Influence of the Timing of Cardiac Catheterization and the Amount of Contrast Media on Acute Renal Failure After Cardiac Surgery

Marco Ranucci, MD[a], Andrea Ballotta, MD[a], Alessia Kunkl, MD[a], Donatella De Benedetti, MD[a], Hassan Kandil, MD[a], Daniela Conti, MD[a], Nadia Mollichelli, MD[b], Eduardo Bossone, MD, PhD[c], and Rajendra H. Mehta, MD, MS[d,*]

Postoperative acute renal failure (ARF) is not uncommon after cardiac surgery and after angiography. However, limited information exists regarding the influence of the interval between cardiac catheterization and subsequent cardiac surgery and amount of contrast agent used during this procedure on the occurrence of postoperative ARF. Data for 423 consecutive adult patients who underwent elective cardiac surgery after cardiac catheterization were examined retrospectively. The influence of interval between cardiac catheterization and cardiac surgery on postoperative ARF (defined as postoperative serum creatinine ≥2 times baseline and >2 mg/dl and/or need for renal replacement therapy) was evaluated using multivariable logistic regression. ARF occurred in 24 patients (5.7%). Median time to angiography was 2 days (interquartile range 1 to 4.5), and median dose of contrast used was 1.36 ml/kg (interquartile range 1.12 to 1.69). Surgery on the day of cardiac catheterization was independently associated with increased risk of ARF (adjusted odds ratio 3.1, 95% confidence interval 1.1 to 8.8). This risk of ARF was highest in patients who underwent surgery on the same day as angiography and with a dose of contrast higher than median (14.6%) and lowest when surgery was delayed beyond 1 day of angiography and contrast dose was median or less (2.4%; adjusted odds ratio for same-day surgery and dose higher than median 4.2, 95% confidence interval 1.2 to 14.2). Cardiac surgery performed on the day of cardiac catheterization and higher dose of contrast agent used were both independently associated with increased risk of postoperative ARF. In conclusion, these findings suggest that delaying cardiac surgery beyond 24 hours of exposure to contrast agents (when feasible) and minimizing the use of these agents have significant potential to decrease the incidence of postoperative ARF in patients undergoing elective cardiac surgery. **(Am J Cardiol 2008;101: 1112–1118)**

Because cardiac surgical procedures often follow diagnostic angiography, there is a potential for the contrast used during angiographic procedures to exacerbate the risk of acute renal failure (ARF) after cardiac surgery. This is particularly so if surgical procedures are performed early after angiography before renal tubules have time to recover from toxic effects of the contrast media. However, limited data exist about the influence of timing of cardiac surgery in relation to diagnostic angiography and/or the impact of amount of contrast used (a predictor of contrast-induced nephropathy[1]) during preceding angiography on patients with ARF after cardiac surgery. The purpose of the present study was to investigate the effect of the interval between diagnostic angiography and cardiac surgery and amount of contrast used during the diagnostic procedure on the incidence of ARF after cardiac surgery. We hypothesized that a shorter time between diagnostic angiography and cardiac surgery would adversely influence the incidence of ARF after cardiac surgery. Furthermore, we theorized that the dose of contrast used would also be directly linked to this adverse postsurgical event.

Methods

Patient population: We evaluated consecutive patients undergoing elective on-pump cardiac surgery at our institution from January 1, 2007, to June 30, 2007. We included all patients who underwent a cardiovascular diagnostic procedure requiring the use of a contrast agent (left ventriculography, coronary or carotid angiography, and thoracic and/or abdominal aorta) followed by cardiac surgical procedure using cardiopulmonary bypass. Timing of the elective cardiac surgery in these stable patients was dictated by the availability of the operating room slot, convenience and willingness of the patient to undergo surgery on a given day rather than by randomized assignment to a particular day, patient clinical condition after angiography, or findings of angiography. We excluded all patients requiring emergent

[a]Department of Cardiothoracic-Vascular Anesthesia and Intensive Care and [b]Cardiac Catheterization Hemodynamic Laboratory, IRCCS Policlinico S. Donato, Milan; [c]Cava de' Tirreni and Amalfi Coast Hospital, Salerno, Italy; and [d]Duke Clinical Research Institute, Durham, North Carolina. Manuscript received November 1, 2007; revised manuscript received and accepted December 9, 2007.

