Relationship of the Time Interval Between Cardiac Catheterization and Elective Coronary Artery Bypass Surgery With Postprocedural Acute Kidney Injury

Rajendra H. Mehta, MD, MS; Emily Honeycutt, MBI; Uptal D. Patel, MD; Renato D. Lopes, MD, PhD; Judson B. Williams, MD; Linda K. Shaw, MS; Sean M. O’Brien, PhD; Robert M. Califf, MD; G. Chad Hughes, MD; Michael H. Sketch, Jr, MD

Background—Some prior studies have suggested that the time to cardiac surgery after cardiac catheterization is inversely related to postoperative acute kidney injury (AKI). However, these studies, because of the small number of patients, were unable to adequately account for patient case-mix and included both those undergoing elective surgery and those undergoing urgent surgery.

Methods and Results—We examined data on 2441 consecutive patients undergoing elective coronary artery bypass surgery (CABG) after cardiac catheterization. The association of post-CABG AKI (defined as increase in post-CABG serum creatinine ≥50% above baseline or the need for new dialysis) and time between cardiac catheterization and CABG was evaluated using multivariable logistic regression modeling. AKI occurred in 17.1% of CABG patients. The risk of AKI was highest in patients in whom CABG was performed ≤1 day after cardiac catheterization (adjusted mean rates [95% CI]: 24.0% [18.0%, 30.9%], 18.4% [14.8%, 22.5%], 17.3% [13.3%, 21.9%], 16.4% [12.6%, 20.8%], and 15.8% [13.7%, 18.0%] for days =1, 2, 3, 4, and ≥5, respectively; P=0.019 for test of trend). Post-CABG AKI was associated with increased risk of long-term death (hazard ratio 1.268, 95% CI 1.093, 1.471).

Conclusions—The risk of post-CABG AKI was inversely and modestly related to the time between cardiac catheterization and CABG, with the highest incidence in those operated ≤1 day after cardiac catheterization despite their lower risk profile. Whether delaying elective CABG >24 hours of exposure to contrast agents (when feasible) has the potential for decreasing post-CABG AKI remains to be evaluated in future studies. (Circulation. 2011;124[suppl 1]:S149–S155.)

Key Words: coronary artery bypass • acute kidney injury • outcome assessment (health care) • renal insufficiency • risk factors

A cute kidney injury (AKI) after coronary artery bypass graft surgery (CABG) remains an important adverse event and has been shown to be associated with higher short-term morbidity and mortality and greater resource utilization.1–6 Many studies have evaluated the risk factors for AKI and the need for dialysis after cardiac surgery and have allowed identification of those at risk for this adverse event after this procedure.1,2,5,7 Cardiac surgery ≤1 day after cardiac catheterization has been shown to be associated with increased risk of postprocedural AKI by some studies8–11 but not by others.12 However, these studies, because of the small number of patients, were unable to adequately account for patient case-mix and included those undergoing elective as well as urgent CABG. Additionally, none of these studies provided any insights into whether outcomes of patients with AKI varied in relation to this time interval.

Accordingly, the goal of this investigation was to investigate the association of the incidence of post-CABG AKI with the time interval between diagnostic angiography and subsequent CABG. We hypothesized that shorter time interval between diagnostic angiography and cardiac surgery is associated with increased incidence of AKI following CABG and that the strength of the association between post-CABG AKI and short- and long-term mortality varies according to the time intervals between cardiac catheterization and CABG.

Methods

Patient Population

Using the Duke Cardiovascular Disease Databank,13–15 we identified patients who underwent elective CABG at Duke University Medical Center between January 1, 1995, and June 30, 2008. We excluded patients with prior dialysis; those undergoing urgent, emergent, or salvage CABG; those undergoing other cardiac surgery besides CABG; those in whom the time interval between cardiac catheterization and CABG was >30 days (as contrast use during preceding cardiac catheterization was unlikely to have a deleterious effect on the kidneys at this point); and those who were referred to Duke for...
CABG but had cardiac catheterization at other institutions. A total of 2441 patients met the study criteria and formed the basis of this analysis.

