SEMINARS IN
NEPHROLOGY

Acute Renal Failure: Much More Than a Kidney Disease

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Acute renal failure is a frequent clinical problem with an increasing incidence, an unacceptably high mortality rate that has not improved in more than 40 years, and no specific treatment, yet renal failure is not the usual cause of death. The role of inflammation has been documented in both acute renal injury and cardiac dysfunction. Several investigators have shown that congestive heart failure is associated with increased mortality in patients with acute renal failure. This article reviews some of the cardiac and other distant organ effects of acute renal injury that may be important in the morbidity and mortality observed clinically. Cardiac changes after experimental renal ischemia include cytokine induction, leukocyte infiltration, cell death by apoptosis, and impaired function. I propose that the extrarenal effects of kidney injury must be considered in designing therapies. Acute renal failure has systemic consequences and must be thought of as more than a kidney disease.

KEYWORDS acute kidney injury, congestive heart failure, cytokines, apoptosis, leukocytes

The prognosis of acute renal failure (ARF) is worse than that of many malignancies. The Acute Dialysis Quality Initiative investigators noted, "it has become increasingly clear that to focus solely on the issue of renal replacement therapy is like trying to change the final score of a football game by focusing on what happened in the last 5 minutes of the match."[1] ARF is a frequent and devastating clinical problem with an increasing incidence. ARF developed in 7.2% of 4,622 patients hospitalized in 1996,[2] however, by using the same definition of ARF, Hou et al[3] found only a 4.9% incidence in those hospitalized in 1979. The mortality rate of patients with ARF remains greater than 50% in most studies[4-7] (>70% in intensive care units[8]), although renal failure is not the usual cause of death.[5,7] For example, with an effective intervention (increased dialysis dose), the mortality rate was improved from more than 60% to more than 40% at only 28 days.[9] Many researchers have addressed the outcome of ARF in different patient populations (see references[10-13]), and although mortality rates vary with the specific patients studied, the rate remains unacceptably high.

Studies of patients with ARF clearly have identified dysfunction of extrarenal organs, particularly the heart, as critical.[14-18] Lohr et al[16] found that both "congestive heart failure" (CHF) and systolic blood pressure less than 110 mm Hg were associated with mortality. In a prospective analysis, Jorres et al[19] reported "cardiac failure" as the cause of death in 71% of ARF patients. Lien and Chan[15] found that "heart failure" influenced survival in a retrospective analysis of 58 patients. ARF is strongly associated with mortality in patients with heart disease (after cardiac surgery or myocardial infarction) with an odds ratio of 4 to 39 in different populations,[20-22] and ARF in the setting of chronic renal dysfunction carries an even greater risk for death.[21] There are no specific treatments for ARF and, unlike the dramatic progress in some diseases (eg, myocardial infarction and stroke), there has been no clear improvement in the mortality rate of ARF in more than 40 years.[6] In a study of 490 patients, the median survival of those with ARF requiring dialysis was 32 days, with only 27% alive at 5 months.[23] Even mild decreases in renal function are associated with increases in both in-hospital[24,25] and long-term (up to 4 y) mortality.[26,27] Significant progress in the understanding of the pathophysiology of ARF has not been translated into large clinical improvements. One consideration in the lack of efficacy of interventions that have been studied is the effect on distant organ systems.[7,28] Dysfunction of the heart and other organs is common in ARF and increases

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the mortality,[16] and thus may be important in designing therapies.

ARF also has a large economic impact. The estimated cost per quality-adjusted life-year saved by initiating dialysis in ARF patients was $61,900 to $274,100 in 1994 dollars.[23] The annual cost of ARF care nationwide is more than $12 billion.[23,29] It has been estimated that 30% of patients in an intensive care unit who survive an episode of ARF are maintained on long-term dialysis and the 1-year mortality of these patients is 31%.[18] Dialysis dependence in ARF survivors is associated with a more than 7-fold increase in the cost of care (compared with survivors with renal recovery).[29] Animal studies suggest that an episode of ARF may have additional long-term consequences. Exaggerated hypertensive response to angiotensin II, markedly decreased peritubular capillary density, proteinuria, and interstitial fibrosis have been found after bilateral renal ischemia in young rats.[30] Twenty-eight percent of ARF survivors require institutional care,[18] and survivors have a median of 1 dependency in activities of daily living.[23] Morgera et al[31] reported that 41% of ARF survivors had "significantly impaired" renal function. Long-term mortality is increased significantly (hazard ratio, 1.83; 95% confidence interval, 1.38-3.20) after an episode of ARF, even with recovery of renal function.[26]

