Perioperative Increases in Serum Creatinine Are Predictive of Increased 90-Day Mortality After Coronary Artery Bypass Graft Surgery

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Background—Impaired renal function after coronary artery bypass graft (CABG) surgery is a key risk factor for in-hospital mortality. However, perioperative increases in serum creatinine and the association with mortality has not been well-studied. We assessed the hypothesis that perioperative increases in creatinine are associated with increased 90-day mortality.

Methods and Results—We studied 1391 patients in northern New England undergoing CABG in 2001 and evaluated preoperative and postoperative creatinine. Patients with preoperative dialysis were excluded. Data were linked to the National Death Index to assess 90-day survival. Kaplan-Meier and log-rank techniques were used. Patients were stratified by percent increase in creatinine from baseline: <25%, 25% to 49%, 50% to 99%, >100%. We assessed 90-day survival and calculated adjusted hazard ratios (HR) and 95% confidence intervals (95% CI) for creatinine groups, adjusting for age and sex. Patients with the largest creatinine increases (50% to 99% or >100%) had significantly higher 90-day mortality compared with patients with a smaller increase (<25%; P < 0.001). Adjusted HR and 95% CI confirmed patients in the higher 2 groups had an increased risk of mortality compared with the referent: 1.80 (95% CI: 0.73 to 4.44), 6.57 (95% CI, 3.03 to 14.27), and 22.10 (95% CI, 11.25 to 43.39).

Conclusions—Patients with large creatinine increases (≥50%) after CABG surgery have a higher 90-day mortality compared with patients with small increases. Efforts to identify patients with impaired renal function and to preserve renal function before cardiac surgery may yield benefits for patients in the future. (Circulation. 2006; 114[suppl I]:I-409–I-413.)

Key Words: coronary artery bypass graft ■ creatinine ■ kidney ■ surgery ■ survival

A
cute renal failure (ARF) is a common and lethal outcome after coronary artery bypass graft (CABG) surgery. Patients with ARF in the intensive care unit have a 50% to 70% risk of death.1 Among CABG patients, 30% to 50% without preoperative renal failure develop ARF within 2 days after the surgery and have been shown to have a 60% increased risk of mortality.2,3 ARF has been independently associated with high mortality,4 especially in-hospital mortality.2,5–8

Elevations in serum creatinine (Cr) have been a commonly used marker of ARF in hospitalized patients. However, many methods have been used to characterize ARF including preoperative Cr,9,10 postoperative Cr, the absolute increase from preoperative Cr to the highest postoperative level, or the relative percent increase from preoperative to postoperative Cr (%ΔCr). The definition of ARF has varied widely, ie, %ΔCr=20%,5,11 25%,8,12 30%,7 or 50%.3,7 Studies demonstrated their definition of ARF (ie, %ΔCr) was associated with in-hospital mortality after CABG. However, little has been shown with regard to survival after hospitalization. One long-term survival study demonstrated higher preoperative levels of Cr were associated with 1-year mortality,13 confirming the high risk of mortality for patients with preoperative renal failure.14 A similar study examined survival by dividing patients into groups by the absolute change from preoperative Cr to postoperative Cr, showing higher absolute changes in Cr were associated with higher 3-year mortality.15 One study

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examined the relative effect of %ΔCr on long-term mortality; however, this study only assessed the survival for patients discharged alive, stratified patients into 1 of 2 groups of %ΔCr (<25% and ≥25%ΔCr) and showed patients with a ≥25%ΔCr had slightly higher 8-year mortality. Although the difference was significant, the magnitude of the effect was not substantial.

To date, the literature does not examine the effect of differing levels of percent increases in Cr (%ΔCr) on longer-term mortality. In this study, we examined stratified levels of %ΔCr with respect to 90-day mortality. We hypothesized that a 25% to 49%, 50% to 99%, ≥100%ΔCr at 48 hours after CABG surgery would exhibit a sequential increase in 90-day mortality.

**Methods**

The Northern New England Cardiovascular Disease Study Group (NNECDSG) was founded in 1987 as a regional voluntary consortium capturing 100% of the coronary revascularizations and/or valve procedures in northern New England including 8 medical centers in Vermont, New Hampshire, and Maine. The group consists of clinicians, hospital administrators, and health care research personnel who seek to improve continually the quality, safety, effectiveness, and cost of medical interventions in cardiovascular disease. The NNECDSG has Institutional Review Board approval for data collection and analysis at all participating centers. The authors had full access to the data and take full responsibility for their integrity. All authors have read and agree to the manuscript as written. We prospectively enrolled 1412 CABG procedures at participating NNECDSG centers between January 2001 and December 2001 and obtained preoperative and postoperative serum creatinine measurements (mg/dL). Twenty-one patients with preoperative renal failure requiring dialysis were excluded from the analysis, leaving 1391 patients that contributed to this analysis. We excluded patients undergoing CABG occurring with heart valve repair or replacement, resection of ventricular aneurysm, or another surgical procedure.

