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Slightly Elevated Serum Creatinine Predicts Renal Failure Requiring Hemofiltration after Cardiac Surgery

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ABSTRACT

Background: Acute renal failure (ARF) after cardiac surgery is a serious adverse event that is associated with high perioperative mortality and prolonged hospitalization. The aim of our study was to evaluate pre- and intraoperative risk factors for the development of ARF requiring hemofiltration after cardiac surgery.

Methods: From February 2002 through February 2003, 913 patients underwent cardiac surgery at our institution. Seventy-three patients developed ARF (8.1%), 16 patients were excluded from the study because of chronic end-stage renal insufficiency. Patient characteristics and operative variables were analyzed. A multivariate logistic regression analysis was performed to determine risk factors for ARF.

Results: Patients who developed ARF were older ($P < .001$; odds ratio [OR], 1.084; 95% confidence interval [CI], 1.037-1.133) than patients who did not develop ARF. Furthermore, cardiopulmonary bypass duration ($P = .007$; OR, 1.013; 95% CI, 1.004-1.032) and emergent surgery ($P = .011$; OR, 6.667; CI, 1.538-28.571) were predictive for development of ARF. The strongest predictor for ARF was a preoperative creatinine level ≥2 mg/dL ($P < .001$; OR, 97.519; 95% CI, 22.363-425.252). Most interestingly, even moderately elevated preoperative creatinine levels (1.3-1.99 mg/dL) independently predict ARF after cardiac surgery ($P = .001$; OR, 3.838; 95% CI, 1.793-8.217).

Conclusion: Our data indicate that emergent surgery as well as advanced age and long duration of cardiopulmonary bypass independently predict ARF after cardiac surgery. Most importantly, even slightly impaired preoperative creatinine levels predict the development of ARF requiring hemofiltration after cardiac surgery.

INTRODUCTION

Acute renal failure (ARF) following cardiac surgery is a well-known complication that results in a marked increase in morbidity, mortality, and resource use [Chertow 1998]. Although some renal dysfunction is inevitably associated with cardiac surgery, renal reserve is usually sufficient to prevent clinically significant consequences [Ip-Yam 1994]. The incidence of ARF ranges from 1% through 30% [Mangos 1995, Chertow 1998, Suen 1998, Conlon 1999], and renal replacement therapy is necessary in up to 15% of patients [Suen 1998]. According to literature data, despite advances in dialytic technology as well as in intensive care management, mortality of patients with ARF requiring renal replacement therapy exceeds 60% [Chertow 1997, 1998]. Thus, assessing alterations of kidney function integrity in cardiac operation patients appears to be of high importance in developing strategies to avoid renal dysfunction in the postoperative period.

The aim of this retrospective analysis was to determine risk factors for the development of ARF requiring hemofiltration after cardiac surgery. We had already noted by clinical observation that patients with moderately elevated preoperative creatinine levels appear to be at higher risk for ARF. Therefore, we conducted a multivariate analysis with regard to different levels of preoperative renal impairment.

PATIENTS AND METHODS

Study Population

A consecutive series of 913 patients underwent cardiac surgery at our institution between February 2002 and February 2003. This sample includes all types of cardiac procedures, including rescue procedures. Four hundred and seventy-five patients underwent isolated coronary artery bypass grafting (CABG), 112 patients underwent isolated aortic valve replacement (AVR), and 61 patients isolated mitral valve surgery (MVR). Sixty patients underwent combined AVR and CABG; in 34 patients, MVR and CABG were performed simultaneously. Twenty-eight patients underwent atrial-septal defect closure, 56 patients underwent surgery of the thoracic aorta and one or more of 87 types of procedures (eg, transplantation, ventricular assist device, ventricular aneurysm treatment). We evaluated preoperative patient characteristics, operation-related variables, and postoperative outcome.

Preoperative patient characteristics that were analyzed as predictive factors included common cardiovascular risk factors such as arterial hypertension, hypercholesterolemia, diabetes mellitus, and family history of coronary artery disease as

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Table 1. Patient Characteristics