Cardiac catheterization and CABG were performed in the standard manner, and the day of elective surgery was decided by cardiac surgeons. Routine precardiac catheterization protocol at our institution includes the use of intravenous normal saline, avoidance of nephrotoxic drugs, limiting of volume of contrast used and the nonionic contrast, and use of N-acetylcysteine for patients with serum creatinine ≥1.5 mg/dL.

Definitions and Follow-Up
Acute renal failure was defined as an increase in post-CABG peak creatinine ≥50% above baseline or the need for new dialysis. Hypertension, diabetes mellitus, dyslipidemia, peripheral vascular disease, and presenting heart failure were ascertained from a report of present or absent on the data collection form. After their index CABG, patients were followed at 6 months, 1 year, and annually thereafter for mortality status and other adverse events by telephone contact, mailed questionnaire, and National Death Index search. Mortality (defined as all-cause death) was ascertained from the time of index hospitalization. Information from clinic visits and rehospitalizations was also evaluated to ascertain follow-up and end point determination. The methods used by the Cardiovascular Databank have been described previously. Considering all time intervals and all patients, follow-up was 98.4% complete.

Statistical Analyses
A total of 2441 patients formed the basis of this study. We stratified these patients on the basis of their time interval between cardiac catheterization and CABG into those with ≤1 day, 2 days, 3 days, 4 days, and ≥5 days between the 2 procedures. Summary statistics are presented as frequencies and percentages or as median values (with 25th and 75th percentiles). Comparisons between the patients having AKI when operated on ≤1 day after versus >1 day after cardiac catheterization were made using the chi-square test for categorical variables and the Wilcoxon 2-sample test for continuous variables. Unadjusted rates of AKI were compared across time interval categories using the Mantel chi-square trend test. The multivariable association between time interval from catheterization to CABG and risk of AKI was assessed using a nonparsimonious logistic regression model with adjustment for the following characteristics: age, sex, race, body mass index, diabetes, hypertension, chronic lung disease, cerebrovascular disease, peripheral vascular disease, history of congestive heart failure, history of CABG, history of percutaneous coronary intervention, history of myocardial infarction, cardiogenic shock, number of diseased vessels, left main disease, left ventricular ejection fraction, total contrast volume, nonionic contrast use, internal mammary artery use, year of surgery, cross-clamp time, pre-CABG serum creatinine, and hemoglobin. These model covariates were selected on the basis of clinical judgment and the literature and were retained in the model regardless of statistical significance. Continuous variables were modeled as restricted cubic splines with 4 data-driven knot locations to account for possible nonlinear regression relationships.

Days from catheterization to CABG was modeled both as an ordinal variable (linear across the categories) and as a set of category (0/1) indicator variables using 0 to 1 day as the reference group. In addition to reporting odds ratios with 95% confidence intervals, risk-adjusted AKI rates were calculated by the method of indirect standardization and displayed for each of the 5 time interval categories. For each category, the risk-adjusted AKI rate was calculated by dividing the category-specific observed AKI rate by the category-specific average predicted probability of AKI and then multiplying this ratio by the overall aggregate AKI rate in the study sample. Predicted probabilities for the adjusted AKI rate calculation were based on a separate logistic regression model that included all of the covariates listed above with the exception of days from catheterization to CABG. Confidence intervals for the adjusted AKI rate were calculated on the basis of the binomial distribution by treating the average predicted rate in each category as constant. As a subsequent sensitivity analysis, we reestimated the multivariable model after including after including 2 interaction terms (age×prior CABG and age×baseline creatinine), which were identified from previous risk models.

Finally, the association between occurrence of perioperative AKI and long-term all-cause mortality was assessed using Cox proportional hazards model with adjustment for the following covariates: age, ejection fraction, chronic lung disease, diabetes, history of congestive heart failure, peripheral vascular disease, cerebrovascular disease, body mass index, dyslipidemia, left main disease, use of internal mammary artery graft, preprocedure creatinine level, and time interval between cardiac catheterization and CABG. This model was then reestimated after including the interaction of the time interval from cardiac catheterization to CABG×AKI to assess whether the association of postoperative AKI was constant across the time intervals of interest. Probability values of <0.05 were considered significant. The software SAS version 8.2 (SAS Institute, Cary, NC) was used for all analyses.

