REVIEW ARTICLE

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Identification of Renal Injury in Cardiac Surgery: The Role of Kidney-Specific Proteins

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RENAL DYSFUNCTION IS ONE OF the most serious organ complications of cardiac surgery. It appears to be common in patients undergoing cardiac surgery with cardiopulmonary bypass (CPB).[1] Of the approximately 600,000 patients undergoing coronary revascularization per year in the United States, 1.1% to 1.4% develop postoperative acute renal failure (ARF) requiring dialysis.[2] Many more patients suffer from occult, subclinical, and transient renal injury without requiring hemodialysis.[2] ARF after cardiac surgery is an independent predictor of mortality, and even renal dysfunction not requiring dialysis appears to be an independent predictor of mortality in this situation.[1,3,4] Mortality in cardiac surgery patients developing ARF requiring hemodialysis is approximately 10% to 20%, compared with a 1% mortality in patients without ARF.[3] In addition, ARF with dialysis increases in-hospital stay 2- to 3-fold resulting in increased costs.[4] There is increasing evidence that small decreases in kidney function are important for patients' outcome as well. Chertow et al[5] defined kidney dysfunction as an increase of serum creatinine >0.3 mg/dL and found this was independently associated with mortality. In a prospective cohort study in cardiac surgery patients, Lassnigg et al[6] showed that acute kidney dysfunction, defined as an increase of serum creatinine of 0.5 mg/dL or above was associated with worse survival.

Early preventive measures may be a way of reducing postoperative ARF and hence may help to decrease mortality in these patients. Thus, sensitive markers of renal injury are desirable for early intervention.[7] Because it is conceivable that injuries at different segments of the nephron may benefit from different therapies, markers that allow identification of the site of nephron injury might also be advantageous. Traditional markers of renal dysfunction (eg, serum creatinine concentration [sCr] and creatinine clearance [CrCl]) lack diagnostic sensitivity and specificity, particularly in the early stages of renal injury,[4,8,9] and they do not allow localization of the site of injury. Other biomarkers of renal injury have been suggested to be useful for early and reliable diagnosis and rapid initiation of therapy.[7,8] Accordingly, this overview's purpose is to analyze the role of kidney-specific proteins as markers of kidney injury in cardiac surgery patients.

THE ETIOLOGY OF RENAL DYSFUNCTION IN CARDIAC SURGERY

ARF is defined as a rapid deterioration of glomerular filtration rate (GFR).[10] It is further characterized by the loss of renal ability to concentrate urine, maintain fluid homeostasis, and conserve electrolytes.[10] Renal injury can vary from subclinical injury with minimally elevated sCr to complete failure of kidney function requiring dialysis. Thus, the more encompassing term "acute kidney injury" (AKI) was proposed because it includes altered renal function in addition to ARF requiring hemodialysis.[2] According to the RIFLE system (acronym indicating Risk of renal disease, Injury to the kidney, Failure of kidney function, Loss of kidney function, End-stage kidney disease) patients with or at risk of renal failure are categorized as being at risk, as having renal injury, and as having complete failure[11] (Table 1).

Factors initiating ARF are classified as either (1) prerenal (inadequate perfusion and hypoxia), (2) renal (intrinsic kidney diseases, toxins, and ischemia), or (3) postrenal (obstructive uropathy).[12]

One important pathophysiologic mechanism for the development of kidney injury is the alteration of renal blood flow resulting in kidney ischemia.[12] Renal blood flow is autoregulated by several mechanisms including catecholamines, atrial natriuretic peptide, angiotensin, and prostaglandins. ARF induced by ischemia or cellular toxins is characterized by alterations in glomerular hemodynamics. Cardiac surgery triggers complex cardiovascular and biochemical responses by various mechanisms. Although prerenal factors (hypotension, low output, volume depletion, and hypoxia) are likely the most common cause of renal dysfunction in cardiac surgery,[1,3] there is substantial evidence for the involvement of inflammation in the pathogenesis of impaired renal function after cardiac surgery. Cardiac surgery is associated with activation of the complement system, the coagulation and fibrinolytic cascade, synthesis and release of various cytokines, activation of neutrophils with subsequent protease enzyme release, and production of

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Table 1. The RIFLE Criteria to Define Renal Dysfunction (Risk of Renal Disease, Injury to the Kidney, Failure of Kidney Function, Loss of Kidney Function, End-Stage Kidney Disease)

	GFR Criteria	Urine Output Criteria
Risk of renal dysfunction	Increased Scr × 1.5 or GFR decrease >25%	<0.5 mL/kg/h × 6 h
Injury to the kidney	increased Scr × 2 or GFR decrease >50%	<0.5 mL/kg/h × 12 h
Failure of kidney function	increased Scr × 3 or GFR decrease >75% or Scr >4 mg/dL (when there was an acute increase of >0.5 mg/dL)	<0.5 mL/kg/h × 24 h or anuria × 12 h
Loss of kidney function	Persistent acute renal failure (complete loss of kidney function >4 weeks)	
End-stage kidney disease	Persistent acute renal failure (complete loss of kidney function >3 months)	