Inflammation and Acute Kidney Injury

Increased plasma cytokine levels are predictive of death in ARF patients.[32] The importance of inflammation in renal injury after ischemia has been shown in several models.[33] Neutrophils,[34] macrophages/monocytes,[35] and T lymphocytes[36] accumulate in the kidney in experimental renal ischemia. Increases in renal myeloperoxidase activity, an index of leukocyte infiltration/activation, can be shown 1 hour after ischemia.[36] Linas et al[37] showed that reperfusion of isolated postischemic kidneys with polymorphonuclear cells results in a lower glomerular filtration rate than reperfusion with buffer alone. These investigators also showed that polymorphonuclear cell infiltration is dependent on the duration of ischemia and the activation state of the neutrophil. Kielar et al[38] showed production of granulocyte colony stimulating factor by postischemic kidneys in vivo and by medullary thick ascending limb cells after exposure to reactive oxygen species in vitro. Increases in the number of neutrophils in rat kidneys after ischemia and insulin-like growth factor-1 (IGF-1; 172.5 ± 30.0/mm^2 medulla versus 42.1 ± 9.6 ischemia alone) have been shown,[39] suggesting that increased neutrophil accumulation might be responsible for the increases in mortality seen in critically ill patients treated with some growth factors.[40]

We have reported increases in renal white cells and systemic cytokines (tumor necrosis factor [TNF]-α and interleukin [IL]-1) after experimental renal ischemia.[41] Other investigators have shown induction of renal TNF messenger RNA (mRNA) 30 minutes after renal ischemia. In that study, TNF binding protein decreased both renal leukocyte infiltration and functional impairment after renal ischemia.[42] Increases in hepatic TNF after renal ischemia in mice also have been shown.[43] In a recent study, the urinary TNF level was measured in 10 neonates with ARF and 10 asphyxiated neonates without ARF. The increase in urinary TNF level in the ARF group in the first day of life was not statistically significant, perhaps because of the small number given the standard error observed.[44]

Increases in systemic IL-6[38] and renal IL-8[45] levels have been shown within hours after experimental renal injury. We have reported that increased levels of urinary IL-6 and IL-8 in renal allograft recipients (without rejection) are predictive of sustained ARF. In that series, the urinary TNF level was undetectable in control urine and was increased after ischemia.[46] A recent study found that increases of IL-6 and IL-8 levels were predictive of mortality in ARF patients.[32] The complex and overlapping mechanisms of cytokine generation in renal injury are understood incompletely, but blocking mitogen-activated protein kinases or transcription factor(s) that regulate many inflammatory mediators offers therapeutic potential.[47,48]

Leukocyte infiltration also is found in human ARF. Renal leukocyte accumulation, in some cases the only histologic abnormality, was found in 95% of unselected cases of ARF in an autopsy study.[49] Hakim et al[50] found that ARF patients dialyzed with a relatively biocompatible polymethylmethacrylate (PMMA) membrane that results in less leukocyte activation were more likely to recover renal function than those dialyzed with a bioincompatible cuprophane membrane. Although there was a trend (p = .10) toward better survival in the PMMA group, a randomized study found no difference in mortality between the PMMA and cuprophane groups.[19]