**Data Collection**

The following data were recorded prospectively for all patients. Preoperative characteristics: age, sex, height, weight, body surface area, hypertension, chronic obstructive pulmonary disease, preoperative use of an intra-aortic balloon pump (IABP), and preoperative renal failure requiring dialysis (hemodialysis, peritoneal dialysis). Last preoperative serum creatinine (mg/dL) and highest postoperative creatinine (highest for postoperative index admission) were documented. Methods for data collection and definitions for these variables have been described previously. Percent change in serum creatinine (%ΔCr) was calculated by: [(highest postoperative Cr)/(last preoperative Cr)] − 1] × 100%. The percent change values were divided into 4 groups: <25%, 25% to 49%, 50% to 99%, ≥100%. These groups were based on previous studies that define ARF as 25%8,12 or 50%3,7,16 increase in serum creatinine. Relative verses absolute effects were compared using terciles of baseline Cr. Terciles (T1, T2, T3) were generated for each %ΔCr group: T1 Cr ≤0.9, T2 0.9 to 1.2, T3 >1.2 (mg/dL).

**Patient Follow-Up**

The primary outcome of this analysis was all-cause mortality at 90 days. Mortality was determined by a match of the NNECDSG regional registry to the National Death Index (US Department of Health and Human Services) using name, social security number, date of birth, sex, date last known alive, and state of last known residence.

<table>
<thead>
<tr>
<th>TABLE 1. Patient and Disease Characteristics</th>
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<td>Creatinine Change Preoperative to Highest Postoperative</td>
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<td>Variables</td>
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<tr>
<td>Patient demographics</td>
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<tr>
<td>Age, mean±SD</td>
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<tr>
<td>Female, %</td>
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<tr>
<td>BSA, mean±SD (m²)</td>
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<tr>
<td>Preoperative characteristics</td>
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<tr>
<td>Hypertension, %</td>
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<tr>
<td>COPD, %</td>
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<tr>
<td>PVD, %</td>
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<tr>
<td>Diabetes, %</td>
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<tr>
<td>Preoperative creatinine, mean±SD (mg/dL)</td>
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<tr>
<td>Cardiac profile</td>
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<tr>
<td>Surgical priority</td>
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<tr>
<td>Elective, %</td>
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<tr>
<td>Urgent, %</td>
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<tr>
<td>Emergent, %</td>
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<tr>
<td>Left main disease (≥50% stenosis), % yes</td>
</tr>
<tr>
<td>Unstable angina, %</td>
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<tr>
<td>Number of diseased vessels, mean±SD</td>
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<tr>
<td>Ejection fraction, mean±SD</td>
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<tr>
<td>LVEDP, mean±SD (mm Hg)</td>
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<tr>
<td>Prior CABG, %</td>
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</tbody>
</table>

P value: χ² test, test of trend.
SD indicates standard deviation; BSA, body surface area; COPD, chronic obstructive pulmonary disease; PVD, peripheral vascular disease; LVEDP, left ventricular end diastolic pressure; CABG, coronary artery bypass graft surgery.
Statistical Analysis
Baseline characteristics and clinical outcomes were summarized by
percentages and means (±standard deviation). We used χ² tests and
tests of trend to assess similarities between categories of ΔCr.
Kaplan-Meier techniques were used to conduct the survival analysis;
patients were stratified by ΔCr from baseline: <25%, 25% to 49%,
50% to 99%, ≥100%. Incidence of death (deaths per 10 000
person-days) was calculated for each category. Cox’s proportional
hazard models were used to calculate crude and adjusted hazard
ratios (HR): <25% as referent, adjusting for age and sex. Adjusted
HRs were reported with 95% confidence intervals and subsequent
probability values. Relative verses absolute effects for ΔCr and
baseline Cr were compared graphically, using Kaplan-Meier and
log-rank methods. Analyses were conducted using Stata 9.0 (Stata,
College Station, TX).

Results
Patient Characteristics
Patients were divided into 4 groups based on ΔCr. Patient
baseline characteristics are reported in Table 1. Age and
female sex were significantly higher across ΔCr groups.
More patients had chronic obstructive pulmonary disease and
diabetes in the higher ΔCr groups. Body surface area,
hypertension, PVD, and preoperative serum creatinine
(mg/dL) were similar across all groups. Patients across the
categories had similar left main disease and previous CABG
surgery. Differences were noted across all groups with
respect to unstable angina, number of diseased vessels,
ejection fraction, and LVEDP.