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*Corresponding author: Tel: +1-919-668-8971; fax: +1-919-668-7059.

E-mail address: mehta007@dcri.duke.edu (R.H. Mehta).

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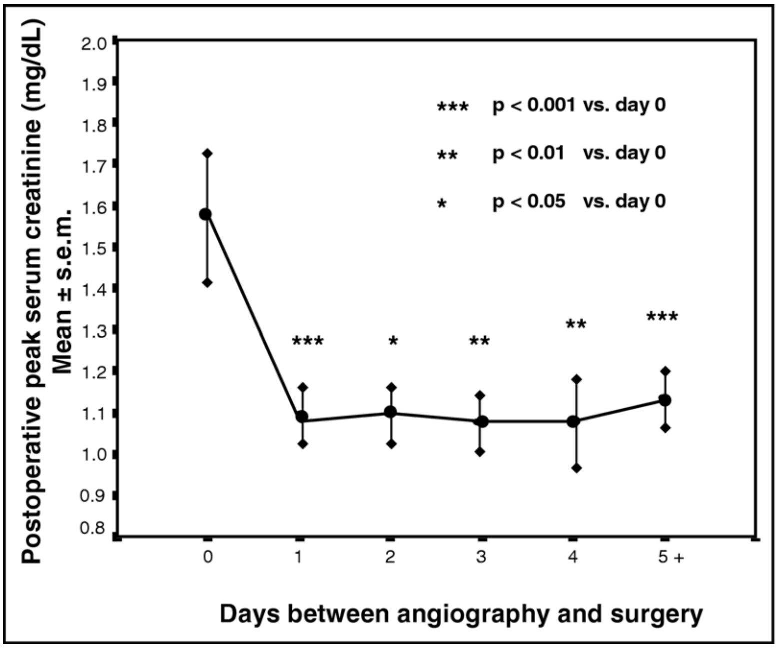

Figure 1. Relation of the interval between angiography and surgery and postoperative serum creatinine.

salvage or emergent surgery, on dialysis therapy at baseline, with congenital heart disease, or undergoing the procedure off-pump. Additionally, because we did not have systematic information for the date of angiography for patients who underwent these diagnostic procedures at other institutions and were referred for cardiac surgery to our hospital, we also excluded these patients. A total of 423 patients met study criteria and formed the basis of this analysis.

Protocol for angiographic procedure: The routine protocol for patients scheduled for angiography at our institution includes (1) hydration with 0.9% saline solution intravenously at a rate of 1 ml/kg of body weight per hour (0.5 ml/kg for patients with congestive heart failure and/or left ventricular ejection fraction <30%) for 12 hours before administration of the contrast agent and 12 hours after the end of the angiography or until initiation of the cardiac surgery, and (2) *N*-acetylcysteine orally at a dose of 1,200 mg twice daily on the day before and the day of angiography (second dose not administered if angiography was performed on the same day as the operation). The contrast agent used was Iobitridol 350 (Xenetix; Guerbet, Roissy, France) or Iodixanol 270 (Visipaque; Nycomed Imaging AS, Oslo, Norway) in patients with preoperative serum creatinine >1.3 mg/dl. Use of nonsteroidal anti-inflammatory agents and other nephrotoxic drugs were avoided or withheld for 48 hours before angiography.

Intraoperative management: Premedication included atropine sulfate (0.5 mg), promethazine (50 mg), and fentanyl (50 to 100 μg according to patient weight) intramuscularly administered 1 hour before the induction of anesthesia. Anesthesia was induced in standard fashion. Cardiopulmonary bypass was conducted using either closed or open circuits, standard or phosphorylcholine-coated hollow-fiber oxygenators, and roller or centrifugal pumps according to availability. Regardless of the circuit used, priming volume was minimized to 800 to 1,000 ml.

