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Renal Dysfunction after Myocardial Revascularization: Risk Factors, Adverse Outcomes, and Hospital Resource Utilization

[Articles]

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Outline

Graphics

Abstract^

Background: Acute changes in renal function after elective coronary bypass surgery are incompletely characterized and represent a challenging clinical problem.

Objective: To determine the incidence and characteristics of postoperative renal dysfunction and failure, perioperative predictors of dysfunction, and the effect of renal dysfunction and failure on in-hospital resource utilization and patient disposition after discharge.

Design: Prospective, observational, multicenter study.

Setting: 24 university hospitals.

Patients: 2222 patients having myocardial revascularization with or without concurrent valvular surgery.

Measurements: Prospective histories, physical examinations, and electrocardiographic and laboratory studies. The main outcome measure was renal dysfunction (defined as a postoperative serum creatinine level > or = to 177 micromol/L with a preoperative-to-postoperative increase > or = to 62 micromol/L).

Results: 171 patients (7.7%) had postoperative renal dysfunction; 30 of these (1.4% overall) had oliguric renal failure that required dialysis. In-hospital mortality, length of stay in the intensive care unit, and hospitalization were significantly increased in patients who had renal failure and those who had renal dysfunction compared with those who had neither (mortality: 63%, 19%, and 0.9%; intensive care unit stay: 14.9 days, 6.5 days, and 3.1 days; hospitalization: 28.8 days, 18.2 days, and 10.6 days, respectively). Patients with renal dysfunction were three times as likely to be discharged to an extended-care facility. Multi-variable analysis identified five independent preoperative predictors of renal dysfunction: age 70 to 79 years (relative risk [RR], 1.6 [95% CI, 1.1 to 2.3]) or age 80 to 95 years (RR, 3.5 [CI, 1.9 to 6.3]); congestive heart failure (RR, 1.8 [CI, 1.3 to 2.6]); previous myocardial revascularization (RR, 1.8 [CI, 1.2 to 2.7]); type 1 diabetes mellitus (RR, 1.8 [CI, 1.1 to 3.0]) or preoperative serum glucose levels exceeding 16.6 mmol/L (RR, 3.7 [CI, 1.7 to 7.8]); and preoperative serum creatinine levels of 124 to 177 micromol/L (RR, 2.3 [CI, 1.6 to 3.4]). Independent perioperative factors that exacerbated risk were cardiopulmonary bypass lasting 3 or more hours and three measures of ventricular dysfunction.

Conclusions: Many patients having elective myocardial revascularization develop postoperative renal dysfunction and failure, which are associated with prolonged intensive care unit and hospital stays, significant

increases in mortality, and greater need for specialized long-term care. Resources should be redirected to mitigate renal injury in high-risk patients.

Each year, 600 000 patients undergo myocardial revascularization with cardiopulmonary bypass and sustain profound physiologic perturbations that precipitate ischemia and infarction in several organ systems [1-3]. Although medical resources have been redirected to address perioperative cardiac and neurologic illness, the clinical effect of cardiac surgery on renal function has not been studied rigorously. Nonpulsatile blood flow, increases in levels of circulating catecholamines and inflammatory mediators, macroembolic and microembolic insults to the kidney, and release of free hemoglobin from traumatized erythrocytes result in numerous pathophysiologic renal responses [4-6]. Many studies [7-9] have shown that patients who have undergone cardiac surgery developed maldistributed renal blood flow, increases in renal vascular resistance, and substantive decreases (25% to 75%) in renal blood flow and glomerular filtration rate.

The effect of these phenomena on clinical outcome is not well known but is thought to be considerable. Studies have reported incidences of oliguric renal failure requiring dialysis as high as 5% and mortality rates as great as 89%. Previous studies [10-19] have many limitations because of a wide variability (threefold or more) in estimates of adverse renal outcomes: All of the studies were conducted at a single center, most were retrospective, and most were done more than a decade ago. No previous study provided adjusted estimates of risk factors; in addition, the definition chosen for renal dysfunction was arbitrary, or the study sample consisted only of patients requiring dialysis [11,13,15-17]. Finally, few studies have investigated resource utilization in patients with renal dysfunction or failure.

We therefore studied 2400 patients who underwent myocardial revascularization with cardiopulmonary bypass. Our goals were to determine 1) the incidence and characteristics of postoperative renal dysfunction and failure, 2) the predictors of renal dysfunction (determined by the use of multivariate modeling techniques), and 3) the effect of renal dysfunction on in-hospital resource utilization and patient disposition after discharge.