Results
Patients and Baseline Clinical and Angiographic Characteristics
Of the 2441 patients undergoing CABG who were eligible for this study, AKI occurred in 417 subjects (17.1%). Median follow-up for the entire group was 9.2 years (interquartile range 5.3 to 11.9 years). Table 1 shows the distributions of baseline clinical and angiographic features of patients with post-CABG AKI stratified by the time interval between cardiac catheterization and CABG. Compared with patients who had CABG performed after >1 day, those having CABG performed after ≤1 day were younger, were more frequently male, and had fewer comorbidities (including diabetes mellitus, peripheral vascular disease, prior CABG, chronic obstructive airway disease, and presenting heart failure). The volume of contrast used was similar, whereas the use of nonionic contrast was lower in the early CABG cohort. Baseline serum creatinine was lower and hemoglobin was higher in the early CABG group compared with those who had CABG >1 day after cardiac catheterization. Angiographic features (such as the presence of coronary artery disease of 2 or more vessels and left ventricular ejection fraction) and surgical features (such as the number of bypass graft uses, on-pump surgery, and circulatory and cross-clamp time) were similar in the different categories, whereas the use of internal mammary artery conduit was higher in the early CABG group.

Relationship of the Time Interval Between Cardiac Catheterization and CABG With Post-CABG AKI
The observed rate of AKI was highest when CABG was performed early (unadjusted probability value for trend=0.38). Multivariable logistic regression analyses suggested that the risk of post-CABG AKI was inversely (albeit modestly) associated with the interval between cardiac catheterization and CABG (adjusted odds ratio [OR] per each time interval 0.90, 95% CI 0.83, 0.98, P=0.019). The inverse association of time interval between cardiac catheterization and post-CABG AKI persisted even after adding interaction terms for age×prior CABG and age×baseline serum creatinine (OR 0.91, 95% CI 0.83, 0.99, P=0.0253). Figure shows the observed and adjusted rates (95% CI), whereas Table 2 demonstrates unadjusted and adjusted odds ratios (95% CI) of AKI for patients with different time intervals between cardiac catheterization and CABG.
catheterization and CABG. The highest adjusted mean rate (adjusted OR) of post-CABG AKI occurred when the interval was \(1\) day.

In-hospital events and long-term mortality (median follow-up 9.2 years; interquartile range 5.3 to 11.9 years) are shown in Tables 2 and 3. Post-CABG AKI was associated with an increased risk of long-term mortality compared with patients without any AKI (hazard ratio 1.27, 95% CI 1.09, 1.47; \(P=0.0017\)). In contrast, for the overall study population, the time interval between cardiac catheterization and CABG was not significantly associated with an increased risk of long-term mortality (hazard ratio 0.99, 95% CI 0.94, 1.04, \(P=0.70\)). For other in-hospital adverse events, there was no apparent increasing or decreasing relationship with the time interval between cardiac catheterization and CABG (Table 3).

**Discussion**

**Our Study Findings**

This investigation demonstrates that among patients undergoing elective CABG, the risk of postprocedural AKI was inversely and modestly associated with time between cardiac catheterization and subsequent CABG. After we adjusted for numerous covariates, including volume and type of contrast, the risk was highest among patients undergoing CABG \(\leq 1\) day after cardiac catheterization and declined over 5 days. Furthermore, our data suggested that although post-CABG
AKI was independently associated with higher long-term mortality, the time interval between cardiac catheterization and subsequent CABG was not associated with long-term death.