Data collection and definitions: Data for all patient demographics, clinical characteristics, co-morbid conditions, medical treatments, laboratory data, angiographic data (including amount and type of contrast used), cardiac procedural data (including its timing in relation to the preceding angiography), and peri- and postoperative events were routinely collected in a computerized database for all patients undergoing cardiac surgery at our institution prospectively. We used these existing data for our analysis.

Creatinine clearance was determined using the Cockcroft-Gault equation.[2] Postoperative renal risk was assessed using the 2 different risk scores of a simplified predictive index for renal replacement therapy after cardiac surgery[3] and a risk score for prediction of contrast-induced nephropathy.[1] The main outcome of interest was the incidence of postoperative ARF, defined as postoperative serum creatinine ≥2 times baseline and >2 mg/dl and/or need for renal replacement therapy.[4]

Statistical analysis: Continuous variables were presented as median and interquartile range, and categorical variables, as frequency and percentage. Comparisons were made using 2-sided chi-square test or, when appropriate, 2-sided Fisher's exact test for categorical variables and nonparametric test for continuous variables. Patients were grouped according to time (days) between angiography and surgery. We examined the incidence of ARF according to intervals of 0, 1, 2, 3, 4, and ≥5 days and found that the maximum incidence of ARF was when surgery was performed on day 0, or the same day as angiography. Thus, for all subsequent analysis, we characterized this time variable as day 0 and ≥1 day. Amount of contrast was entered into the model as both a linear (continuous variable) and a

Table 1
Clinical features

Variable	Overall (n = 423)	No Postoperative ARF (n = 399)	Postoperative ARF (n = 24)	p Value
Age (yrs)	68 (59–74)	68 (59–74)	74 (68–79)	0.015
Men	275 (65%)	264 (66%)	11 (46%)	0.049
Height (cm)	168 (160–173)	168 (160–173)	165 (155–172)	0.22
Weight (kg)	72 (64–82)	73 (64–83)	70 (60–80)	0.31
Hypertension	287 (68%)	259 (65%)	17 (71%)	0.662
Diabetes mellitus	42 (10%)	41 (10%)	1 (4.2%)	0.494
Current smoker	138 (33%)	123 (31%)	8 (33%)	0.822
Previous myocardial infarction	87 (21%)	78 (20%)	5 (21%)	0.796
Previous stroke	19 (4.5%)	17 (4.3%)	2 (8.3%)	0.294
Previous peripheral vascular disease	86 (20%)	75 (19%)	6 (25%)	0.429
Previous heart failure	28 (6.6%)	21 (5.3%)	7 (29%)	0.001
Previous cardiac surgery	28 (6.6%)	24 (6.0%)	4 (16.7%)	0.065
Previous vascular surgery	20 (4.7%)	16 (4.0%)	4 (17%)	0.021
Preoperative intra-aortic balloon pump	4 (0.9%)	4 (1.0%)	0 (0%)	0.622
Preoperative left ventricular ejection fraction (%)	55 (50–60)	55 (50–60)	50 (35–60)	0.024
Preoperative serum creatinine (mg/dl)	0.9 (0.8–1.0)	0.9 (0.8–1.0)	1 (0.8–1.27)	0.42
Preoperative creatinine clearance (ml/min)	62.5 (48.3–85.1)	64.2 (49.2–83.5)	50.7 (40.2–92.1)	0.175
ARF risk score	1.0 (1.0–2.0)	1.44 (1.0–2.0)	2.0 (1.0–3.0)	0.001
Contrast-induced nephropathy risk score	3.0 (1.0–5.0)	2.0 (1.0–5.0)	6.5 (2.0–9.0)	0.001
Preoperative hematocrit (%)	40 (36–42)	40 (37–42)	37 (34–40)	0.005

Values expressed as median (interquartile range) or number (percent).