Methods^

Patients^

The Multicenter Study for Perioperative Ischemia (McSPI) Research Group studied 2417 patients undergoing myocardial revascularization between 1991 and 1993. Twenty-four diverse U.S. health care facilities-small and large academic institutions, private medical centers, health maintenance organization groups, and Veterans Affairs hospitals-participated in this study. Most patients were representative of consecutive patients seen at a given medical center. We enrolled every nth patient on the basis of a proportion of the site-specific expected annual caseload (n = 2 through 30 in 24 centers). Comprehensive data were collected from preoperative cardiac, surgical, and medical histories; invasive and noninvasive cardiologic testing; surgical procedures and techniques; perioperative hemodynamic events; postoperative in-hospital events (illness and death); and hospital resource utilization. In addition, serial

preoperative and postoperative 12-lead electrocardiograms were obtained and were centrally analyzed by a consensus panel of cardiologists. Serum creatinine values were recorded before and after surgery. Of the 2417 patients enrolled, 195 were excluded from analysis because of preexisting renal failure (n = 99) or dysfunction (serum creatinine level > 177 micromol/L [n = 81]) or lack of perioperative serum creatinine measurements (n = 68). The latter group included patients who died before a postoperative sample could be obtained.

Definitions of Renal Failure, Renal Dysfunction, and Comorbid Events^

Postoperative renal failure was defined by the need for dialysis after surgery. Renal dysfunction was defined as a postoperative serum creatinine level of 177 micromol/L or greater and an increase in serum creatinine level of 62 micromol/L or greater from preoperative to maximum postoperative values. The criteria for dysfunction were derived from the distribution of serum creatinine values in an uncomplicated patient subset. This subset excluded patients with preoperative renal disease (serum creatinine level > 124 micromol/L) or medical risk factors (age > 70 years; history of congestive heart failure or type 1 diabetes mellitus), or a complicated postsurgical course (in-hospital death; concomitant valvular surgery; intraaortic balloon pump insertion; administration of at least three nonroutine inotropic drugs; measures of hemodynamic instability; ventricular fibrillation or dysrhythmia requiring a pacemaker; complications necessitating a return to cardiopulmonary bypass, the intensive care unit, or the operating room; or chest tube output exceeding 1 L/d). Less than 1% of patients meeting these criteria had a maximum postoperative creatinine level greater than 177 micromol/L and a maximum preoperative-to-postoperative change in creatinine level of 62 micromol/L.

Comorbid events, assessed through the first postoperative day, consisted of postoperative myocardial infarction, congestive heart failure (hemodynamic or clinical), use of an intraaortic balloon pump or other mechanical circulatory assist device, administration of three or more inotropic drugs, and hemorrhage. A myocardial infarction was defined as either a Q-wave or a non-Q-wave infarction. A Q-wave myocardial infarction was diagnosed centrally by the presence of a new Q wave on each of two postoperative 12-lead electrocardiograms, as defined by Minnesota Code criteria, that were scored by a consensus panel of cardiologists. A non-Q-wave myocardial infarction was determined by an elevated creatine kinase-MB level, a new wall-motion abnormality detected by echocardiography, or a new perfusion defect on a scintigraphy scan. Low output state (an ordered, categorical variable) was defined as one of the following: 1) severe ventricular dysfunction-intraaortic balloon pump counterpulsation required, 2) moderate ventricular dysfunction-"hemodynamic" congestive heart failure or at least three nonroutine inotropic drugs prescribed after surgery, and 3) mild ventricular dysfunction-"clinical" congestive heart failure. We defined hemodynamic congestive heart failure on the basis of a cardiac index less than 1.5 L/min per m^2 body surface area for at least 30 minutes, a central venous pressure greater than 12 mm Hg, or a pulmonary artery occlusion pressure/left ventricular end diastolic pressure greater than 18 mm Hg. Clinical congestive heart failure was defined according to the presence of pulmonary rales, S3 gallop, or chest radiographic findings suggestive of heart failure. We defined hemorrhage as 1) chest tube output of at least 1 L/d, 2) return to the critical care unit or operating room within the first postoperative day because of bleeding, or 3) administration of three or more units of blood products in the operating room or critical care unit within 48 hours of surgery.