Comparison With Prior Studies
Some prior studies have focused on evaluating the influence of the time interval between cardiac catheterization and CABG (Table 4). Brown et al\(^\text{12}\) examined the safety of performing elective valve surgery on the day of cardiac catheterization, limited to pressure measurements and only coronary angiography (no left ventriculogram or aortogram). They showed that postprocedural AKI occurs in a small minority (1.8%), with only 2 patients (0.9%) needing renal replacement therapy. They surmised that valve surgery on the same day as cardiac catheterization in selected patients is safe and is associated with no significant influence on renal function. Del Duca et al\(^\text{8}\) studied patients undergoing elective or urgent cardiac surgery and showed that CABG performed \(\leq 5\) days of cardiac catheterization is associated with increased risk of AKI compared with those operated later (OR 1.82, 95% CI 1.17, 2.84). Patients operated on \(\leq 1\) day after cardiac catheterization had the highest risk (OR 1.70, 95% CI 0.91, 3.20 [reference, patients operated on \(>5\) days after cardiac catheterization]). Ranucci et al\(^\text{9}\) and Medalion et al\(^\text{10}\) demonstrated similar heightened risk when cardiac surgery was performed after \(\leq 1\) day compared with those operated on after 1 day (OR 3.1, 95% CI 1.1, 8.8, and OR 3.7, 95% CI 1.4, 8.3, respectively). Finally, Henessey et al\(^\text{11}\) replicated similar results among patients undergoing valve surgery, show-

### Table 2. Unadjusted and Adjusted Odds Ratios and 95% CIs for AKI in Patients Undergoing Elective CABG and Adjusted HRs and 95% CIs for Long-Term Mortality in Patients With AKI

<table>
<thead>
<tr>
<th>Days from Cardiac Catheterization to CABG</th>
<th>0 to 1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>(\geq 5)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Unadjusted post-CABG AKI odds ratios (95% CI)</strong> (reference, (\geq 5) days)</td>
<td>1.34 (0.93, 1.93)</td>
<td>1.00 (0.75, 1.34)</td>
<td>0.87 (0.63, 1.20)</td>
<td>0.86 (0.62, 1.20)</td>
<td>1.00</td>
</tr>
<tr>
<td><strong>Adjusted post-CABG AKI odds ratios (95% CI)</strong> (reference, (\geq 5) days)</td>
<td>1.74 (1.13, 2.68)</td>
<td>1.26 (0.91, 1.74)</td>
<td>1.11 (0.77, 1.59)</td>
<td>1.15 (0.80, 1.63)</td>
<td>1.00</td>
</tr>
<tr>
<td><strong>Adjusted post-CABG mortality in patients with AKI (reference, no AKI) HR (95% CI)</strong></td>
<td>1.27 (1.09, 1.47)</td>
<td>1.37 (0.92, 2.04)</td>
<td>1.11 (0.80, 1.53)</td>
<td>1.13 (0.75, 1.69)</td>
<td>1.56 (1.10, 2.20)</td>
</tr>
</tbody>
</table>

AKI indicates acute kidney injury; CABG, coronary artery bypass graft surgery; HR, hazard ratio.
ing high risk of AKI when the operation was performed ≤1 day after cardiac catheterization.

Our study results are consistent with those of the above studies and suggest a similar association between post-CABG AKI and early cardiac surgery after cardiac catheterization (particularly ≤1 day). However, unlike most of the above studies, which included relatively smaller numbers of patients undergoing elective or urgent cardiac surgery, we studied a relatively larger cohort undergoing only elective CABG. Patients undergoing urgent operations are more likely to be sicker, with hemodynamic instability and more comorbid conditions that generally mandate immediate operations, biasing those operated on earlier to demonstrate higher incidence of AKI. Additionally, we demonstrated that there was a declining trend up to 5 days rather than just an increased risk ≤1 day after cardiac catheterization.