Leukocyte localization to sites of injury or inflammation is mediated largely by adhesion receptors.[51] The initial rolling of leukocytes on activated endothelium is mediated by members of the selectin family. This allows exposure of white blood cells (WBC) to inflammatory mediators such as IL-1 and TNF and activation of the rolling leukocytes. Adhesion receptors, including intercellular adhesion molecule-1 (ICAM-1), on endothelial cells interact with their counterreceptors on leukocytes, resulting in immobilization of leukocytes on the endothelium and diapedesis of WBCs across the vessel wall. ICAM-1 expression is increased by IL-1 and TNF in vitro.[51] We have reported that anti–ICAM-1 antibody protects against ischemic ARF in the rat, even when administered 2 hours after reperfusion.[52] ICAM-1–deficient mice are protected from the functional and histologic consequences of renal ischemia.[41] Other investigators also have found protection with anti–ICAM-1 antibody[53] or ICAM-1 antisense oligonucleotides.[54] Azuma et al[55] found a second peak of IL-1, TNF, ICAM-1, monocyte chemotactic protein-1 expression, and leukocyte infiltration 16 to 52 weeks after unilateral ischemia, providing evidence that acute renal injury can result in ongoing inflammation.

Cytokines and Cardiac Dysfunction

Although myocardial depressant factors have been postulated, the pathophysiology of cardiac dysfunction in ARF remains unclear.[56] Leukocytes are critical in cardiac dysfunction after ischemia and reperfusion[57] and agents that block leukocyte function or localization protect against injury.[58-60] An increased WBC count markedly increases the risk for acute myocardial infarction in human beings,[61] and removing WBCs from cardioplegia solution improves myocardial function in stressed piglet hearts.[62] ICAM-1 mRNA is increased in myocardial tissue after ischemia/reperfusion.[63] Anti–ICAM-1 antibody, which blocks leukocyte adhesion, has been shown to decrease the area of necrosis and myeloperoxidase activity and to improve acetylcholine-induced endothelial relaxation in a feline model of myocardial ischemia.[58] Blocking other adhesion receptors also protects against myocardial injury.[59,60] In other syndromes of multiorgan failure (sepsis or TNF-induced damage), neutrophils are important. Neutrophil depletion prevents multiple organ damage caused by TNF infusion in animals.[64]

Cytokines are thought to be critical in the pathophysiology of heart failure by many,[65,66] but not all,[67] investigators. Increased levels of inflammatory cytokines were documented in human congestive heart failure more than 10 years ago.[68] Proinflammatory mediators are activated earlier in the course of clinical heart failure than neurohormones such as norepinephrine and angiotensin II.[69,70] Increased levels of proinflammatory cytokines, including TNF, IL-1, and IL-6, are correlated with worsening New York Heart Association functional status[71] and are significant independent predictors of mortality. For example, circulating TNF levels in the highest quartile were associated with a mortality rate more than 2-fold greater than that in patients with circulating TNF in the lowest quartile.[70] Evidence also supports a role for TNF in cardiac dysfunction associated with sepsis, myocardial infarction, myocarditis, allograft rejection, and atherosclerosis.[72] The *cytokine hypothesis* proposes that cardiac dysfunction results, at least in part, from deleterious effects, including death of myocytes and decreased contractility[73] of endogenous cytokine cascades on the heart and peripheral circulation.[74]

Infusion of TNF in rats and dogs results in decreased left ventricular (LV) systolic function.[75,76] Cardiac overexpression of TNF in mice results in leukocyte infiltration of the heart, myocyte apoptosis, severely impaired cardiac function, and 100% mortality by 4 months of age.[77] Cardiac apoptosis is increased approximately 14-fold when compared with wild-type animals.[78] In the isolated rat heart, perfusion with TNF results in a decrease in LV developed pressure and coronary vasoconstriction.[79] Injury to hearts transplanted into rat abdomen results in increases in TNF and decreased function (decrease in LV fractional shortening, increase in LV end-diastolic diameter) in native hearts. Thus, TNF can mediate potent effects in remote regions.[73] After experimental myocardial infarction, the level of late cytokine activation in the noninfarcted region correlates with LV end-diastolic diameter 20 weeks after infarction.[80] In human beings, IL-6 levels at 24 hours correlate with collagen formation at discharge after myocardial infarction.[81] Chronic treatment with IL-1 in the dog results in sustained myocardial dysfunction, WBC infiltration of the heart, and increased cardiac myeloperoxidase activity. Myocardial dysfunction can be prevented by blocking adhesion receptors.[82]