Statistical Analysis^

Distributions and univariate measures of preoperative, postoperative, and preoperative-to-postoperative changes in serum creatinine values were examined. Unadjusted relative risks and 95% CIs were calculated for all perioperative factors. Adjusted relative risk estimates were derived from multivariate logistic regression models because an 8% incidence of renal dysfunction is relatively rare. Models were analyzed in a piece-wise fashion (separate models were developed for each preoperative, operative, and postoperative period from the significant unadjusted factors in each period). A final model with adjusted estimates of relative risk was derived with factors that remained significant (P < or = to 0.05) in the three time period models. Operative and postoperative variables were entered into the model in a forward stepwise fashion after adjustment for preoperative variables. No appreciable differences were noted when all perioperative factors were allowed to enter into the model in forward or backward stepwise selection procedures.

The best-fitting models were selected from evaluation of the Hosmer-Lemeshow goodness-of-fit test statistic and the smallest values of the Akaike Information Criterion. The predictive ability of the models of preoperative risk factors alone, as well as the final model, were also evaluated with the area under the receiver-operating characteristic curve (the concordance or c-index). The c-index was also derived from a "validation" process that involved comparison of the c-index derived from a random sample of half of the patients from each site and a computed c-index derived from modeling the remaining sample's predicted probability of renal dysfunction calculated from the variable estimates from the original 50% random sample. In other words, a predicted probability was derived from variable estimates from those obtained from the 50% within-center sample; these estimates were applied to the patients' combination of risk factors in the remaining sample. The c-index was then calculated from modeling the remaining sample's predicted probabilities as a single predictor.

From the final model of preoperative risk factors, both observed and predicted probabilities were described and the sensitivity and specificity of the preoperative model were reported. The sensitivity and specificity were determined by selecting the highest sensitivity and specificity from a classification Table ofobserved and predicted events (this occurred with a probability of renal dysfunction > or = to 6%).

Theoretically, each of the 24 medical centers in the study sample may have characteristics that were not measured and could have influenced patients' outcomes. To address potential within-center correlation, ancillary analyses were conducted. Logistic regression models using generalized estimating equations with an exchangeable correlation matrix were used to account for within-center correlation. Estimates of SEs are considered corrected for potential within-center correlation; CIs are considered improved when this technique is used.

Generalized linear models were used to compare average length of stay in critical care units by renal dysfunction; the number of days was log transformed to approximate a normal distribution. Least-square means and their SEs are presented as back-transformed (exponentiated). All analyses were done by using SAS/STAT software, release 6.12 (SAS Institute, Inc., Cary, North Carolina).

Role of Funding Source^

The funding source (Ischemia Research and Education Foundation) had no role in gathering these data but did help the investigators analyze and interpret the measures. The Ischemia Research and Education Foundation had no authority to influence the content or publication of this report.

Results^

Postoperative renal dysfunction occurred in 171 (7.7%) of the 2222 patients in our study; 30 of these (18%), or 1.4% of all study patients, required dialysis. Among the 24 centers, the median +/- SE incidence of renal dysfunction was 8.5% +/- 0.8% (range, 1.0% to 13.7%). The average incidence and median incidence of renal dysfunction in a 50% within-center random sample of patients were 7.8% and 7.3% +/- 1.0% (range, 0% to 18%), respectively. The similar descriptive statistics for the remaining patients were 7.5% and 6.3% +/- 1.0% (range, 0% to 17.3%). This average incidence among the within-center random sample of patients was similar to the overall incidence of 7.7%. The mortality rate was 19% (27 of 141 patients) among patients with renal dysfunction who did not require dialysis, 63% (19 of 30 patients) among those who required dialysis, and 0.9% (20 of 2051 patients) among patients without renal dysfunction or failure.

Preoperative Risk Factors for Renal Dysfunction^

The characteristics of patients with and those without postoperative renal dysfunction are listed in Table 1 and Table 2. The proportion of patients developing renal dysfunction increased with advancing age: 10% of patients in their 60s, 15% of those in their 70s, and nearly 25% of those older than 80 years of age (Table 1). Almost half of the patients had a history of unstable angina, but their risk for renal dysfunction was not increased. A history of type 1 diabetes mellitus, a preoperative glucose level greater than 16.6 mmol/L, congestive heart failure (defined by New York Heart Association class III or IV criteria), previous coronary artery bypass graft surgery, and preoperative creatinine levels between 124 and 177 micromol/L were associated with an approximate twofold increased risk for post-operative renal dysfunction. The risk among patients with moderate or severe congestive heart failure was nearly threefold higher. Estimates of the risks associated with age, congestive heart failure, previous myocardial revascularization, type 1 diabetes mellitus, and elevated serum creatinine and glucose levels remained significant when adjusted for each other. The model containing the seven preoperative risk factors (Table 3) had a goodness-of-fit P value of 0.045 and a c-index of 0.75. Given a probability of postoperative renal dysfunction of at least 6%, the sensitivity and specificity of the model with the seven preoperative risk factors were 77.2% and 70.6%, respectively.