	Acute Renal Failure	No Acute Renal Failure	*P*
No. of patients	73	824	
Female sex, %	21.9	29.1	.191
Body mass index >30, %	6.9	14.5	.076
Family history of coronary artery disease, %	6.8	13.9	.087
Arterial hypertension, %	71.2	66.6	.422
Hypercholesterolemia, %	58.9	67.6	.130
Diabetes mellitus, %	21.9	15.9	.183
Peripheral vascular disease, %	17.8	12.5	.195
Previous cerebrovascular accident, %	11.0	5.0	.031
Chronic obstructive pulmonary disease, %	43.8	23.7	<.001
Arrhythmia, %	49.3	20.9	<.001
Previous cardiac intervention, %	35.6	15.8	<.001
Previous coronary artery bypass graft, %	16.4	3.3	<.001
Previous valve surgery, %	8.2	3.6	.056
Previous myocardial infarction, %	9.6	7.5	.526
Congestive heart failure, %	27.4	9.5	<.001
Previous resuscitation, %	4.1	1.6	.135
Preoperative ventilation, %	2.7	.7	.133
Left main disease, %	5.5	8.3	.505
Endocarditis, %	4.1	2.6	.474
Mitral insufficiency >II°, %	50.7	31.8	<.001
Tricuspid insufficiency >II°, %	17.8	5.2	<.001
Emergent surgery, %	13.7	4.4	<.001
Age, y	69.3 ± 10.1	63.7 ± 13.3	<.001
Preoperative creatinine, mg/dL	1.46 ± .61	1.09 ± .29	<.001
Preoperative creatinine ≥2, %	10.4	0.6	
Preoperative creatinine 1.3-<2, %	44.8	14.7	
Preoperative creatinine ≤1.3, %	44.8	84.7	<.001
Left ventricular ejection fraction, %	45.1 ± 17.2	56.2 ± 15.1	<.001

well as other comorbidities including peripheral vascular or cerebrovascular disease, pulmonary disease, and arrhythmias. Furthermore, the past medical history was documented including previous cerebrovascular accident, previous cardiac interventions, and history of myocardial infarction or congestive heart failure.

Operation-related variables included status and type of surgery and duration of aortic cross clamping and extracorporeal circulation as well as use of blood products. Perioperative mortality was defined as any death occurring within the first 30 days after surgery or within the time of hospitalization after surgery.

Management of Cardiopulmonary Bypass

The cardiopulmonary bypass (CPB) circuit consisted of a hollow fiber oxygenator (Capiox RX 25; Terumo, Eschborn, Germany), a roller pump (Stöckert S3; Stöckert GmbH, Munich, Germany), and a heat exchanger (Stöckert GmbH). Priming consisted of 500 mL gelatin (Gelofusin; B Braun Melsungen AG, Melsungen, Germany), 1100 to 1300 mL Ringer's lactate (B Braun Melsungen AG), 250 mL mannitol (Mannit 10%; Fresenius Kabi, Graz, Austria), 1 million IE aprotinine (Trasylol; Bayer AG, Vienna, Austria), and 4500 to 6000 IE heparin (Baxter Bio Science, Vienna, Austria). Flow during CPB was maintained at 2.5 L/min per m^2.

Anesthesia and Postoperative Care

General anesthesia was induced with 100 μg/kg midazolam, 0.5 mg fentanyl, and 0.6 mg/kg rocuroniumbromide. Anesthesia and analgesia were maintained with 5 μg/kg per minute remifentanil and 1 vol% sevoflurane. Prior to cannulation, 300 IU/kg heparin was administered in order to achieve an ACT (activated clotting time) of >480 seconds. During CPB, sevoflurane was administered to the CPB system. After venous decannulation heparin was antagonized with protaminesulphate until preoperative ACT was achieved. Hematocrit during CPB was kept above 24%; packed red blood cells were transfused if necessary.

Perfusion pressure during CPB was kept above 50 mm Hg with phenylephrine if necessary. Mean arterial pressure after CPB was kept above 60 mm Hg with volume (Gelofusin or Ringer's lactate) and phenylephrine as appropriate. Additionally, every patient received 3 μg/kg per minute dopamine. In case of low cardiac output, inotropic therapy was induced with intraaortic balloon counterpulsation, milrinone, and epinephrine or levosimendan. The indication for hemofiltration in case of ARF was set as follows: (1) oliguria < 50 mL/h, (2) creatinine clearance < 10 mL/min, (3) blood urea nitrogen > 100 mg/dL, and/or (4) serum potassium > 5 mmol/L.

Sixteen patients already suffered preoperatively from chronic renal failure requiring hemodialysis and were excluded from the study. Therefore, 897 patients remained for analysis.

We tried to evaluate independent risk factors for the development of ARF requiring hemofiltration based on pre- and intraoperative variables. Outcome data were not included in the analysis.