Many negative effects of TNF in experimental models reverse when the exposure ceases[75] and the myocardial dysfunction seen in dogs with IL-1 can be prevented by blocking adhesion receptors.[82] Thus, the regulation of inflammatory mediators has potential therapeutic use. However, despite promise in early clinical trials, blocking TNF action with antibodies or a receptor antagonist has not shown benefit in human congestive heart failure.[83] Recent data, however, show that increases in TNF and IL-6 in patients without heart failure are predictive of the development of CHF. In that study, serum IL-6 levels in the highest tertile were associated with a more than 4-fold increase in the incidence of heart failure when compared with patients with IL-6 levels in the lowest tertile.[84]

TNF-mediated apoptosis is one of the proposed mechanisms for the association of TNF with cardiac dysfunction.[77] Apoptosis or programmed cell death is a coordinated, energy-requiring process that, unlike necrosis, does not result in local tissue inflammation. Apoptosis in the heart is mediated by caspases, a family of cysteine proteases, that are synthesized as proenzymes and are activated sequentially and amplify the apoptotic response.[85,86] In the death receptor or extrinsic pathway, apoptosis can be triggered by ligands such as TNF or Fas ligand binding to cell-surface death receptors (including TNF receptor 1 and Fas), resulting in receptor oligomerization and recruitment of death-domain–containing proteins and then initiator caspases (eg, caspase-8), forming a death-inducing signaling complex. Caspase-8 activates caspase-3, an executioner caspase, directly via proteolysis in Fas type I cells. This leads to the caspase cascade, resulting in cleavage of critical cellular proteins and apoptotic cell death.[85,87] In the intrinsic or mitochondrial pathway, stimuli such as hypoxia or oxidative stress result in mitochondrial release of cytochrome *c*, which binds apoptosis activation factor-1. Apoptosis activation factor-1, caspase-9, and adenosine triphosphate form an apoptosome that can activate caspase-9 proteolytically. In both of these overlapping pathways, the initiator caspases then cleave and activate effector procaspases (-3, -6, and -7), which cleave critical proteins leading to apoptosis.[85,87] TNF also may mediate apoptosis via a caspase-independent mechanism.[88] Caspases also play an important role in inflammation. Caspase-1 and caspase-11 process interleukin-1 to the mature, active form. It has been suggested that activation of caspases with apoptosis also can result in inflammation.[89]

The loss of cardiomyocytes via apoptosis is critical in the pathogenesis of cardiac dysfunction.[90] Multiple human studies have found evidence of apoptosis in 0.02% to 5% of nuclei in severe CHF.[91-94] Because apoptotic cells are cleared rapidly, the functional significance of an ongoing loss of small