Table 1. Preoperative Characteristics of the Study Patients*

Table 2. Intraoperative and Postoperative Characteristics of the Study Patients

Table 3. Final Model of Risk Factors for Postoperative Renal Dysfunction in 2222 Patients Undergoing Coronary Artery Bypass Graft Surgery

(Table 4) lists the predicted probability of renal dysfunction for each preoperative risk factor combination. Although there is uncertainty around some of the point estimates (indicated by relatively wide CIs and the observed-to-predicted differences for some combinations), several patterns emerge that emulate the estimates from the multivariate model. Compared with younger patients, the risk for renal dysfunction is approximately tripled for patients at least 80 years of age and doubled for patients between 70 and 80 years of age. In each age group, the risks generally doubled with one risk factor and tripled with two risk factors. A preoperative creatinine level of at least 124 micromol/L doubled the predicted risk for postoperative renal dysfunction. The predicted relative risk with one, two, or three risk factors (any combination of congestive heart failure, previous coronary artery bypass graft, type 1 diabetes mellitus, and creatinine level > 124 micromol/L) would be doubled for patients 70 to 79 years of age and tripled for patients at least 80 years of age.

Table 4. Preoperative Risk Factors and Predicted Probabilities of Renal Dysfunction*

Although a low ejection fraction (< or = to 0.30) was not a statistically significant factor after simultaneous adjustment for other preoperative factors, small subsets of patients with low ejection fractions and type 1 diabetes mellitus, moderately elevated creatinine levels, or angiography within 1 day of surgery had higher risks for postoperative renal dysfunction. Patients with low ejection fractions and type 1 diabetes mellitus, creatinine levels greater than 124 micromol/L, or recent angiography had a risk of 24% (4 of 17 patients), 36% (9 of 25 patients), and 23% (3 of 13 patients), respectively. For patients who underwent angiography within 24 hours of surgery and had type 1 diabetes mellitus or those who had preoperative renal dysfunction (creatinine level > 124 micromol/L), the risk for postoperative dysfunction was 16.7% (3 of 10 patients) compared with 9.6% (17 of 178 patients) in those without diabetes; the risk was 27.3% (6 of 22 patients) compared with 8.1% (14 of 174 patients) in those with normal renal function. These observations regarding high-risk patient subsets should be interpreted with caution given the small numbers and the proportion of patients for whom information on ejection fraction was missing.

Intraoperative Risk Factors for Renal Dysfunction^

A small proportion of patients (6.1%) underwent cardiopulmonary bypass without the use of an arterial filter to minimize emboli; compared with patients who underwent bypass with arterial filters, the unadjusted relative risk for renal dysfunction was increased (relative risk, 1.8 [95% CI, 1.1 to 3.1]) (Table 2). Risks for renal dysfunction were elevated among patients with aortic cross-clamp and total cardiopulmonary bypass lasting at least 2 hours (unadjusted relative risks, 2.5 and 2.3, respectively). Cardiopulmonary bypass lasting 3 hours or longer was associated with a nearly fourfold elevated risk

(unadjusted relative risk, 3.7 [CI, 2.8 to 4.9]) compared with cardiopulmonary bypass lasting less than 2 hours.

Patients undergoing concomitant procedures (such as valve replacement or carotid surgery) also had a twofold increased risk. However, the risk for postoperative renal dysfunction was significantly greater among those with longer cardiopulmonary bypass durations with or without concomitant intracardiac procedures. Hemodynamic instability during cardiopulmonary bypass was associated with a moderately elevated risk, although the statistical power to detect an effect from hemodynamic instability was low because of the small number of patients (n = 30). Hemodynamic instability during the period immediately after bypass surgery (intraaortic balloon pump insertion, a return to cardiopulmonary bypass, or use of several inotropic drugs), which occurred in 340 of these patients (20%), was associated with an approximately fourfold increased risk.

