Association of Genetic Polymorphisms With Risk of Renal Injury After Coronary Bypass Graft Surgery

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• ***Background:*** **Post–cardiac surgery renal dysfunction is a common, serious, multifactorial disorder, with interpatient variability predicted poorly by preoperative clinical, procedural, and biological markers. Therefore, we tested the hypothesis that selected gene variants are associated with acute renal injury, reflected by a serum creatinine level increase after cardiac surgery.** ***Methods:*** **One thousand six hundred seventy-one patients undergoing aortocoronary surgery were studied. Clinical covariates were recorded. DNA was isolated from preoperative blood; mass spectrometry was used for genotype analysis. A model was developed relating clinical and genetic factors to postoperative acute renal injury.** ***Results:*** **A race effect was found; therefore, Caucasians and African Americans were analyzed separately. Overall, clinical factors alone account poorly for postoperative renal injury, although more so in African Americans than Caucasians. When 12 candidate polymorphisms were assessed, 2 alleles (interleukin 6 −572C and angiotensinogen 842C) showed a strong association with renal injury in Caucasians ($P < 0.0001$; >50% decrease in renal filtration when they present together). Using less stringent criteria for significance ($0.01 > P > 0.001$), 4 additional polymorphisms are identified (apolipoproteinE 448C [ε4], angiotensin receptor1 1166C, and endothelial nitric oxide synthase [eNOS] 894T in Caucasians; eNOS 894T and angiotensin-converting enzyme deletion and insertion in African Americans). Adding genetic to clinical factors resulted in the best model, with overall ability to explain renal injury increasing approximately 4-fold in Caucasians and doubling in African Americans ($P < 0.0005$).** ***Conclusion:*** **In this study, we identify genetic polymorphisms that collectively provide 2- to 4-fold improvement over preoperative clinical factors alone in explaining post–cardiac surgery renal dysfunction. From a mechanistic perspective, most identified genetic variants are associated with increased renal inflammatory and/or vasoconstrictor responses.** ***Am J Kidney Dis*** **45:519-530.**

INDEX WORDS: Acute renal failure (ARF); polymorphism; genetic; postoperative; intensive care; cardiopulmonary bypass (CPB); heart surgery; cardiac surgery; human; angiotensin-converting enzyme (ACE); associate study; candidate genes.

ACUTE RENAL dysfunction, evidenced by a rapid decline in glomerular filtration rate and accumulation of nitrogenous waste products (blood urea nitrogen and creatinine), is a major medical problem occurring in 5% of all patients admitted to the hospital and 30% of those admitted to an intensive care unit.[1] Furthermore, acute renal injury remains a common serious complication of cardiac surgery.[2] Multiple causes for this observation have been proposed, including nephrotoxins, atheroembolism, ischemia-reperfusion, and cardiopulmonary bypass (CPB)–induced activation of inflammatory pathways. Renal failure requiring dialysis occurs in up to 5% of patients undergoing cardiac surgery; an additional 8% to 15% have moderate renal injury (eg, >1.0-mg/dL [88 μmol/L] peak creatinine level increase).[2-9] Lesser renal injuries are even more common (>50% of patients undergoing aortocoronary bypass surgery have a ≥25% postoperative increase in serum creatinine level). In many settings, including cardiac surgery, acute renal failure is associated independently with the in-

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See Appendix for a list of members of the Perioperative Genetics and Safety Outcomes Study (PEGASUS) Investigative Team.