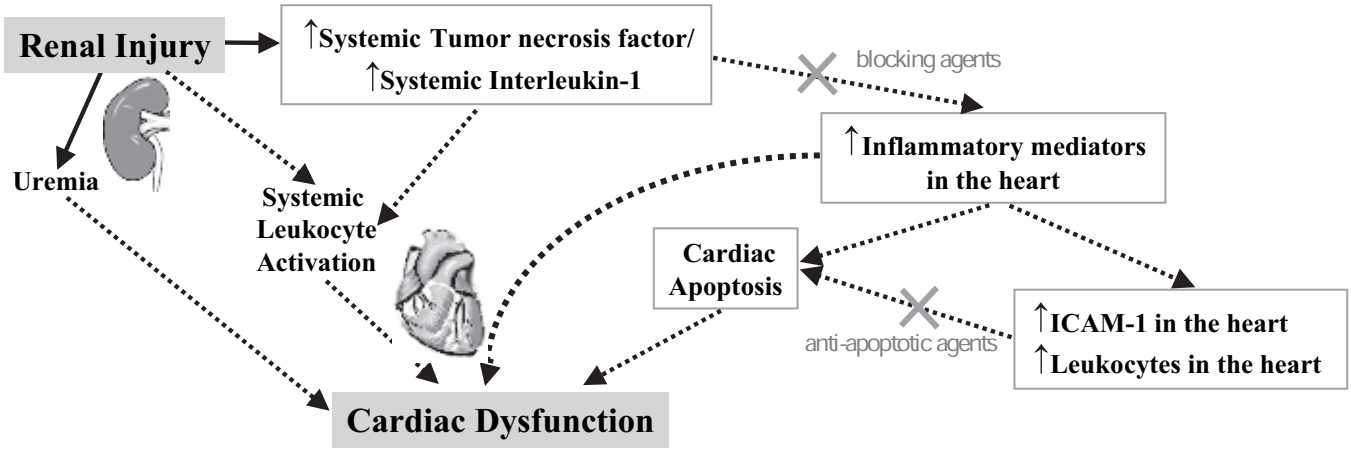

Figure 1 Proposed mechanism of distant organ effects of acute kidney injury. Given the inflammation seen with experimental renal ischemia, we propose that the inflammatory mediators generated with renal ischemia/reperfusion injury result in alterations in other organ systems. Renal injury results in systemic inflammatory mediators that lead to systemic leukocyte activation, in turn increasing inflammatory mediators, upregulation of adhesion receptors, and leukocyte infiltration in distant organs, resulting in apoptosis and dysfunction of extrarenal organs.

numbers of cells can be great.[90] Transgenic models have shown that apoptosis alone can result in lethal heart failure.[85,95] For example, Wencker et al[85] constructed a mouse with cardiac-specific overexpression of caspase-8, a protease that cleaves a number of critical cellular proteins and results in apoptosis. These investigators found apoptosis in the hearts of these mice that was accompanied by dilated left ventricles with decreased fractional shortening on echocardiography and death from 20 days to 7 months after birth. In a murine model, inhibition of cardiac apoptosis prevents cardiac dilation and dysfunction.[96] Thus, prevention of cardiac apoptosis, for example, by caspase inhibitors, may be a potential treatment for CHF.[85]

End-Organ Effects of ARF

In a recent study of patients with ARF, the adjusted odds ratio for death was 7.7 for cardiovascular failure, which was greater than that for respiratory failure (odds ratio, 3.6), hepatic failure (odds ratio, 6.3), neurologic failure (odds ratio, 3.0), massive transfusion (odds ratio, 5.3) or age more than 60 years (odds ratio, 3.7).[5] The program to improve care in acute renal disease (PICARD) study group found a 40% incidence of cardiac failure in a study of 552 intensive care unit patients with ARF.[97] In experimental ARF, multiple end-organ effects, including cardiac,[98] pulmonary,[98-100] hepatic,[38,101] cerebral,[102] and phagocyte alterations,[103] have been observed.

Given the inflammation seen with experimental renal ischemia and the role of cytokines in cardiac dysfunction, we hypothesized that the inflammatory mediators[41] generated with renal ischemia/reperfusion injury result in alterations in other organ systems (Fig 1). This hypothesis was tested in an animal model of renal ischemia. An increase in mRNA level for ICAM-1, leukocyte infiltration and increased cell death by apoptosis in the heart, and decreased cardiac function were found after experimental ARF (Fig 2). To determine the role of uremia and ischemia in the apoptosis observed, we examined hearts from animals that underwent 15 minutes of ischemia that did not result in an increase in serum creatinine level, and those that underwent bilateral nephrectomy that resulted in a mean serum creatinine level of more than 5 mg/dL 48 hours after renal ischemia. Cardiac apoptosis was found in the 15-minute ischemia group, but very little was seen after nephrectomy, suggesting that ischemia is necessary for the apoptosis observed. We also found that blocking the action of TNF limited cardiac apoptosis. To determine the functional significance of the changes observed, echocardiography was performed. In representative tracings (Fig 2), LV dilation is apparent. Quantification of echocardiographic parameters showed increases in LV end-diastolic and end-systolic diameters, relaxation time, and decreased fractional shortening. No differences in anterior or posterior wall thickness were seen. There were no differences in blood pressure, hematocrit level, or body weight between the sham and ischemia groups.[104] In another animal study, sustained ventricular fibrillation after cardiac ischemia was much more frequent (80% versus 0% in the absence of ARF) and of longer duration with ARF.[105] Clark et al[106] also found increases in LV diastolic diameter with ARF and this was ameliorated with treatment with a vessel dilator. The peak serum creatinine level was not significantly lower in the treated group, yet survival was improved markedly, suggesting that the distant organ effects must be considered when treating ARF.