Statistical Analysis

Continuous data are given as mean ± SD. Categorical data are given as percentage of the total number. Comparison of 2 patient groups was performed for categorical variables with the chi-square, McNemar, or Fisher exact test as appropriate and for continuous variables with the Student *t* test after testing for normality of distribution. Multivariate analysis of risk factors influencing perioperative outcome was performed by logistic regression analysis. Entrance level into multivariate analysis was set to $P < .05$ in the univariate analysis. A *P*-value < .05 was considered significant. Statistical analysis was performed with SPSS 11.0 (SPSS Institute, Chicago, IL, USA).

RESULTS

Patient Characteristics

Preoperative patient characteristics are shown in Table 1. Of the study population, 73 patients (8.1%) developed ARF requiring hemofiltration. Patients who developed ARF

Table 2. Operative Variables

	Acute Renal Failure	No Acute Renal Failure	*P*
No. of patients	73	824	
Coronary artery bypass graft, %	65.7	65.4	.953
Unplanned coronary artery bypass graft, %	1.4	1.3	.980
No. of grafts ≥3, %	46.6	48.6	.732
Surgery without cardiopulmonary bypass, %	4.1	6.1	.496
Aortic valve surgery, %	30.1	21.2	.078
Mitral valve surgery, %	10.9	13.5	.544
Aortic surgery, %	6.8	6.1	.790
Use of blood products, %	49.3	32.5	.004
No. of grafts	2.2 ± 1.7	2.2 ± 1.8	.831
Cross-clamp time, min	95.0 ± 42.1	78.1 ± 38.1	.002
Cardiopulmonary bypass time, min	171.4 ± 73.9	131.9 ± 54.3	<.001
Perioperative mortality, %	28.7	1.8	<.001

requiring hemofiltration were older and had a higher incidence of impaired left ventricular function, chronic obstructive pulmonary disease, and arrhythmia than patients who did not develop ARF. Furthermore, the incidence of ARF was higher in patients undergoing emergent procedures or who were in a more severely compromised preoperative state. Additionally, a higher degree of valvular insufficiency was found in the patients who developed ARF.

As expected, patients with a preoperative serum creatinine level ≥2 mg/dL developed ARF more frequently. Interestingly, even patients with a slightly elevated creatinine, between 1.3 and <2 mg/dL, were more likely to develop ARF than patients with a serum creatinine ≤1.3 mg/dL. Both patient groups were comparable according to sex and cardiovascular risk factors such as arterial hypertension, hypercholesterolemia, and diabetes mellitus (Table 1).

Operative Variables

Aortic cross-clamp time as well as extracorporeal perfusion time were longer in patients who developed ARF (Table 2). Additionally, these patients received blood products more frequently. No differences, however, were found concerning the type of procedure (Table 2).

Multivariate Analysis of Predictors for ARF

Multivariate logistic regression analysis revealed that advanced age and emergent surgery as well as longer CPB times were independently predictive for the development of ARF (Table 3). The strongest predictor for ARF was a preoperative creatinine level ≥2 mg/dL (odds ratio [OR], 97.519). Most importantly, an even slightly elevated creatinine value of 1.3 to <2 mg/dL turned out to be an independent predictor for the development of ARF (OR, 3.838). Further variables with significant influence in univariate analysis failed to show an independent influence in multivariate analysis (Table 3).

Table 3. Logistic Regression Analysis for Acute Renal Failure

	Odds Ratio	95% Wald Confidence Limits	*P*
Emergent surgery	6.667	1.538-28.571	.011
Age	1.084	1.037-1.133	<.001
Preoperative creatinine ≥2	97.519	22.363-425.252	<.001
Preoperative creatinine 1.3-<2	3.838	1.793-8.217	.001
Previous cerebrovascular accident	2.345	0.707-7.780	.164
Chronic obstructive pulmonary disease	2.039	0.961-4.326	.063
Arrhythmia	1.768	0.791-3.954	.165
Previous cardiac intervention	1.192	0.387-3.668	.759
Previous coronary artery bypass graft	3.387	0.727-15.778	.120
Congestive heart failure	1.230	0.490-3.084	.659
Mitral insufficiency >II°	1.016	0.459-2.248	.969
Tricuspid insufficiency >II°	1.918	0.670-5.491	.225
Left ventricular ejection fraction	0.986	0.961-1.011	.258
Use of blood products	1.892	0.867-3.990	.094
Cross-clamp time	0.994	0.978-1.010	.429
Cardiopulmonary bypass time	1.013	1.004-1.023	.007

DISCUSSION

Based on multivariate logistic regression analysis, our data indicate that advanced age, longer CPB time, and emergent operation, as well as preoperatively elevated creatinine levels, are independent risk factors for the development of ARF after cardiac surgery. Most importantly, even slightly elevated creatinine levels preoperatively predict the development of ARF requiring hemofiltration.