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hospital mortality rate, even after adjustment for comorbidities and other complications[2,10,11]; all degrees of renal injury are associated with increased mortality and other adverse outcomes.[12] The grave prognosis associated with this complication may be caused, at least in part, by distant effects of acute renal injury on other organ function.[13,14] Unfortunately, typical characteristics of those presenting for cardiac surgery (eg, advanced age and history of atherosclerotic vascular disease) make these patients a group at high "renal risk."[2,15-17]

Many of the insults sustained by the kidney as part of cardiac surgery (eg, CPB, atheroembolism) are believed to result in ischemic- and/or inflammation-mediated renal injury. The oxygen diffusion shunt characteristic of renal circulation and metabolic demands from active tubular reabsorption contribute to the precarious physiological process of renal perfusion, including low medullary Po_2 (10 to 20 mm Hg).[18] Key to the regulation of renal blood flow are paracrine systems (eg, renin-angiotensin system and nitric oxide) that modulate microvascular function and oxygen delivery in the renal medulla.[19] The inflammatory response to CPB generates cytokines (eg, tumor necrosis factor α [TNF-α] and interleukin 6 [IL-6]), both systemically and locally in the kidney,[20,21] that have major effects on the renal microcirculation and may lead to tubular injury.[22] Recent evidence suggests that heritable differences modulate the activation of these pathways.

Although many preoperative and procedural predictors and biological markers have been identified, risk stratification based on these factors explains only a small part of the variability in post-cardiac surgery renal dysfunction.[2-9,17,23-32] In addition, little is known regarding the relationship of the several known polymorphisms associated with altered activation of renal paracrine and/or inflammatory pathways with acute renal injury after aortocoronary bypass graft surgery. The few existing studies focused on only 2 genetic polymorphisms (apolipoprotein E [APOE] 448C [ϵ4] and IL-6 -174C)[33-35] and did not take into account other important pathways and/or proteins or interactions between potentially synergistic insults. Therefore, we tested the hypothesis that genetic variants of inflammatory and paracrine pathways at multiple loci are associated with susceptibility to acute renal injury after cardiac surgery.

METHODS

Study Population

This analysis is a substudy of the Perioperative Genetics and Safety Outcomes Study, an ongoing Institutional Review Board–approved, prospective, longitudinal study at Duke University Medical Center (Durham, NC) in which 3,149 patients have been prospectively enrolled and consented to have clinical and genetic data analyzed in relation to perioperative outcomes. The current substudy targets 2,075 patients undergoing primary elective (ie, scheduled) aortocoronary bypass graft surgery using CPB between April 1995 and May 2002, a prespecified period in which detailed perioperative serum creatinine and dialysis data were systematically and prospectively collected. Three hundred seven patients with missing or misleading serum creatinine data were excluded, including those who died within 2 days of surgery and those requiring perioperative dialysis. Of the final 1,768 patients examined, 1,464 were Caucasian, 207 were African American, and 97 were of another race. Because of small numbers in each of the other race categories, our analysis was limited to Caucasians and African Americans.

Clinical Data Collection

Selection of both an appropriate surgical procedure and a relevant marker of renal function is important in the assessment of subtle differences in renal injury that may occur with genetic variation. The impact of procedure type on the incidence and severity of renal injury is important.[2] To best study allele effects, patients undergoing the same procedure should be examined; in this regard, nonemergent first-time coronary bypass surgery with CPB is a common, highly monitored, and highly reproducible model.

Conversely, an obvious selection for the most appropriate marker of renal function for postoperative studies does not exist. Rigorous study of postoperative acute renal injury has been hampered by a lack of consensus on definitions (1 review evaluated 26 controlled studies, and no 2 reports used the same criteria for acute renal dysfunction or acute renal failure).[17] Urine protein markers of tubular cell injury or dysfunction are an alternative, but we previously highlighted serious limitations specific to drugs administered during cardiac surgery that render them essentially without value in this setting.[36] New-onset dialysis is a firm end point, but occurs too rarely ($<2\%$) to be a practical marker.

At our institution, serum creatinine determinations are available daily as part of standard post–cardiac surgery care protocols. We selected peak fractional change in postoperative serum creatinine level (%ΔCr) as the primary outcome variable for this study, defined as the percentage of difference between preoperative serum creatinine and highest of the daily in-hospital postoperative values; this is a continuous variable generally unaffected by baseline renal function. Serum creatinine level is determined by using a dry slide enzymatic reflectance technique (Vitros 950; Johnson and Johnson, New Brunswick, NJ) with a normal range of 0.5 to