What is the significance of the changes in the heart observed after renal ischemia? ARF often occurs in patients with multiple comorbidities. In human heart failure, levels of TNF and IL-6 and other inflammatory mediators not only predict survival in patients with heart failure,[70] but also predict the development of CHF.[84] Apoptosis has been shown in multiple studies of human beings with severe CHF.[91-94] Activation of the Fas/Fas ligand system, which results in apoptosis of cardiomyocytes, is correlated with the severity of heart failure.[107,108] Symptomatic heart failure after myocardial infarc-

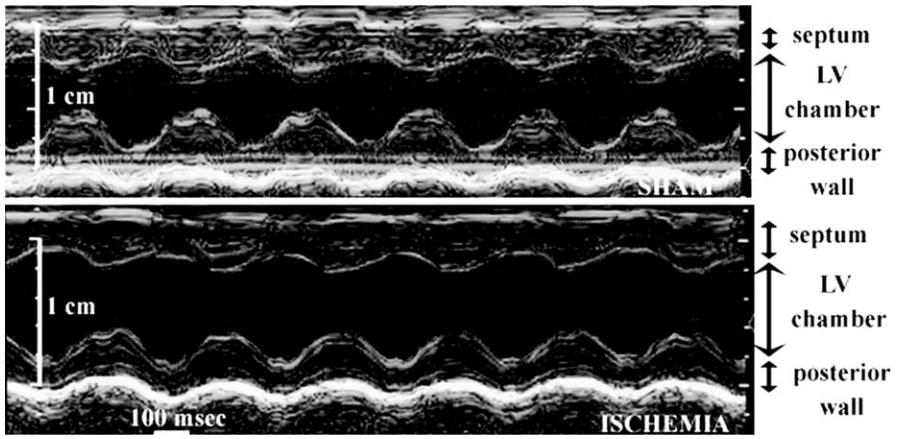

Figure 2 Effect of renal ischemia on cardiac function. Representative M-mode echocardiographic tracings 48 hours after sham surgery (top panel) or renal ischemia (30 min; bottom panel) in the rat. Mean values of echocardiographic parameters showed an increase in LV end-diastolic and end-systolic diameter and fractional shortening. Reprinted with permission from Kelly.[104]

tion is associated with more than a 4-fold greater myocardial apoptotic rate than that in patients without CHF.[109] In CHF patients treated with a ventricular assist device, an increase in cardiac index from 1.9 ± 0.1 to 2.5 ± 0.2 (L/min/m^2) was associated with a 75% decrease in apoptosis.[110] In patients with decompensated heart failure, activated caspase-9 and DNA fragmentation factor 45 (which is cleaved by caspase-3 and leads to DNA degradation) in myocardial biopsy specimens were increased when compared with levels in less-severe CHF.[111] Studies in transgenic mice also showed that cardiac overexpression of TNF[77] and cardiac apoptosis[85] results in lethal heart failure and that inhibition of apoptosis improved both cardiac function and survival in different animal CHF models.[112,113] Thus, changes in extrarenal organs in ARF may affect morbidity and mortality and treatment should consider the distant organ effects.

