4]. This unacceptably high mortality as well as increasing costs of critical care treatment exerts pressure to develop a better

understanding of the underlying pathology of this disease and to generate new therapeutic strategies with the potential to attenuate ARF. Although the pathophysiology of ARF is not fully understood, there is general agreement that in several clinical situations renal hypoperfusion and a concomitant lowering of the glomerular filtration rate (GFR), induced by a decrease in systemic and/or renal perfusion pressure, are hallmarks of the genesis of ARF [5–10].

In this issue of *Intensive Care Medicine*, Dr. Saotome and co-authors further our knowledge of the significance of different states of renal hypoperfusion on the formation of ARF [11]. The authors conducted a study of a ewe model with various degrees of renal hypoperfusion. This was realized solely by reducing the renal blood flow to 25–80% of baseline. Additionally, they achieved severe, sustained subtotal renal hypoperfusion. Summarizing their findings, 25, 50 or 75% impairment of renal blood flow for 30 min was not associated with extended loss of renal function. During 2 h of 80% hypoperfusion, urine output decreased from 80 to 17 ml, and creatinine clearance from 32 to 3 ml/min, while plasma creatinine increased from 103 to 132 $\mu\text{mol/l}$. Restoration of normal renal blood flow induced brief hyperemia before all measured variables returned to normal within 8 h and remained normal for the following 72 h, leading to the conclusion that, “unlike total ischemia, severe hypoperfusion alone is insufficient to induce subsequent persistent AKI.”

At first glance, these findings are in strict contrast to what we have learned about hypoperfusion-associated AKI—commonly referred to as acute pre-renal failure—so far [5–10], raising the question of whether we should start to re-write our pathophysiology and critical care textbooks. This is clearly not the case. However, this elegant study broadens our horizon regarding the impact of extrarenal factors on kidney function during renal circulatory dysfunction.

It is important to realize that—with a few exceptions like atheroembolic kidney disease—the experimental model employed is highly different from the renal hypoperfusion states we are confronted with in clinical practice and from the experimental renal failure models used in the past [12]. It is well established that renal hypoperfusion accompanied by low mean arterial pressure is ultimately associated with the classical signs of pre-renal AKI, often referred to as “acute tubular necrosis” (ATN) [5–10]. In contrast, the model applied in the present study resembles the one-kidney Goldblatt model used to study renal (arterial) hypertension [13]. And indeed, the authors clearly demonstrate that *reduced* renal blood flow resulted in *increased* systemic mean arterial pressure (MAP), something rarely encountered in a systemic hypoperfusion state. This is highly suggestive that it is not the low flow to the kidney but the concomitant circulatory state that translates renal hypoperfusion either into overt ATN (i.e., AKI) or allows renal function to recover immediately if renal blood flow is restored again, at least within the time frame tested in the present study.

This information is not really new, but rarely recognized in the current literature. Almost 30 years ago, Gorfinkel and coworkers—while comparing the effects of hemorrhagic and cardiogenic shock on renal function and histopathology in a conscious dog model—showed that renal blood flow and the histological signs of ATN were completely different during both shock states (despite a comparable mean arterial pressure and cardiac index). Interestingly, renal function was somewhat preserved during cardiogenic shock, and this renoprotective effect was abolished by cardiac denervation and thus mediated by cardiopulmonary receptors [14].

More recently, Douzinas and colleagues have shown that increasing arterial blood pressure during hemorrhagic shock ameliorates post-shock kidney dysfunction [15],

suggesting a comparable role of high pressure baroreceptors in this setting. Both observations are not astonishing, since the sympathetic nervous and efferent renal nerves as well as catecholamines and the renin-angiotensin-aldosterone system (RAAS) play an important role in regulating and distributing renal blood flow as well as the mediating tubular reabsorptive capacity [16].

Studies employing the Goldblatt model have shown that acute reductions in renal blood flow are not only followed by a significant increase in the RAAS activity, mediating the observed changes in arterial blood pressure, but also a counterregulatory increase in natriuretic peptides [17, 18]. This may be important for kidney function, since these hormones have been shown to mediate natriuresis and diuresis and are thus capable of modulating the effects of increased RAAS activity.

Unfortunately, Saotome and co-authors [11] did not determine the humoral responses to renal hypoperfusion in this model; however, such analyses may offer important insights into why this specific model of isolated renal low flow behaves so differently from the established models of combined systemic and renal hypoperfusion. This may ultimately help to understand which factors make the difference and which measures should thus therapeutically be addressed in future studies.

Nonetheless, we have to thank the authors for reminding us that the kidney may play different roles during AKI. Additionally, we have to change our attitude about this organ: the kidney may be suspect due to the upregulation of intrarenal mechanisms translating prolonged hypoperfusion into overt ATN, a victim of the extrarenal mechanisms translating systemic hypoperfusion into renal failure, and sometimes only an innocent bystander like in this model. This largely depends on the prevailing circulatory state.

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