Table 2
Contrast and cardiac surgery data

Variable	Overall (n = 423)	No postoperative ARF (n = 399)	Postoperative ARF (n = 24)	p Value
Type and dose of contrast agent used				
Iodixanol 270 (ml/kg)	1.63 (1.13–2.48)	1.68 (1.29–2.54)	1.42 (0.93–2.45)	0.054
Iobitridol 350 (ml/kg)	1.34 (1.12–1.69)	1.33 (1.12–1.66)	1.6 (1.17–2.9)	0.606
Contrast agent dose > median value	209 (49%)	193 (48%)	16 (67%)	0.064
Cardiac surgical data				
Time between angiography and surgery (d)	2 (1–4.5)	2 (1–4)	1 (0–5)	0.149
Patients undergoing surgery on same day as angiography	89 (22%)	79 (20%)	10 (42%)	0.018
Isolated coronary surgery	131 (31%)	128 (32%)	3 (13%)	0.066
Isolated valve surgery	171 (40%)	166 (42%)	5 (21%)	0.053
Combined procedure	121 (29%)	105 (26%)	16 (67%)	0.001
Cardiopulmonary bypass time (min)	70 (50–94)	69 (50–90)	111 (96–188)	0.001
Lowest hematocrit on cardiopulmonary bypass (%)	26 (24–29)	26 (24–29)	24 (23–27)	0.01
Lowest temperature on cardiopulmonary bypass (°C)	31 (30–32)	31 (30–32)	29 (26–31)	0.001
Peak postoperative serum creatinine (mg/dl)	1 (0.8–1.3)	1 (0.8–1.2)	2.6 (2.1–3.9)	0.001

Values expressed as median (interquartile range) or number (percent).

dichotomous term (median or less and greater than median value). Multivariable logistic regression analysis (stepwise forward selection) was used to identify independent predictors of ARF using variables found to have marginal association ($p < 0.10$) on univariate analysis with this event. We also tested the effect of the interaction between time (0 and ≥1 day) and contrast dose (median or less and greater than median value) on postoperative ARF. Diagnostic routines (Hosmer-Lemeshow test for lack of fit) were used for the final model selection. Odds ratios (ORs) and 95% confidence intervals (CIs) were constructed to provide an estimate of adjusted risk posed by postprocedural ARF. The c index was calculated to evaluate model discrimination. A p value <0.05 was considered statistically significant. All statistical analyses were performed using SPSS 11.0 (SPSS, Inc., Chicago, Illinois).

Results

Baseline characteristics: Of 423 patients who underwent cardiac surgery after angiography (median 2 days, interquartile range [IQR] 1 to 4.5), ARF occurred in 24 (5.7%); 2 of these patients needed dialysis. Median dose of contrast agent used overall was 1.36 ml/kg (IQR 1.12 to 1.69), and median overall postoperative peak serum creatinine and lowest creatinine clearance were 1.0 mg/dl (IQR 0.8 to 1.3) and 81 ml/min (IQR 58 to 109), respectively. Overall postoperative peak creatinine was highest on day 0, then decreased and remained similar beyond this period

Table 3
Clinical events

Variable	Overall (n = 423)	No postoperative ARF (n = 399)	Postoperative ARF (n = 24)	p Value
Length of stay				
Time on ventilator (h)	12 (8–18)	12 (8–18)	72 (31–365)	0.001
Length of ICU stay (d)	2 (1–3)	2 (1–3)	10 (5–19)	0.001
Length of hospital stay (d)	6 (5–8)	6 (5–8)	13 (8–28)	0.001
In-hospital events				
Death	7 (1.7%)	0 (0%)	7 (29.1%)	0.001
Mediastinitis	0 (0%)	0 (0%)	0 (0%)	NS
Need for renal replacement therapy	2 (0.5%)	0 (0%)	2 (8.3%)	0.003
Postoperative atrial fibrillation	97 (23%)	87 (22%)	10 (42%)	0.041
Pneumonia	12 (2.8%)	3 (0.1%)	9 (38%)	0.001
Sepsis/multisystem organ failure	8 (1.9%)	1 (0.02%)	7 (29%)	0.001
Stroke	3 (0.7%)	0 (0%)	3 (13%)	0.001
Reoperation for bleeding/tamponade	15 (3.5%)	12 (0.3%)	3 (13%)	0.001

Values expressed as median (interquartile range) or number (percent).
ICU = intensive care unit.