In addition to changes in the heart, alterations in other organs have been shown after renal ischemia. Meldrum et al[114] found induction of TNF with injury in the contralateral kidney with unilateral renal ischemia in the rat. Daemen et al[101] showed increased α_1-glycoprotein and serum amyloid P levels in the liver after renal ischemia. Hepatic production of IL-10 after experimental renal ischemia also has been shown.[38] Liu et al[115] have shown increases in hepatocyte growth factor in the lung, liver, and spleen after experimental renal injury. Kramer et al[99] showed congestion, increased vascular permeability, and increased expression of aquaporin 5 in the lung after renal ischemia. Deng et al[100] found that treatment of renal ischemia in rats with α-melanocyte hormone ameliorated pulmonary leukocyte infiltration, edema, and upregulation of TNF and ICAM-1. Ischemia/reperfusion injury to other organs (eg, intestine,[116] liver,[117] muscle,[118] and contralateral lung[119]) resulted in lung injury. In contrast, Shin et al[120] found no difference in pH level, partial pressure of carbon dioxide, partial pressure of oxygen, or lung water after renal ischemia in sheep. Matsumoto and Nakamura[121] isolated a factor they called *injurin* from the sera of rats with renal injury that when injected into normal rats resulted in induction of hepatocyte growth factor in the lung. Sousa et al[103] found alterations in phagocyte uptake of sulfur colloid in experimental renal injury. Alterations in spontaneous electrical activity and expression of the immediate early gene Fos in the nucleus paragigantocellularis of rat brains was also found after renal ischemia.[102] Studies in animal models are, by their nature, simplistic to allow the examination of specific questions in a controlled fashion. Nevertheless, these studies provided valuable information and suggested that the effects of renal injury on other organs may be critical and amenable to therapy.

Ischemia to other organs also has been shown in diverse models to result in distant organ injury. Renal dysfunction also has been shown after ischemic injury in other organ systems.[122] In many of these models, dysfunction in other organ systems was associated with increased systemic levels of cytokines after ischemic injury.[117,122-124] Upregulation of the adhesion receptor ICAM-1 in multiple distant organs has been shown after hepatic ischemia in the rat.[125] In a model of aortic cross-clamping in the dog, Roux et al[126] found a 40% (±4%) decrease in cardiac output, a 36% increase in mean pulmonary artery pressure, and an increase in peripheral vascular resistance of 120%. Yassin et al[122] found decreases in renal function, increases in serum TNF levels, and liver enzymes and decreases in intestinal mucosal thickness after lower limb ischemia. After mesenteric ischemia, Yao et al[124] found a decrease in cardiac index that could be ameliorated with anti-TNF antibody, which also markedly prolonged survival in this model.

Therapeutic Implications

Many agents have been shown to provide marked protection from ARF in animals.[6,33] In contrast to studies in animals, studies in human beings have been disappointing. For instance, synthetic atrial natriuretic peptide did not result in improved survival or dialysis-free survival in a randomized trial of 504 patients with ARF.[127] In this study, cardiac abnormalities were associated with an increased risk for mortality and provision of dialysis (relative risk, 1.51-3.14).[7] A randomized trial of IGF-1 in ARF was terminated because of a lack of efficacy after an interim analysis of 72 patients.[28] The investigators of that study concluded, "Recombinant human insulin-like growth factor-1 does not accelerate the recovery of renal function in acute renal failure patients with substantial comorbidity."[28] There are many possible explanations for

the lack of efficacy of these interventions, but one consideration is the effect the interventions have on dysfunction of other organ systems. Cardiac dysfunction is common in ARF, increases the mortality rate,[16] and is thought to be a key factor in the IGF-1[28] and atrial natriuretic peptide trials.[7] An understanding of the cardiac changes after renal ischemia and the mechanisms involved will have therapeutic implications.

In summary, animal and human studies show inflammation after renal injury and the negative effects of inflammation on cardiac function. There are a large number of anti-inflammatory and antiapoptotic agents available, many of which have been administered safely to human beings. Many factors must be considered when designing and evaluating therapies for ARF, for example, early diagnosis. Distant organ effects and inflammatory consequences should be considered. Although it was an uncontrolled phase I trial, initial clinical results of the bioartificial kidney showed decreased cytokine levels and improvement in multi-organ dysfunction (acute physiologic score) in treated patients followed-up for more than 3 days.[128] Investigating the many remaining questions concerning the nature and extent of distant effects of renal injury and the effect of potential therapies hopefully will allow effective intervention before the "last 5 minutes of the match"[1] and improve patient outcomes.

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