Postoperative Risk Factors for Renal Dysfunction^

In the postoperative period, markers of a low output syndrome were associated with the development of renal dysfunction. Table 2 lists the unadjusted relative risks for renal dysfunction for the following postoperative factors: the ordered, categorical variable of a low output state; Q-wave and non-Q-wave myocardial infarction; and hemorrhage. Patients requiring an intraaortic balloon pump (indicative of a severe low output state) had a nearly sevenfold higher risk for postoperative renal dysfunction. Patients identified as having a moderately severe compromise in ventricular function had an approximate fourfold increase in risk. Renal dysfunction occurred in 20% of 66 patients with a reduced cardiac index (<1.5 L/min per m^2) on the day of surgery and in 61% of the 18 patients with a reduced cardiac index on the day of surgery and on postoperative day 1. In patients with clinically defined congestive heart failure (mild ventricular dysfunction), risk for postoperative renal dysfunction was increased fivefold. Postoperative renal dysfunction developed in only 32 of 171 (19%) patients without identifiable postoperative hemodynamic instability or hemorrhage. All but 4 of these 32 patients had at least one of the previously described preoperative risk factors. Although the use of at least three inotropic drugs was associated with an increased risk for postoperative renal dysfunction, the use of fewer drugs was not. The administration of "renal-dose" dopamine did not decrease the likelihood of postoperative renal dysfunction.

Multivariate Model of Predictors of Renal Dysfunction^

We selected a final model that retained all of the preoperative factors and that evaluated adjusted risks and model fits associated with the addition of intraoperative and postoperative factors. With the simultaneous adjustment for all of the factors in the model, intraaortic balloon pump insertion (severe ventricular dysfunction) and clinical congestive heart failure (mild ventricular dysfunction) were associated with the highest risk (increased more than fourfold) for renal dysfunction. Factors associated with a greater than threefold increased risk were age 80 years or older, a preoperative serum glucose level of at least 16.6 mmol/L, and moderate ventricular dysfunction. Moderately elevated preoperative serum creatinine levels (>124 and <177 micromol/L) and long cardiopulmonary bypass duration were associated with a greater than twofold increased risk. In this predictive model, patients 70 to 80 years of age and those who had previously had coronary artery bypass graft surgery or had a history of type 1

diabetes mellitus had a 50% higher risk for postoperative renal dysfunction. No appreciable differences resulted from within-center correlations, as reflected by the similar CIs derived from the logistic regression models that ignored and accounted for clustered within-center sampling (generalized estimating equations models).

Length of Stay in Critical Care Units^

The average length of stay in critical care units was evaluated for patients who had postoperative renal dysfunction, those who had renal dysfunction but did not require dialysis, and those who had renal failure and thus required dialysis (Table 5). The mean length of stay in critical care units was approximately twice as long for patients with renal dysfunction as for patients without. For patients requiring dialysis, the stay in critical care units was twice as long as the stay for patients with renal dysfunction and was more than five times as long as the stay for patients without renal dysfunction. These patterns persisted even when center-specific utilization and in-hospital mortality rates were considered.

Table 5. Mean Length of Stay in Critical Care Unit and Hospital Ward among Patients without Renal Dysfunction, Those with Renal Dysfunction but without Renal Failure, and Those with Renal Failure

Prognosis^

Of the 171 patients with renal dysfunction, 30 (17.5% of those with renal dysfunction and 1.4% of the study sample) required dialysis: Eight required temporary dialysis, 3 were discharged with a continued need for dialysis, and 19 died. The total number of days on which dialysis was performed ranged from 1 to 90. The in-hospital mortality rate among all patients with renal dysfunction was 27% (46 deaths); this represented 70% of all deaths from any cause in the entire study sample. In contrast, only 0.9% of patients without postoperative renal dysfunction died. Among patients who survived hospitalization, those with renal dysfunction were less likely to be discharged to their home. Discharges to extended-care, acute-care, skilled-nursing, or rehabilitation facilities were two to five times more frequent for patients with renal failure (44% [7 of 16 patients]; relative risk, 7.3 [CI, 2.7 to 19.3]) and for patients with renal dysfunction who did not require dialysis (22% [33 of 151 patients]; relative risk, 25 [CI, 1.7 to 3.6]) compared with patients without renal dysfunction (9% [200 of 2160 patients]).

