Possible Protective Effect of Chronic Renal Failure against Sepsis and Endotoxin-Induced Organ Failure and Mortality in Acute Renal Failure

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Dear Sir,

Acute renal failure (ARF), particularly if associated with sepsis, other organ system failure, is a severe condition in critically ill patients and carries a mortality exceeding 60% [1,2]. Although prior chronic renal failure (CRF), sepsis and cardiopulmonary failure predispose to the development of ARF [2], outcome in ARF patients with CRF is paradoxically not worse or even better than in those without CRF in most studies [2,3], probably due to a lower prevalence of cardiovascular failure with hypotension and other sepsis-induced organ damage [2]. This protective effect of CRF can be explained in at least three different but not mutually exclusive ways.

One possible explanation is given by Vijaykumar et al. [4] in a recent letter in Nephron. They found that most ARF patients with sepsis had high levels of plasma endotoxin, and in those without CRF a rise in antibodies to lipid-A (the most active component of endotoxin), probably as a consequence of translocation of gram-negative bacteria or endotoxin from the gut [5,6]. Patients with CRF, however, had already an accumulation of these antibodies before the development of ARF [4]. Since lipid-A acts as a primary signal for mononuclear and endothelial cells to release many biologically active factors that are responsible for the septic host response (tumor necrosis factor (TNF), interleukin-1 (IL-1), interleukin-6 (IL-6) and nitric oxide (NO)), exogenous antibodies directed against the lipid-A domain of endotoxin indeed significantly reduced mortality in patients with gram-negative bacteremia, particularly in those with concomitant shock and organ failure [7].

The second explanation involves inhibition of NO. NO is a potent vasodilator which is endogenously synthesized from L-arginine by two distinct NO synthase enzymes [8]. One of these NO synthases can be induced by endotoxin and cytokines such as TNF, and interleukins. This inducible enzyme is responsible for an excessive production of NO observed in various acute and chronic inflammatory conditions such as sepsis and inflammatory bowel disease [9-11], which has been implicated in the sustained hypotension, resistance to vasoconstrictors that are characteristic features of septic shock [9,10]. Furthermore, overproduction of NO may be cytotoxic for target cells [8,12]. Inhibition of NO synthase by appropriate doses of specific inhibitors like N^G-monomethyl-L-arginine or N^G-nitro-L-arginine-methyl ester results in an increase in blood pressure and systemic vascular resistance in animals and humans with septic shock [9,10]. Similarly, a rise in blood pressure was generated both in vitro and vivo by another

endogenous inhibitor of NO synthase, NG, NG-dimethylarginine (asymmetrical dimethylarginine, ADMA) [13]. In normal human, this inhibitor is secreted unchanged in the urine. In patients with CRF, however, in whom the ability of elimination by the kidneys is strongly reduced, circulating levels of ADMA rise sufficiently to inhibit nitric oxide synthesis. Another explanation is accumulation of endogenous inhibitors of cytokines. TNF-soluble receptors, and antibodies to IL-1 and IL-6 were more prevalent in serum of patients with CRF, while the levels of these cytokines were not elevated or even reduced [14-16]. Similarly, the production of IL-1 re-

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ceptor antagonist by unstimulated and stimulated peripheral mononuclear cells was directly correlated with renal function, while the production of IL-1 by these cells was reduced in patients with CRF [17]. The protective effect of CRF may be dependent on the balance between cytokines on the one hand and naturally occurring cytokine-specific inhibitors or antagonists on the other hand. In patients with Lyme arthritis, for instance, the balance between IL-18 and IL-1 receptor antagonist in the synovial fluid is associated with the time of resolution of an attack of the disease [18].

Taken together, it is conceivable that the higher serum concentrations of antibodies to lipid-A, endogenous inhibitors of cytokines and NO synthesis in CRF patients might contribute to the reduction of cardiovascular failure and other organ system failures, and consequently the relatively fair prognosis in patients with prior CRF. More studies, however, are needed to unravel the precise role of these cytokine-specific inhibitors and inhibitors of NO synthesis in influencing the course of inflammation and sepsis. Since the outcome in patients with ARF has not improved despite major advances in hemopurification techniques and supportive therapy over the past decades, and prognosis in ARF is likely to be dependent on other organ system failures other than the kidneys [19], future research should perhaps focus on the possible therapeutic effects of natural inhibitors of cytokines or NO synthesis.

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