Table 4
Univariate association between pre and intraoperative variables and acute renal failure rate

Factor	Constant	Regression Coefficient	OR (95% CI)	p Value
Angiography on surgery day	−3.13	1.06	2.9 (1.24–6.75)	0.014
Contrast agent (ml/kg)	−3.92	0.68	1.97 (1.3–3.1)	0.002
Age (yrs)	−6.5	0.054	1.06 (1.01–1.1)	0.016
Ejection fraction (%)	−0.73	−0.04	0.96 (0.93–0.99)	0.027
Cardiopulmonary bypass duration (min)	−5.79	0.03	1.03 (1.02–1.04)	0.001
Lowest hematocrit on cardiopulmonary bypass	1.52	−0.17	0.85 (0.74–0.96)	0.011
Heart failure	−3.1	2.00	7.4 (2.8–19.8)	0.001
Redo operation	−2.93	1.14	3.12 (0.99–9.9)	0.052

(Figure 1). Baseline clinical features between the 2 cohorts with and without postoperative ARF are listed in Table 1. Compared with patients without postoperative ARF, those with postoperative ARF were older and women, with >4-fold higher history of previous heart failure and previous vascular surgery, but lower left ventricular ejection fraction and preoperative hematocrit. These patients were more likely to have received higher than the median dose of contrast agent. Patients with ARF were also more likely to have undergone surgery the same day as angiography and have combined coronary artery bypass grafting and valve surgery accounting for their longer cardiopulmonary bypass time (Table 2). The lowest hematocrit and lowest temperature on cardiopulmonary bypass were also lower in this cohort (Table 2).

Clinical events: As listed in Table 3, almost all clinical events were higher in patients with compared with those without postoperative ARF. Importantly, the 7 deaths and 3 strokes in these stable patients undergoing cardiac surgery occurred in those who had postoperative ARF. Duration of ventilator time was 6-fold longer and lengths of intensive care unit and hospital stays were 5- and 2-fold higher in this group of patients.

Univariate and multivariate analysis: Table 4 shows pre- and interoperative variables associated with postoperative ARF on univariate analysis. As listed, risk of ARF was higher in patients who underwent surgery on the same day as cardiac catheterization (Figure 2) and in those with increasing doses of contrast agents used (Figure 3). Furthermore, the effect of surgery on the same day as cardiac catheterization and high dose of contrast seemed to be additive. Thus, patients receiving a 4-ml/kg dose of contrast agent who underwent cardiac surgery on the same day as cardiac catheterization had a 50% incidence of ARF after cardiac surgery (Figure 3). Conversely, ARF occurred in <20% of patients who received the same amount of contrast, but who underwent surgery beyond 24 hours (Figure 3). Similarly, when contrast dose exceeded the median amount (1.36 ml/kg), surgery on the same day was associated with a 14.6% incidence of ARF (Figure 2). Conversely, this incidence was only 2.4% when the dose was less than the median amount and surgery was delayed beyond the day of cardiac catheterization (Figure 2).

Independent correlates of postoperative ARF are listed in Table 5. Duration of cardiopulmonary bypass was the strongest predictor of postoperative ARF, followed by lower left ventricular ejection fraction. Cardiac surgery on the same day as cardiac catheterization ranked third in terms of risk of ARF, with a 3-fold increase in risk, followed by older age (c index = 0.948, Hosmer-Lemeshow chi-square = 12.34, degrees of freedom = 8, p = 0.137).

