Need to Intervene in Established Acute Renal Failure

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An acute myocardial infarction is universally associated with some degree of residual tissue damage in the heart. There are, nevertheless, interventions, which can attenuate the degree of tissue damage with a heart attack, (*e.g.*, aspirin, beta blockers, angiotensin converting enzyme inhibitor or receptor antagonist.) In contrast, with clinical acute renal failure (ARF), although the mortality is much higher (40–80%) than with a heart attack, there is no effective intervention even though there is evidence for a functional component with potential recovery in the absence of residual tissue damage (1). Specifically, during ARF the histology of the renal parenchyma demonstrates only minimal changes – the glomeruli are normal, there is modest interstitial edema and occasional patchy tubular necrosis. In the absence of knowledge about the clinical history, this histologic picture could be projected as being associated with near normal renal function, in contrast to the actual GFR of less than 10–15 ml/min, which occurs with ARF. Moreover, if the patient with ARF survives the secondary complications of ARF, primarily infections and cardiopulmonary events, in the majority of patients the renal function returns to normal without evidence of residual renal tissue damage. Why then, are there effective interventions, which can alter the course of a heart attack, but no such intervention has been demonstrated for ARF?

One explanation for this disparity is that, in contrast to the early diagnosis of acute myocardial infarction, *e.g.*, troponins, early interventions have rarely been studied in established ARF in patients. Interventions *before* the insult have been shown in several experimental models to attenuate or prevent the ARF. The same has been reported with some forms of clinical ARF, *e.g.*, radiocontrast media, delayed graft function with cadaveric kidney transplantation. What has not been shown, is that the clinical course of ARF and the resultant high mortality can be altered by an intervention, which occurs *after* the ischemic or nephrotoxic insult.

In the present issue of *JASN*, Jo *et al.* (2) have shown that an intervention, namely the antioxidant effects of DMSO, administered *after* the mercuric chloride insult attenuates the course of the ARF. The window of intervention was, however, only three hours after the insult, a period of time which is difficult to achieve in a clinical setting. Nevertheless, it seems clear that the earlier the intervention, the better the chance of shortening the course of ARF. This is quite important, since the longer the clinical duration of ARF and/or the need for dialysis, the higher the mortality. Presently, there are several efforts underway to develop early urinary markers of ARF including interleukin-18, kidney injury molecule (KIM), or tubular enzymes (3). It is known that prolonged pre-renal azotemia with normal tubular function can progress to established ARF with tubular dysfunction. Pre-renal azotemia, *e.g.*, secondary to volume depletion, early sepsis, is a state of diminished GFR with intact tubular function as assessed by a fractional excretion of sodium (FE_{Na}) less than one. This is the optimal time to intervene, since with diminished tubular function and a greater fall in GFR (*i.e.*, established ARF with $FE_{Na} > 2.0$) it is much more difficult to alter the course of the ARF.

In the past, there was focus of renal blood flow (RBF) as an important pathogenetic factor in the pathogenesis of ARF. When paraaminohippurate (PAH) was used to assess RBF, it was proposed that RBF was virtually absent in patients with ARF. This conclusion was incorrect and related to the defect in tubular secretion of PAH which occurs in ARF. Using other methods it is clear that RBF in ARF remains at a level comparable to patients with chronic renal insufficiency who have only modestly decreased GFRs. Moreover, normalizing RBF in ARF with an intrarenal vasodilator does not reverse clinical or experimental ARF. Thus, the focus on the tubule in the pathogenesis of ARF emerged, as noted by the clinical use of the term acute tubular necrosis (ATN).

There is substantial experimental evidence that intraluminal tubular obstruction with cast formation in the distal nephron is an important maintenance factor in experimental ischemic ARF (3). Moreover, in experimental ARF, placing a micropipette into the proximal tubule lumen and returning tubular flow rate to normal can reverse tubular obstruction and increase GFR in the same nephron. In the clinical setting, however, it is difficult to normalize or increase tubular flow rate in obstructed nephrons of established ARF, because of the very low GFR and the impaired tubular secretion. It is for this reason that a combination of a renal vasodilator and an impermeant solute has been proposed. In one experimental model it was shown that, although neither atrial natriuretic peptide (ANP) nor mannitol alone altered the course of ARF, the combination of these agents was protective (4). An advantage of combined vascular and tubular interventions is that the administration of systemic vasodilators alone causes an increase in circulating catecholamines, angiotensin, and increased renal sympathetic tone that can obscure any potentially beneficial effect of renal vasodilation. This is no doubt the reason that the randomized brain natriuretic peptide (BNP) clinical trial was negative (5),

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since mean arterial pressure (MAP) decreased significantly during the intravenous BNP infusion. The addition of mannitol with a natriuretic peptide would not only attenuate any systemic fall in MAP, but also may be associated with enhanced filtration of the mannitol with increased tubular flow and relief of tubular obstruction. Administration of mannitol before an ischemic insult has been shown to relieve tubular obstruction in experimental ARF (6). Mannitol has also been shown to decrease the incidence of ARF and the need for dialysis in post-transplant cadaveric kidneys (7).