ARF requiring hemofiltration is one of the most serious complications after cardiac surgery and has tremendous impact on mortality, intensive care stay, and resource utilization [Chertow 1998, Tuttle 2003]. In a study of more than 42,000 patients, Chertow and colleagues report an incidence of 1.1% for ARF requiring dialysis after cardiac surgery [Chertow 1997, 1998]. They reported a mortality rate of 63.7% in patients with ARF requiring dialysis compared with a mortality rate of 4.3% in those without ARF. Compared to this landmark study, the incidence for ARF was higher in our patient cohort (8.1%). Perioperative mortality, however, was considerably lower in our study population (28.7%) compared to that of Chertow and coworkers. This discrepancy might relate to a number of factors. First of all, the vast majority of patients in the above mentioned study underwent elective CABG. Furthermore, there were few patients at both extremes of age, and only <1% were women. Therefore, the 2 study populations are probably not comparable. However, these factors may account only for the relatively high number of cases of ARF requiring hemofiltration, but not for the comparably low mortality of our patients. The reason for the lower mortality might be the liberal use of hemofiltration at our institution. Unfortunately, the majority of studies on ARF after cardiac surgery do not clearly define the criteria for installation of hemofiltration [Ostermann 2000, Fischer 2002, Eriksen 2003, Grayson 2003, Tuttle 2003]. In the study of Provenchère and colleagues [2003], dialysis was used only in case of severe ARF with volume overload, hyperkalemia, or metabolic acidosis. In contrast to that study, which describes a 3.2% incidence of dialysis, hemofiltration is installed earlier at our institution, in line with the work of Bent et al, who recommend the early and intensive use of continuous hemofiltration for ARF after cardiac surgery [Bent 2001]. They report an in-hospital mortality of 40%, which was the lowest reported in the literature at the time of publication of that article. In contrast to their study [Bent 2001], perioperative mortality was even lower in our population.

A further difference of our study compared to the majority of the literature published so far lies in the different exclusion criteria. Most studies exclude from analysis patients with preoperatively impaired renal function [Chertow 1998, Albahrani 2003, Eriksen 2003, Grayson 2003]. In our study, however, we excluded only patients already on hemodialysis preoperatively. Furthermore, by classifying the preoperative creatinine levels into 3 classes, we were able to demonstrate that a creatinine value ≥2 mg/dL (177 mmol/L) was the strongest predictive factor for the development of ARF requiring hemofiltration after cardiac surgery, with an OR of 97.519. Even more interesting is the fact that a slightly elevated creatinine level between 1.3 and <2 mg/dL is the second strongest predictor for ARF, with an OR of 3.838. This finding probably indicates the relation between serum creatinine and creatinine clearance and implies that a reduction of 50% in creatinine clearance does not lead to a significant increase in serum creatinine [Vere 1964]. Patients with slightly elevated creatinine levels, as in our study population, are therefore likely to suffer from a significant renal disorder with reduction of creatinine clearance preoperatively. This finding goes along with the study of Fortescue and coworkers, which demonstrates a correlation between creatinine clearance and risk for ARF [Fortescue 2000]. In clinical routine, however, the preoperative evaluation of creatinine clearance is not applicable because the measurement of 24-hour urine excretion leads to prolonged preoperative hospitalization. An attractive, although still controversial, alternative might be the estimation of creatinine clearance by the Cockcroft-Gault formula [Cockcroft 1976] as performed in the study by Fortescue and coworkers [2000]. Even though we did not estimate the creatinine clearances in our study population, our results clearly show that patients with slightly elevated creatinine levels are especially at risk for postoperative ARF. If one keeps in mind that an "almost normal" creatinine value might be an early indication of significantly reduced renal function, the preoperative evaluation of creatinine clearance is therefore not absolutely necessary to determine patients at risk for postoperative ARF.

Another interesting finding of our analysis is that duration of CPB, but not aortic cross-clamping time, independently predicts the development of ARF requiring hemofiltration after cardiac surgery. CPB is characterized by a systemic inflammatory response syndrome [Edmunds 1998], albeit one that typically is moderate in terms of time and scope. Investigating the high prevalence of renal failure in sepsis and adult respiratory distress syndrome, which has been linked to systemic inflammatory response, a recent study by Rinder and colleagues has shown a correlation of components of the inflammatory response to post-CPB renal injury [Rinder 2003]. Furthermore, more pronounced kidney damage in patients with longer CPB times has been shown just recently [Boldt 2003]. An association with aortic cross-clamping time has not yet been shown, and our study is the first to demonstrate that only duration of CPB itself and not aortic cross-clamping time is predictive for the development of ARF.