Survival Analysis
Patients were followed-up prospectively and linked to the
National Death Index with 102 129 person-days of follow-up
and 54 deaths (Table 2). The 90-day incidence of death (per
10 000 person-days of follow-up) for <25% (2.0), 25% to
49% (4.2), 50% to 99% (18.0), and ≥100% (54.6). Each
increase in ΔCr category had a higher 90-day death rate and
adjusted HR for each ΔCr category (Table 3). The Kaplan-
Meier survival plot demonstrates an increased 90-day mor-
tality for patients with a 50% to 99% and ≥100% ΔCr (Figure
1). The survival curves for 50% to 99% and ≥100% ΔCr were
significantly different at P<0.001, as calculated by a log-rank
test, suggesting a 50% or greater ΔCr results in worse
90-day survival. We repeated our analysis adjusting for
baseline creatinine and perioperative factors (clamptime,
pumptime, IABP and inotrope use, perioperative myocardial
infarction, and stroke), which showed no difference in the
reported findings. All interactions were assessed and ruled
out.

We examined the relative (%ΔCr) effect compared with
the absolute (terciles of baseline Cr) for our analysis (Figure
2). We found patients in all 3 terciles of baseline Cr with
<50%ΔCr did not have different incidence of death (per
10 000 person-days) within their respective %ΔCr group.
However, patients in the higher risk %ΔCr groups
(≥50%ΔCr) showed an increase in cumulative incidence
across terciles of baseline Cr; this trend within each tercile
was consistent with the survival curves (Figure 1).

Clinical Outcomes
Patients with a ≥50%ΔCr or more were more likely to have
worse outcomes (Table 4); there was a significant association
with an increase in poor outcome with increasing category of
%ΔCr. Patients with ≥50%ΔCr were more likely to have low
cardiac output, atrial fibrillation, hypotension, and infection
(mediastinitis and/or pneumonia). These outcomes identify an
association with %ΔCr and renal injury; such outcomes may
have been caused by renal hypoperfusion as a result of
cardiopulmonary bypass, circulating toxins, increase in in-
flammation or perioperative hypotension. Hypotension and
inflammatory mediators may cause the increase in creatinine
resulting in renal damage and increased risk of mortality.
Inflammation may be a factor for the onset of atrial fibrilla-
tion as noted with a more than a doubling of atrial fibrillation
rates from the lowest to highest creatinine groups.18

Discussion
We examined 90-day mortality associated with %ΔCr. We
found ≥50%ΔCr was associated with increased 90-day mor-
tality versus patients experiencing <25%ΔCr. Patients with a
doubling of serum creatinine (≥100%ΔCr) during the peri-
operative period experienced the highest 90-day mortality.

| TABLE 2. Incidence Rates of Death by Creatinine Categories |
|-----------------|-------------------|------------------|-------------------|
| Percent Creatinine Increase | No. of Patients | No. of Deaths | Person-Days of Follow-Up | Incidence Rate of Deaths per 10 000 Person Days |
| <25% | 1004 | 15 | 76 265 | 2.0 |
| 25% to 49% | 224 | 7 | 16 551 | 4.2 |
| 50% to 99% | 98 | 12 | 6671 | 18.0 |
| ≥100% | 65 | 20 | 3661 | 54.6 |

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| TABLE 3. Postoperative Survival |
|-----------------|-------------------|-------------------|
| Percent Creatinine Increase | No. of Patients | 90-Day Death | Adjusted HR | 95% CI | P |
| <25% | 1004 | 1.49 | 1.00 | Reference | — |
| 25% to 49% | 224 | 3.13 | 1.80 | 0.73–4.44 | 0.201 |
| 50% to 99% | 98 | 12.24 | 6.57 | 3.02–14.27 <0.001 |
| ≥100% | 65 | 30.77 | 22.1 | 11.25–43.39 <0.001 |

Adjusted HR is adjusted hazard ration from Cox’s proportional hazard model, adjusted for age and sex.
This finding suggests a patient with more than a doubled creatinine (preoperative to postoperative) has a 22-fold increased risk of dying within 90 days after CABG surgery. A patient with 50% to 99% ΔCr has a 7-fold increased risk of dying within 90 days. Strikingly, patients with 25% to 49% ΔCr were no different from patients with <25% ΔCr.