| Table 3. In-Hospital Outcomes and 30-Day Mortality |
|----------------------------------|------------------|------------------|------------------|------------------|------------------|------------------|
| Event                           | Overall          | Days 0 to 1      | Day 2            | Day 3            | Day 4            | Day ≥5           |
| No. of patients                 | 2441 (100%)      | 206 (8.4%)       | 450 (18.4%)      | 372 (15.2%)      | 366 (15.0)       | 1047 (43.0%)     |
| 30-d death                      | 62 (2.54%)       | 4 (1.94%)        | 11 (2.44%)       | 10 (2.69%)       | 5 (1.37%)        | 32 (3.06%)       |
| Permanent stroke                | 36 (1.47%)       | 5 (2.43%)        | 1 (0.22%)        | 7 (1.88%)        | 5 (1.37%)        | 18 (1.72%)       |
| Perioperative MI                 | 3 (0.12%)        | 1 (0.49%)        | 1 (0.22%)        | 1 (0.27%)        | 0               | 0               |
| Prolonged ventilation           | 142 (5.82%)      | 12 (5.83%)       | 29 (6.44%)       | 20 (5.38%)       | 22 (6.01%)       | 59 (5.64%)       |
| Pneumonia                       | 43 (1.76%)       | 7 (3.40%)        | 6 (1.33%)        | 6 (1.61%)        | 5 (1.37%)        | 19 (1.81%)       |
| Any blood product use           | 1096 (44.9%)     | 91 (44.2%)       | 202 (44.9%)      | 166 (44.6%)      | 153 (41.8%)      | 484 (46.2%)      |
| Postoperative IABP use          | 14 (0.57%)       | 1 (0.49%)        | 3 (0.67%)        | 4 (1.08%)        | 2 (0.55%)        | 4 (0.38%)        |
| Deep sternal wound infection    | 24 (0.98%)       | 4 (1.94%)        | 4 (0.89%)        | 1 (0.27%)        | 6 (1.64%)        | 9 (0.86%)        |
| Septicemia                      | 5 (0.20%)        | 1 (0.49%)        | 1 (0.22%)        | 0               | 2 (0.55%)        | 1 (0.10%)        |
| Postoperative length of stay, median (25th, 75th percentiles), days*    | 5 (4, 7)         | 5 (4, 7)         | 5 (4, 6)         | 5 (4, 7)         | 5 (4, 7)         | 5 (4, 8)         |

IABP indicates intraaortic balloon pump; MI, myocardial infarction.

*Variables presented as median (25th, 75th percentiles).

| Table 4. Studies Evaluating the Relationship of AKI With the Time Interval Between Cardiac Catheterization and CABG |
|----------------------------------|------------------|------------------|------------------|------------------|------------------|
| Study (n)                       | Patient Population | Status of Procedure | Exclusion Criteria | Definition of AKI | AKI (Dialysis) Incidence | Comparison Group in Logistic Model |
| Brown et al (226 patients)12     | Valve surgery     | Elective          | Serum creatinine >1.8 mg/dL, urgent, emergent, salvage | Serum creatinine >2× baseline and total >2 mg/dL | 1.8% (0.9%) | None |
| Del Duca et al (649 patients)8   | CABG, valve and other cardiac surgeries | Elective or urgent | Preoperative dialysis, cardiac transplantation, ventricular assist devices, aortic dissection, emergent/salvage surgery | Serum creatinine ≥25% above baseline | 24% (4.2%) | ≤5 vs >5 d (OR 1.82, 95% CI 1.17, 2.84) |
| Ranucci et al (423 patients)9    | CABG, valve and other cardiac surgeries | Elective or urgent | Emergent/salvage surgery, preoperative dialysis, congenital heart disease, off pump surgery | Serum creatinine ≥2× baseline and total >2 mg/dL | 5.7% (0.5%) | ≤1 vs >1 d (OR 3.1, 95% CI 1.1, 8.8) |
| Medalon et al (395 patients)10   | First time CABG   | Elective or urgent | Emergent/salvage surgery, preoperative dialysis, off pump surgery | ≥25% decrease of creatinine clearance from baseline | 13.6% | ≤1 vs >1 d (OR 3.7, 95% CI 1.4, 8.3) |
| Hennessey et al (1287 patients)61 | Valve surgery     | Elective or urgent | Nonvalvular cardiac surgery, emergent/salvage surgery | Serum creatinine ≥2× baseline and total >2 mg/dL | 6.6% (3.3%) | ≤1 vs >3 d (OR 5.3, 95% CI 1.4, 19.0) |
| Mehta et al (present study) (2441 patients) | CABG | Elective | Non-CABG or urgent/emergent/salvage surgeries, preoperative dialysis. | Serum creatinine ≥50% above baseline | 17.1% (0.9%) | Continuous variable ≤1 to >=5 d (OR 0.90, 95% CI 0.83, 0.98) |