Discussion^

Our study shows that renal dysfunction and failure are important adverse events after cardiac surgery and are associated with increased morbidity, mortality, and in-hospital resource utilization. Using data from 24 U.S. medical centers, we found that renal dysfunction or failure occurred in nearly 8% of all patients undergoing myocardial revascularization and that this proportion seemed to be fairly constant across centers. Patient-specific rather than center-specific factors accounted for increased risks. Compared with patients who do not have postoperative renal dysfunction, patients with renal dysfunction (who do not need dialysis) remain twice as long in both the intensive care unit and hospital wards and have significantly higher mortality rates (1% compared with 19%). Furthermore,

approximately 1 in 6 patients with renal dysfunction will need dialysis; 2 of 3 of these patients will not survive their hospitalization. Finally, patients with dysfunction are three times as likely to require continued, costly extended care after hospital discharge.

The reported incidence of renal dysfunction after cardiac surgery is significantly influenced by the definition used in a given study, the number and type of centers, and the size of the study sample. A limitation common to all previous studies was that each was conducted at a single center; as a result, the findings reflected individual practice patterns and the generalizability of the findings is limited. Furthermore, most previous studies used an absolute creatinine value alone, and the others used widely differing relative-change criteria; this yielded incidences of dysfunction ranging from 3% to 29% [10-19]. We sought to overcome these limitations by studying a large number of patients-more than 2200-from 24 diverse medical centers. We also defined postoperative renal dysfunction on the basis of an absolute creatinine value (> or = to 177 micromol/L) coupled with a relative change in creatinine level (> or = to 62 micromol/L) between the preoperative and the postoperative period.

Most patients at increased risk for postoperative renal dysfunction can be identified before their surgical procedures-that is, patients with advanced age, a history of modcrate to severe congestive heart failure, a previous coronary artery bypass graft, type 1 diabetes mellitus, preoperative hyperglycemia, or preexisting renal disease (as manifested by an elevated serum creatinine level) have an increased risk for postoperative renal dysfunction. This risk approximately doubles with one preoperative risk factor and quadruples with two risk factors. These findings allow identification of high-risk patients and estimation of risk for renal dysfunction, thus enabling informed patient-clinician decisions regarding surgery. Independent perioperative factors-prolonged cardiopulmonary bypass duration and ventricular dysfunction developing after bypass surgery-may be modified in the high-risk subgroup. Finally, these findings also mandate allocation of resources that may be redirected to mitigate this problem.

Although pathophysiologic changes occur during coronary revascularization, most patients can withstand the renal ischemic insult associated with cardiopulmonary bypass. Advanced age was an important prognostic factor for the development of postoperative renal dysfunction: Patients 70 years of age had a twofold increased risk, and patients at least 80 years of age had an almost fourfold increase in risk. Impaired renal autoregulation and perioperative hemodynamic instability are more likely in older patients and increase the risk for postoperative renal dysfunction. Our results also show that in patients with preexisting, moderately impaired renal function (possibly reflecting volume depletion or poor renal perfusion) and type 1 diabetes mellitus, risk for postoperative dysfunction was increased almost twofold. These findings are consistent with those of smaller, single-center studies [10,14,15,17,18,20].

We found that preoperative patient characteristics, which probably reflect diffuse atherosclerosis, were the most important prognostic factors for the development of postoperative renal dysfunction. Markers of preoperative congestive heart failure and intraoperative and postoperative factors suggestive of compromised renal perfusion were associated with an increased risk for postoperative renal dysfunction in our patients. The association between surrogate markers of compromised renal perfusion and adverse renal outcomes has been noted by several investigators in the past two decades [12,14,15,18,19]. The

importance of a low output state for postoperative renal dysfunction is emphasized by our finding that more than 80% of patients with renal dysfunction had experienced intraoperative or postoperative hemodynamic instability or hemorrhage. Substantive changes in perfusion also occur immediately after surgery and probably exacerbate the renal ischemic insult occurring during extracorporeal circulation [21,22]. Our data support this hypothesis: Renal dysfunction developed in only 20% of our patients with inadequate cardiac output limited to the period immediately after surgery compared with 61% of all patients who had reduced cardiac output through postoperative day 1. Similarly, Hilberman and colleagues [22] found that acute renal failure developing after renal dysfunction may be averted by hemodynamic recovery in the first week after cardiac surgery.