Not only have effective interventions not been found in ischemic ARF, but also some of the interventions may actually prolong the clinical course of ARF and potentially increase mortality. Excessive volume resuscitation in ischemic ARF can lead to hypoxia and non-cardiogenic pulmonary edema, particularly in the vasodilated septic patients (Figure 1) (8). We have termed this situation pseudo-adult respiratory distress syndrome (ARDS), since it can occur in the absence of evidence for pulmonary capillary damage, *i.e.*, no decreased compliance as an index of stiff lungs. Frequently, cumulative positive fluid balances in these ARF patients have not been recognized or determined by the physician, yet may be as much as a 10–15 L increase in an ARF patient who has a normal extracellular fluid volume of 14 liters (20% of 70 kg body weight.) Mechanical ventilation is then instituted for the pulmonary edema and hypoxia rather than fluid removal by ultrafiltration. With prolonged mechanical ventilation in ARF patients, mortality may approach more than 80%. In addition to pulmonary barotrauma, oxygen toxicity and infection with ventilatory support, studies have shown that increased cytokine release may occur and contribute to renal injury (9). Thus, nephrologists should be as committed, or even more so, to preventing or discontinuing mechanical ventilation in the ARF patient, as they are in avoiding or removing bladder catheters as a source of infection.

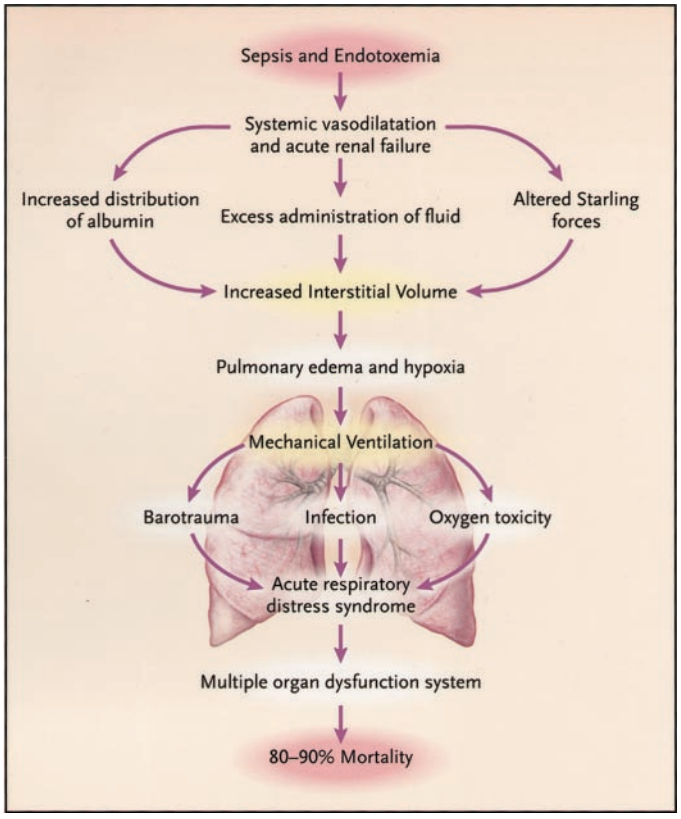

Figure 1. Effects of Systemic Arterial Vasodilatation in Patients with Sepsis and Acute Renal Failure.
Sepsis and endotoxemia with acute renal failure can lead to early noncardiogenic pulmonary edema, hypoxia, and the need for mechanical ventilation. With prolonged ventilatory support, acute respiratory distress syndrome, multiple-organ dysfunction syndrome, and an extremely high mortality can occur. The goal is to intervene early to prevent excessive fluid administration and to lessen fluid overload by hemofiltration. This will prevent the need for long-term mechanical ventilation that could lead to damage to the pulmonary capillaries. It could also prevent tissue hypoxia and the acute respiratory distress syndrome and reduce the risk of death. Published with permission from reference 8.

Since kidneys with ischemic injury have impaired autoregulation and increased sensitivity to renal nerve stimulation (10), it has been proposed that because of less hemodynamic stress continuous renal replacement therapy (CRRT) may be preferable to intermittent hemodialysis for treating ARF in patients. This hypothesis, however, remains to be proven. In either case, any intervention which obviates the need for any type of dialysis would be expected to decrease the duration and mortality of ARF.

In summary, a rise in serum creatinine and/or blood urea nitrogen (BUN) is the most common reason for a nephrology consultation in hospital. Yet, in contrast to the advances in the therapy of acute myocardial infarction by cardiologists, there has been little progress in decreasing the duration and mortality of the clinical ARF by nephrologists. Experimental studies, such as that by Jo *et al.* (2), further emphasize the need for early intervention, and the importance of distinguishing between pre-renal azotemia and established ARF is critical. Although the pathogenesis of ARF is complex (3), basic science studies in ARF are needed which have the aim of providing background for future prospective interventional clinical studies. As noted in the study by Jo *et al.* (2), antioxidants may be an important component of such intervention, particularly with endotoxemic-related ARF (11). A clinical network for ARF would strongly facilitate the performance of such randomized clinical trials, an area where the efforts of cardiologists have far exceeded those of nephrologists.

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See related article, “Delayed DMSO Administration Protects the Kidney from Mercuric Chloride-Induced Injury,” on pages 2648–2654.