AKI indicates acute kidney injury; CABG, coronary artery bypass graft surgery; OR, odds ratio.
Clinical Implications
Despite the differences between our study and previous studies in patient population, inclusion and exclusion criteria, and the definition of AKI used, these studies provide a consistent unifying message: early cardiac surgery (particularly ≤1 day) may be associated with a higher incidence of postprocedural AKI. Thus, postponing cardiac surgery for 24 to 48 hours (when feasible), especially in elective cases, may have the potential to minimize the additive adverse effect of contrast and cardiopulmonary bypass, a hypothesis that remains to be proven in future studies. These data should not be viewed as being prohibitive for proceeding with early cardiac surgery in patients in whom delaying surgery may have the potential for greater harm. A clinical decision should be made in those needing early surgery based on the perceived risk of immediate surgery on renal function versus that for ischemic events and its consequences while waiting longer. If early surgery is indeed warranted, all efforts should be directed at minimizing the deleterious effects of contrast and cardiopulmonary bypass on renal tubules. Prevention and treatment of prolonged periods of hypotension, shorter cardiopulmonary bypass time, maintenance of adequate hematocrit and oxygenation during cardiopulmonary bypass, and avoidance of nephrotoxic drugs in the perioperative period may help to minimize the risk of AKI in these individuals. Strategies to prevent contrast-induced nephropathy should be routinely adapted during angiography and continued in the postoperative period, with the hope that this may help reduce postoperative AKI in those needing early cardiac surgery following cardiac catheterization.

Limitations
Our study has some limitations. This is a retrospective observational study. Thus, our findings should be regarded as hypothesis generating, and inference regarding causality should be made with caution. As with any retrospective study, we could only adjust for variables collected in our database. Thus, days from cardiac catheterization to CABG may be a marker of unmeasured confounding variables rather than being an independent correlate of post-CABG AKI, and the influence of any unmeasured confounders on the risk of AKI cannot be ascertained. Furthermore, the number of events in patients undergoing elective CABG was still small for making any definitive conclusions regarding the association of AKI and the time interval between cardiac catheterization and CABG with outcomes. The majority of our patients underwent CABG on-pump, and our findings should not be extrapolated to those undergoing off-pump CABG, a strategy also commonly used simultaneously with percutaneous coronary interventions in those undergoing hybrid coronary revascularization/cardiac surgery. Whether or not off-pump compared with on-pump CABG in those undergoing early surgery after cardiac catheterization would help reduce the incidence of post-CABG AKI remains to be proven in future investigations. We did not collect information regarding strategies used to prevent or improve post-CABG AKI that may have influenced patient outcomes. Our results are best applicable to patients undergoing elective isolated CABG.

Conclusions
The current study showed that the risk of post-CABG AKI was inversely but modestly related to the time interval between cardiac catheterization and CABG. The highest incidence of post-CABG AKI occurred when CABG was performed ≤1 day after cardiac catheterization and then declined over 5 days. This high incidence occurred despite the lower risk profile of patients operated on earlier. Whether delaying elective CABG ≥24 hours of exposure to contrast agents (when feasible) has the potential for decreasing post-CABG AKI remains to be proven. In addition, it remains to be studied in the future whether strategies used to prevent or improve post–cardiac catheterization and post-CABG AKI would have the potential for reducing the incidence of AKI among those operated on early and would help improve patient outcomes.

Sources of Funding
Dr Patel is funded by National Institutes of Health Grant K23 DK075929.

Disclosures

References


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Circulation. 2011;124:S149-S155
doi: 10.1161/CIRCULATIONAHA.110.011700

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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