As with the findings of any multicenter study, our findings may not be generalizable to all medical centers. However, we believe that our data emphasize that patient-specific rather than center-specific factors are the predominant determinant of postoperative renal dysfunction. Our analyses are also limited with respect to exploring other potential causes of renal dysfunction-specifically, injury caused by nephrotoxic agents or dyes-and exploring the temporal relation between renal dysfunction and other relevant comorbid events. In addition, although serum creatinine values are easily and inexpensively obtained and increased values correlate well with diminished creatinine clearance, more sensitive early markers of glomerular filtration and renal tubular function are available [8,23,24]. There is no "gold standard" definition of perioperative renal dysfunction not requiring dialysis; thus, we derived a definition using an internal "reference" subset of patients who experienced no perioperative morbidity or mortality. Finally, our data are limited to the postoperative hospitalization stay; the effect of inhospital renal dysfunction on long-term outcomes remains unknown.

What is the impact of these results on clinical practice? First, identification of a high-risk subset allows more comprehensive informed consent by way of communication of this risk to the patient. Second, therapy with potentially nephrotoxic medications (such as aminoglycoside antibiotics, nonsteroidal anti-inflammatory drugs, or angiotensin-converting enzyme inhibitors) before, during, and after surgery in patients with one or more risk factors should be discontinued or replaced. Third, because prolonged cross-clamp time is an independent risk factor, the surgeon should consider modification of surgical techniques by choosing to perform fewer anastomoses or instituting more substantive hypothermic regimens. It is also critical for the anesthesiologist and intensivists to optimize ventricular function aggressively control serum glucose levels, and closely monitor fluid and renal status. Finally, given that an increasing number of elderly patients desire more complex cardiac surgery, clinicians will be continually challenged in these efforts to mitigate perioperative renal injury. It is therefore necessary that new pharmacologic approaches be developed to prevent or treat such costly injury.

On the basis of 600 000 coronary artery bypass graft procedures performed annually throughout the world, and assuming a 7.7% incidence, we estimate that approximately 46 000 patients will develop postoperative renal dysfunction and that 8000 of these patients will require dialysis. According to the length-of-stay results of our study, the effect of such perioperative renal dysfunction and failure will be to increase total intensive care unit stay by more than 200 000 days and total hospital stay by almost 400 000 days. This would result in additional inhospital health care costs, which probably exceed hundreds

of millions of dollars annually. In addition, of the 46 000 patients developing dysfunction, 12 000 will die in the hospital; of the 34 000 patients surviving their hospitalization, approximately 9000 will be discharged to an extended-care facility, further increasing health care costs.

We have determined the incidence, characteristics, and associated resource utilization of renal dysfunction and failure after coronary artery bypass graft surgery. On the basis of these findings, it is clear that postoperative renal dysfunction is relatively common (occurring in 7.7% of our patients) and serious. We have identified the high-risk subset of patients likely to develop perioperative renal dysfunction, thereby allowing modification of the reversible factors, communication of such risk to the patient, and efficient and focused perioperative care in this high-risk group. Further investigation is needed to better define the mechanisms, risk factors, magnitude, and kinetics of postoperative renal dysfunction and to develop clinical and therapeutic strategies to reduce morbidity and mortality.

Appendix: The Multicenter Study of Perioperative Ischemia Research Group^

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REFERENCES^

1. Jones EL, Weintraub WS, Craver JM, Guyton RA, Cohen CL. Coronary bypass surgery: is the operation different today? J Thorac Cardiovasc Surg. 1991;101:108-15. Bibliographic Links [Context Link]

2. Mangano DT. Perioperative cardiac morbidity. Anesthesiology. 1990;72:153-84. Bibliographic Links [Context Link]

3. Shaw PJ, Bates D, Cartilidge NE, French JM, Heaviside D, Julian DG, et al. Neurologic and

neuropsychological morbidity following major surgery: comparison of coronary artery bypass and peripheral vascular surgery. Stroke. 1987;18:700-7. Bibliographic Links [Context Link]

4. Donohoe JF, Venkatachalam MA, Bernard DB, Levinsky NG. Tubular leakage and obstruction after renal ischemia: structural-functional correlations. Kidney Int. 1978;13:208-22. Bibliographic Links [Context Link]

5. Lowe MB. Effects of nephrotoxins on ischemia in experimental haemoglobinuria. J Pathol Bacteriol. 1966;92:319-23. Bibliographic Links [Context Link]

6. Ramsay JG. The respiratory, renal, and hepatic systems: effects of cardiac surgery and cardiopulmonary bypass. In: Mora CT, ed. Cardiopulmonary Bypass. New York: Springer-Verlag; 1995:147-68. [Context Link]