Limitations of the Study

At our institution, cardiac surgery has been performed since 1969. However, documentation of the postoperative course according to the Society of Thoracic Surgeons database did not start until 2002. Therefore, only 897 cases were available for analysis. Thus, the statistical power of our study is much less than the power of large multicenter trials, and further variables potentially affecting ARF requiring hemofiltration might be mimicked.

Furthermore, a more distinct classification of preoperative creatinine levels could help to more precisely predict the development of ARF after cardiac surgery. Because of the limited number of patients, however, a more distinct classification of creatinine levels would have endangered the statistical validity of our analysis and therefore could not be performed.

Taking the above mentioned limitations into consideration, our study clearly demonstrates that in addition to advanced age and urgency of surgery, elevated preoperative creatinine levels are the strongest predictors for development of ARF requiring hemofiltration after cardiac surgery.

REFERENCES

Albahrani MJ, Swaminathan M, Phillips-Bute B. 2003. Postcardiac surgery complications: association of acute renal dysfunction and atrial fibrillation. Anesth Analg 96:637-43.

Bent P, Tan HK, Bellomo R, et al. 2001. Early and intensive continuous hemofiltration for severe renal failure after cardiac Surgery. Ann Thorac Surg 71:832-7.

Boldt J, Brenner T, Lehmann A, Suttner SW, Kumle B, Isgro F. 2003. Is kidney function altered by the duration of cardiopulmonary bypass? Ann Thorac Surg 75:906-12.

Chertow GM, Lazarus JM, Christiansen CL, et al. 1997. Preoperative renal risk stratification. Circulation 95:878-84.

Chertow GM, Levy EM, Hammermeister KE, Grover F, Daley J. 1998. Independent association between acute renal failure and mortality following cardiac surgery. Am J Med 104:343-8.

Cockcroft DW, Gault MH. 1976. Prediction of creatinine clearance from serum creatinine. Nephron 16:31-41.

Conlon PJ, Stafford-Smith M, White WD, et al. 1999. Acute renal failure following cardiac surgery. Nephrol Dial Transplant 14:1158-62.

Edmunds LJ. 1998. Inflammatory response to cardiopulmonary bypass. Ann Thorac Surg 66(suppl 5):S12-6.

Eriksen BO, Hoff KRS, Solberg S. 2003. Prediction of acute renal failure after cardiac surgery: retrospective cross-validation of a clinical algorithm. Nephrol Dial Transplant 18:77-81.

Fischer UM, Weissenberger WK, Warters RD, Geissler HJ, Allen SJ, Mehlhorn U. 2002. Impact of cardiopulmonary bypass management on postcardiac surgery renal function. Perfusion 17:401-6.

Fortescue EB, Bates DW, Chertow GM. 2000. Predicting acute renal failure after coronary bypass surgery: cross-validation of two risk-stratification algorithms. Kidney Int. 57:2594-602.

Grayson AD, Khater M, Jackson M, Fox MA. 2003. Valvular heart operation is an independent risk factor for acute renal failure. Ann Thorac Surg 75:1829-35.

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

Mangos GJ, Brown MA, Chan WY, Horton D, Trew P, Whitworth JA. 1995. Acute renal failure following cardiac surgery: incidence, outcomes, and risk factors. Aust NZ J Med 25:284-9.

Ostermann ME, Taube D, Morgan CJ, Evans TW. 2000. Acute renal failure following cardiopulmonary bypass: a changing picture. Intensive Care Med 26:565-71.

Provenchère S, Plantefeve G, Hufnagel G, et al. 2003. Renal dysfunction after cardiac surgery with normothermic bypass: incidence, risk factors, and effect on clinical outcome. Anesth Analg 96:1258-64.

Rinder CS, Fontes M, Mathew JP, Rinder HM, Smith BR. 2003. Multicenter study of perioperative ischemia research group. Neutrophil CD 11b upregulation during cardiopulmonary bypass is associated with postoperative renal injury. Ann Thorac Surg 75:899-905.

Suen WS, Mok CK, Chiu SW, et al. 1998. Risk factors for development of acute renal failure (ARF) requiring dialysis in patients undergoing cardiac surgery. Angiology 49:789-800.

Tuttle KR, Worrall NK, Dahlstrom LR, et al. 2003. Predictors of ARF after cardiac surgical procedures. Am J Kidney Dis 41:76-83.

Vere DW, Walduck A. 1964. Endogenous creatinine clearance and glomerular filtration rate. Lancet 17:1299.