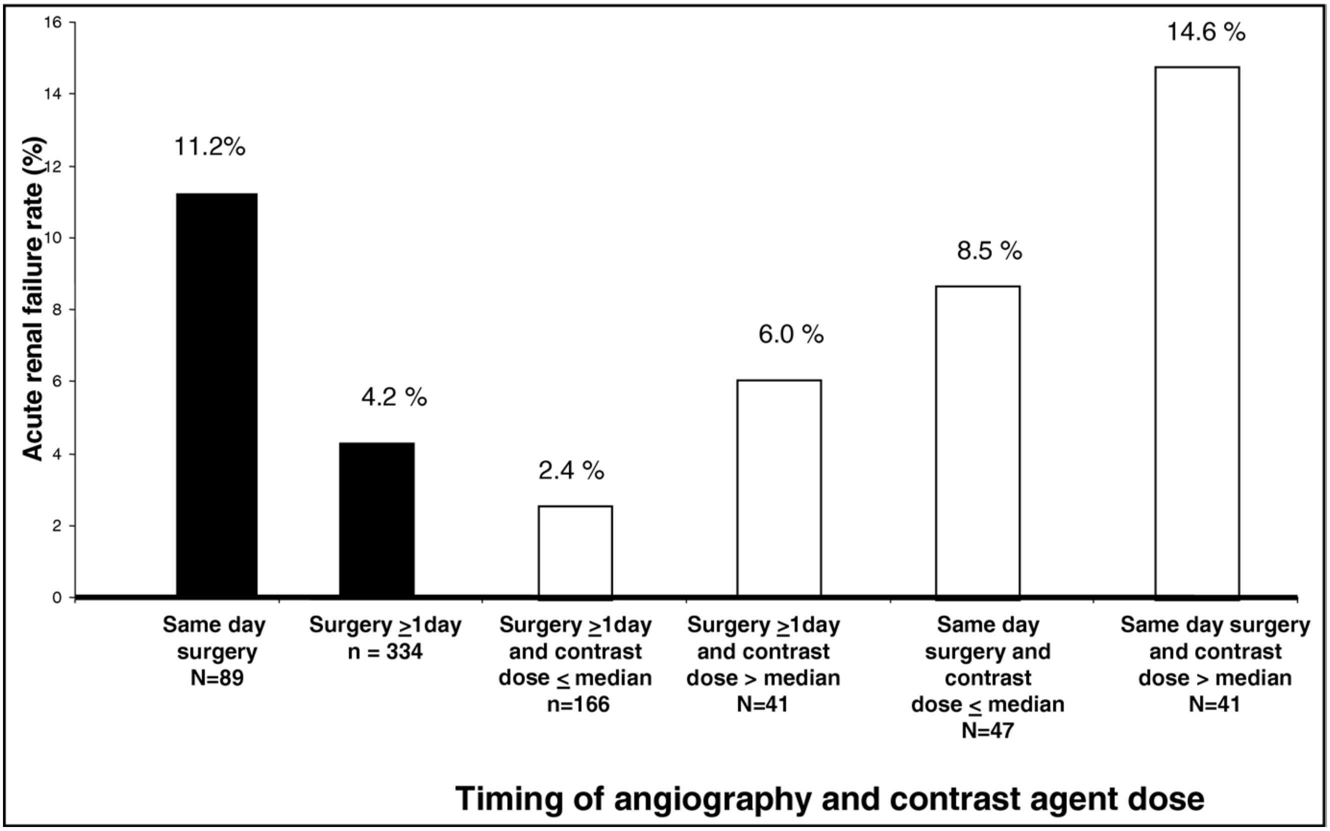

Figure 2. Incidence of postoperative acute renal failure stratified by the interval between the day of angiography and cardiac surgery (day 0 vs ≥1 day) and further by dose of contrast agent used (median or less and greater than median value).