7. Mori A, Watanabe K, Onoe M. Regional blood flow in the liver, pancreas and kidney during cardiopulmonary bypass. Arch Surg. 1988; 124:458-9. [Context Link]

8. Mazzarella V, Gallucci MT, Tozzo C, Elli M, Chiavarelli R, Marino B, et al. Renal function in patients undergoing cardiopulmonary bypass operations. J Thorac Cardiovasc Surg. 1992;104:1625-7. Bibliographic Links [Context Link]

9. Reves JG, Karp RB, Buttner EE, Tosone S, Smith LR, Samuelson PN, et al. Neuronal and adrenomedullary catecholamine release in response to cardiopulmonary bypass in man. Circulation. 1982;66:49-55. Bibliographic Links [Context Link]

10. Yeboah ED, Petrie A, Peak JL. Acute renal failure and open heart surgery. Br Med J. 1972;1:415-8. Bibliographic Links [Context Link]

11. McLeish KR, Luft FC, Kleit SA. Factors affecting prognosis in acute renal failure following cardiac operations. Surg Gynecol Obstet. 1977;145:28-32. Bibliographic Links [Context Link]

12. Bhat JG, Gluck MC, Lowenstein J, Baldwin DS. Renal failure after open heart surgery. Ann Intern Med. 1976;84:677-82. Bibliographic Links [Context Link]

13. Gailiunas P Jr, Chawla R, Lazarus JM, Cohn L, Sanders J, Merrill JP. Acute renal failure following cardiac operations. J Thorac Cardiovasc Surg. 1980;79:241-3. Bibliographic Links [Context Link]

14. Abel RM, Buckley MJ, Austen WG, Barnett GO, Beck CH Jr, Fischer JE. Etiology, incidence, and prognosis of renal failure following cardiac operations. Results of a prospective analysis of 500 consecutive patients. J Thorac Cardiovasc Surg. 1976;71:323-33. [Context Link]

15. Hilberman M, Myers BD, Carrie BJ, Derby G, Jamison RL, Stinson E. Acute renal failure following cardiac surgery. J Thorac Cardiovasc Surg. 1979;77:880-8. Bibliographic Links [Context Link]

16. Lange HW, Aeppli DM, Brown DC. Survival of patients with acute renal failure requiring dialysis after open heart surgery: early prognostic indicators. Am Heart J. 1987;113:1138-43. Bibliographic Links [Context Link]

17. Corwin HL, Sprague SM, DeLaria GA, Norusis MJ. Acute renal failure associated with cardiac operations. A case-control study. Thorac Cardiovasc Surg. 1989;98:1107-12. [Context Link]

18. Slogoff S, Reul GJ, Keats AS, Curry GR, Crum ME, Elmquist BA, et al. Role of perfusion pressure and flow in major organ dysfunction after cardiopulmonary bypass. Ann Thorac Surg. 1990;50:911-8. Bibliographic Links [Context Link]

19. Zanardo G, Michielon P, Paccagnella A, Rosi P, Calo M, Salandin V, et al. Acute renal failure in the patient undergoing cardiac operation. Prevalence, mortality rate, and main risk factors. J Thorac Cardiovasc Surg. 1994;107:1489-95. Bibliographic Links [Context Link]

20. Koning HM, Koning AJ, Defauw JJ. Optimal perfusion during extra-corporeal circulation. Scand J Thorac Cardiovasc Surg. 1987;21:207-13. Bibliographic Links [Context Link]

21. Myers BD, Moran SM. Hemodynamically mediated acute renal failure. N Engl J Med. 1986;314:97-105. Bibliographic Links [Context Link]

22. Hilberman M, Derby GC, Spencer RJ, Stinson EB. Sequential pathophysiological changes characterizing the progression from renal dysfunction to acute renal failure following cardiac operation. J Thorac Cardiovasc Surg. 1980;79:838-44. Bibliographic Links [Context Link]

23. Price RG. Measurement of N-acetyl-beta-glucosaminidase and its isoenzymes in urine: methods and clinical applications. Eur J Clin Chem Clin Biochem. 1992;30:693-705. Bibliographic Links [Context Link]

24. Ip-Yam PC, Murphy S, Baines M, Fox MA, Desmond MJ, Innes PA. Renal function and proteinuria after cardiopulmonary bypass: the effects of temperature and mannitol. Anesth Analg. 1994;78:842-7. Bibliographic Links [Context Link]

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