Data from Han and Bonventre.[8]

oxygen radicals.[13] CPB is likely to be a major trigger of this inflammatory response. Although biomaterials of the extracorporeal circuit equipment have been improved markedly, CPB is known to cause systemic inflammatory response. The damaging effect of CPB is caused by exposure of blood to unphysiologic nonendothelial surfaces, to increased shear stress, and to the administration of various medications. The kidney can no longer be regarded as a passive bystander in the evolving inflammatory response. It is not only involved actively in the control of inflammation, but is also vulnerable to this inflammatory process; although glomerular filtration of proinflammatory mediators could help to reduce inflammation, these substances may be tubulotoxic.[14,15] A variety of factors aside from CPB may increase the likelihood of post–cardiac surgery renal dysfunction. Pre-existing comorbidities, advanced age, certain drugs, and hemodynamic instability are associated with the development of perioperative renal insufficiency.[16,17]

IDENTIFICATION OF RENAL INJURY

In cardiac surgery patients, measures to assess kidney dysfunction are urine output, sCr, CrCl, fractional sodium excretion (FE_{Na}), and cystatin C.[18] Because of its ease of measurement, urine output is the most commonly used measure of renal function. It is specific but not very sensitive for renal dysfunction.[10] Most importantly, severe ARF may be present despite normal urine output (nonoliguric ARF). Sensitivity and specificity of urine output as markers for kidney dysfunction are also lost when diuretics are used.

In the steady state, sCr is inversely proportional to GFR and can thus be used to estimate GFR without the need for urine collection. However, the usefulness of sCr as a marker of renal dysfunction is limited because it is not affected only by GFR but also by tubular secretion, generation, and elimination of creatinine, all of which vary among and within individuals.[19] In addition, it varies with intravascular volume, muscle mass, age, and sex, and it is affected by muscle trauma, fever, liver disease, and immobilization. Approximately 50% of the function of the kidney can be lost without an increase in sCr; sCr only loosely correlates with GFR. Although a sCr of 1.5 mg/dL corresponded to a GFR of approximately 77 mL/min in a 20-year-old black male, it corresponded to merely 36 mL/min in a 80-year-old white female.[9] SCr will mostly

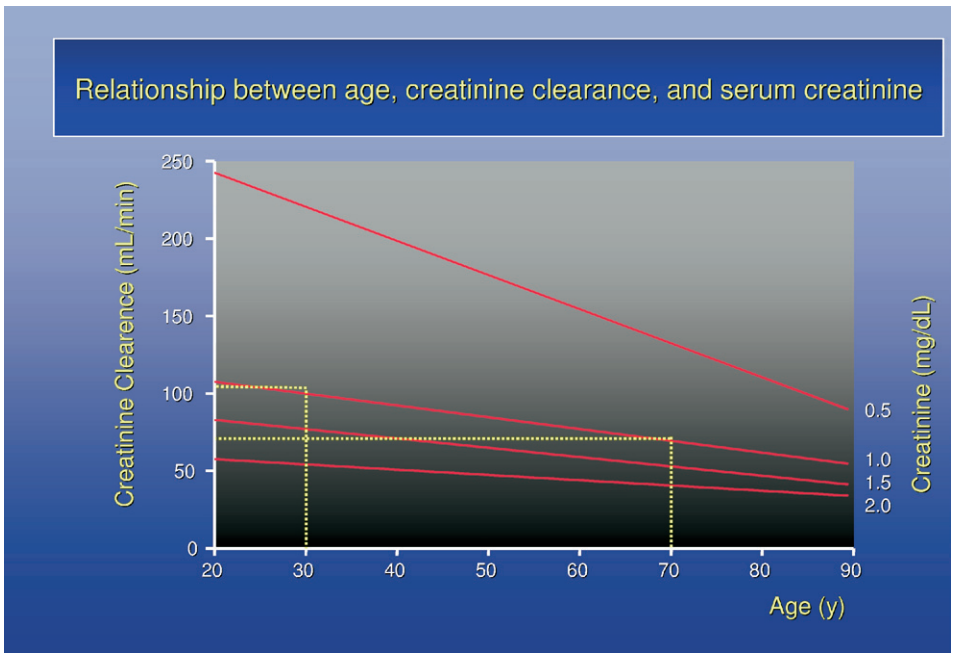

Fig 1. Relationship among age, creatinine clearance, and serum creatinine. The importance of age for assessing creatinine clearance by measuring serum creatinine levels. (Color version of figure is available online.)