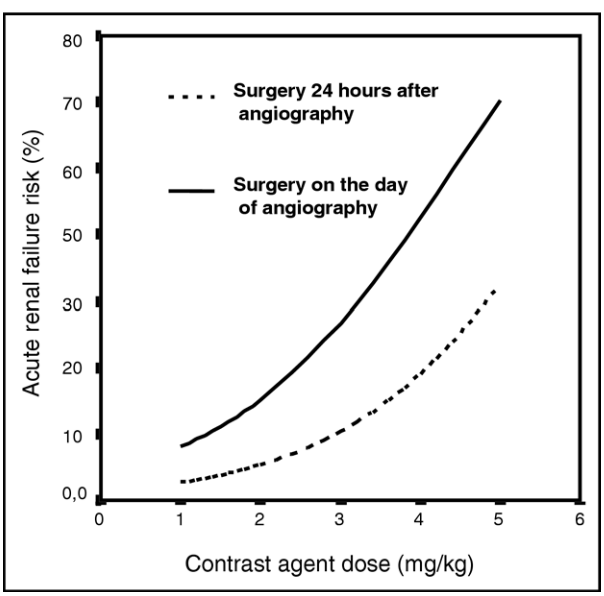

Figure 3. Amount of contrast media used during diagnostic angiography and incidence of acute renal failure after cardiac surgery categorized by interval between the day of angiography and cardiac surgery.

Although the point estimate suggested increased risk, dose of contrast agent (entered as both a continuous and categorical variable) was not independently associated with increased risk of this event when adjusted for other confounders. However, as suggested on univariate analysis, dose of contrast agent seemed to have an additive effect with timing of surgery in relation to cardiac catheterization, with greater risk when surgery was done on the same day as angiography in those receiving a higher than median dose of contrast (adjusted OR for same-day surgery and dose higher than median 4.2, 95% CI 1.2 to 14.2, p = 0.02).

Table 5
Independent correlates of acute renal failure after surgery

Variable	Chi-Square	OR	95% CI	p Value
Age (yrs)	4.2	1.06	1.003–1.11	0.040
Cardiopulmonary bypass duration (min)	25.9	1.03	1.02–1.04	0.001
Left ventricular ejection fraction	4.7	0.96	0.92–0.99	0.021
Surgery same day as cardiac catheterization	4.3	3.05	1.06–8.78	0.039
Contrast agent dose (ml/kg)	1.8	1.5	0.82–2.85	0.181
Interaction surgery (< 24 vs. ≥24 h) * (contrast agent >median vs ≤median dose)				0.132

C statistic for the model = 0.948, Hosmer-Lemeshow chi-square = 12.34, degrees of freedom = 8, p = 0.137.

Discussion

The major findings of our study were (1) cardiac surgery using cardiopulmonary bypass on the same day of cardiac catheterization was associated with an almost 3-fold increase in incidence of postoperative ARF; (2) this risk was minimized by waiting beyond the first 24 hours; (3) dose of contrast agent used was incrementally related to the incidence of ARF after cardiac surgery, with an incidence $\geq$30% at doses >4 ml/kg body weight; and (4) the influence of amount of contrast agent used on postoperative ARF was much higher when surgery was performed the same day as cardiac catheterization compared with a delay >24 hours. Finally, our data also confirmed findings of previous investigations that ARF after cardiac surgery was associated with higher morbidity and mortality and increased length of stay.[1,5–7]