These findings were consistent with other clinical outcomes and suggests acute renal failure should be diagnosed when there is ≥50% ΔCr and not at 20%,6,11 25%,6,12 or 30%.7 Our results are consistent with Lassnigg et al, who report a 0.5 (mg/dL) change in creatinine from preoperation to postoperation was indicative of acute renal failure and associated with an 18-fold risk of 30-day mortality, with no significant risk of mortality after 30 days (HR, 5.76).15 In our study we used a percent increase in serum creatinine, thereby using ΔCr.3,7,11,20 Conlon et al showed an increase in Cr by 1.0 (mg/dL) and new onset of renal failure was associated with mortality.3 We chose rather to calculate the %ΔCr, categorize patients into 4 groups and assessed 90-day mortality. Our analysis includes in-hospital deaths in the 90-day mortality and is in agreement with other reports showing that %ΔCr is associated with mortality.3,7,11 However, our results proved a <50% ΔCr was not associated with an increased risk of 90-day mortality; this is in agreement with the reports favoring at least a 50%ΔCr as a predictor of early mortality.3,7 We add to their analysis of early mortality with the addition of four categories of %ΔCr and extend the mortality assessment to 90-days to suggest patients with a 50% or 100%ΔCr are at increased risk of 90-day mortality.

The mechanism of acute renal failure likely involves hypotension, nephrotoxins, and fluid overloading. Thadhani et al reported renal tubular necrosis accounts for 85% of acute renal failure (50% ischemia, 35% toxins).21 This finding is likely similar in CABG surgical patients as well, whereby hypotension could result from low cardiac output or low pressure from the cardiopulmonary pump. Nephrotoxins may include drugs and contrast dye from a preoperative catheterization among urgent surgical patients. Furthermore, we discovered distinct associations between patients with elevated %ΔCr and low output syndrome and infection; these associations may suggest these clinical manifestations present prior to elevations in serum creatinine, result in damage to the kidney followed by an increase in creatinine. Therefore, hypotension, nephrotoxins, and inflammation may lead to acute renal failure observed as a substantial (≥50%) increase in serum creatinine.

### TABLE 4. Assessment of Clinical Outcomes

<table>
<thead>
<tr>
<th>Variables</th>
<th>&lt;25%</th>
<th>25% to 49%</th>
<th>50% to 99%</th>
<th>≥100%</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postoperative clinical outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Length of postoperative stay, mean±SD (days)</td>
<td>5.8±4.4</td>
<td>7.9±8.0</td>
<td>11.0±10.4</td>
<td>14.9±14.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Renal failure, %</td>
<td>0.3</td>
<td>0.0</td>
<td>2.3</td>
<td>14.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Atrial fibrillation, %</td>
<td>21.9</td>
<td>31.7</td>
<td>41.2</td>
<td>50.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Low output syndrome, %</td>
<td>1.9</td>
<td>3.6</td>
<td>12.2</td>
<td>29.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mediastinitis, %</td>
<td>0.3</td>
<td>1.3</td>
<td>3.1</td>
<td>3.1</td>
<td>0.002</td>
</tr>
<tr>
<td>Return to OR for bleeding, %</td>
<td>2.4</td>
<td>1.8</td>
<td>5.1</td>
<td>6.2</td>
<td>0.099</td>
</tr>
<tr>
<td>Q-wave myocardial infarction, %</td>
<td>0.7</td>
<td>0.6</td>
<td>0.0</td>
<td>3.9</td>
<td>0.076</td>
</tr>
<tr>
<td>Pneumonia, %</td>
<td>0.7</td>
<td>2.8</td>
<td>2.2</td>
<td>13.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Index admission mortality, %</td>
<td>0.8</td>
<td>0.5</td>
<td>7.1</td>
<td>29.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>90-day mortality, %</td>
<td>1.5</td>
<td>3.1</td>
<td>12.2</td>
<td>30.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>One or more outcomes excluding mortality, %</td>
<td>25.5</td>
<td>37.5</td>
<td>50.0</td>
<td>70.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>One or more outcomes including mortality, %</td>
<td>26.0</td>
<td>38.8</td>
<td>54.1</td>
<td>76.9</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
There are several limitations to this study. We prospectively enrolled patients in this study as part of the NNECDSG regional registry cohort, which collects and reports data on 100% of the cardiac procedures in northern New England. Therefore, biases resulting from patient enrollment or data collection are not valid limitations of this study. We noted several baseline differences in patients across the creatinine categories. We were limited by the number of risk factors we could adjust for based on only 54 deaths. Because of this limitation we only report age- and sex-adjusted HRs. However, the unadjusted and age-sex-adjusted HRs did not differ, nor did the HRs differ after adjusting for multiple risk factors. We can only speculate these risk factors were not confounding our results; however, a larger cohort will be required to adequately assess these risk factors in the future. Our findings are limited to 1 year and 90-day mortality. The NNECDSG registry is ongoing and will conduct a 4- to 5-year follow-up analysis on the same categories of mortality. The NNECDSG registry is ongoing and will conduct the future. Our findings are limited to 1 year and 90-day

Sources of Funding

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Disclosures

None.

References

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