Previous studies established clinical and surgical characteristics associated with increased risk of ARF after cardiac surgery. These factors included older age,[1,6–8] preoperative serum creatinine,[1,5–9] diabetes mellitus,[6–8] congestive heart failure,[1,7] emergency surgery,[5,7] concomitant valve surgery with coronary artery bypass grafting,[7] preoperative use of intra-aortic balloon pump,[5] cardiopulmonary bypass duration,[6] severe hemodilution during cardiopulmonary bypass as reflected by nadir hematocrit,[9] low oxygen delivery during cardiopulmonary bypass,[10] and low cardiac output syndrome in the postoperative course.[5,9] However, although most patients who underwent cardiac surgery underwent a preceding angiography, these studies consistently failed to account for the influence of the timing between previous angiography and cardiac surgery and amount of contrast used in this event. Our data provided important insight into this previously missing link between these 2 factors and ARF after cardiac surgery. Our findings supported the association of cardiac surgery performed on the same day as cardiac catheterization with significantly higher risk of postoperative ARF. Additionally, we found a dose–response relation between use of contrast during angiography and ARF after cardiac surgery that was particularly high when the operation was performed on the same day as cardiac catheterization.

We were aware of only 2 other studies that focused on the same issue. Brown et al[11] evaluated 226 consecutive patients undergoing valve surgery on the same day as their diagnostic angiography. Four patients developed transient renal failure (1.8%), 2 of whom required transient hemodialysis therapy. They concluded that in properly selected patients undergoing valve surgery, same-day coronary angiography was safe and had little impact on postoperative ARF. Several differences between this and our study may explain these disparate findings. First, the number of patients in the previous study was half that in our investigation. Second, they excluded patients with preoperative significant renal dysfunction (serum creatinine >1.8 mg/dl). Third, they limited catheterization to selective coronary angiography without left ventriculography, unlike our institution, where left ventriculography in 2 views is routinely performed in most patients, and aortic root angiography, abdominal aortogram, and diagnostic carotid angiograms, in some patients. Finally, unlike our study, they did not compare the incidence of postoperative ARF in patients undergoing valve surgery the same day as angiography with those in whom valve surgery was performed beyond 24 hours of their diagnostic procedure.

Recently, Del Duca et al[12] analyzed 649 patients undergoing cardiac surgery and found that cardiac catheterization performed within 5 days of the operation was independently associated with postoperative ARF (OR 1.82, 95% CI 1.17 to 2.84, $p = 0.010$). The risk of ARF was highest when the time between cardiac catheterization and surgery was 0 to 1 day (OR 1.70, 95% CI 0.91 to 3.20, $p = 0.098$), consistent with our result. However, unlike our study, they did not provide information about the influence of dose of contrast used on postoperative ARF.

Our study had important implications for clinical practice when taken together with the findings of these 2 studies.[11,12] Evidence supported preoperative assessment of all patients undergoing cardiac surgery for risk of ARF; consideration of such alternative strategy in high-risk patients as off-pump surgery, when appropriate[13]; 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 to minimize the risk of ARF. Use of *N*-acetylcysteine for prevention of ARF after cardiac surgery showed disappointing results,[14] and although infusion of nesiritide improved postoperative renal function,[15] validation of these findings in a large-scale randomized clinical trial is lacking, precluding recommendations regarding its use at present. In addition to these measures, our data supported 2 other interventions that could potentially decrease the incidence of ARF after cardiac surgery. First, elective cardiac surgeries may best be postponed beyond 24 hours of diagnostic angiography when feasible, but particularly in patients administered large doses of contrast agent. Second, to minimize the amount of contrast agent during preceding angiography, alternate imaging modalities not requiring the use of iodine-based contrast agents should be used to obtain information about ventricular function, valvular dysfunction, and aortic pathologic characteristics. Finally, routine use of strategies to prevent contrast-induced nephropathy during angiography that is continued in the postoperative period[16] may also have the potential to decrease ARF after early cardiac surgery after a diagnostic procedure.

Our findings should be viewed in light of some limitations. First, this was a retrospective observational study that should be regarding as hypothesis generating, precluding definitive inference regarding causation. Second, our results were best applicable to patients undergoing elective surgery, and extrapolation of our findings to patients undergoing emergent or emergent salvage procedures should be done with caution. Specifically, our data should not be used to decline early emergent surgery after diagnostic angiography in appropriate patients when indicated because of the fear of increased risk of postoperative ARF.

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