Minimal Changes of Serum Creatinine Predict Prognosis in Patients after Cardiothoracic Surgery: A Prospective Cohort Study

ANDREA LASSNIGG,* DANIEL SCHMIDLIN,† MOHAMED MOUHIEDDINE,* LUCAS M. BACHMANN,‡ WILFRED DRUML,§ PETER BAUER,‖ and MICHAEL HIESMAYR*

**Department of Cardiothoracic and Vascular Anesthesia and Intensive Care Medicine, University Hospital of Vienna, Vienna, Austria; †Division of Anesthesia and Intensive Care, Hirslanden Klinik Im Park, Zurich, Switzerland; ‡Horten Centre, University Zurich, Zurich, Switzerland; §Acute Dialysis Unit, Department of Internal Medicine III, University Hospital of Vienna, Vienna, Austria; and ‖Department of Medical Statistics, University of Vienna, Vienna, Austria*

Abstract. Acute renal failure increases risk of death after cardiac surgery. However, it is not known whether more subtle changes in renal function might have an impact on outcome. Thus, the association between small serum creatinine changes after surgery and mortality, independent of other established perioperative risk indicators, was analyzed. In a prospective cohort study in 4118 patients who underwent cardiac and thoracic aortic surgery, the effect of changes in serum creatinine within 48 h postoperatively on 30-d mortality was analyzed. Cox regression was used to correct for various established demographic preoperative risk indicators, intraoperative parameters, and postoperative complications. In the 2441 patients in whom serum creatinine decreased, early mortality was 2.6% in contrast to 8.9% in patients with increased postoperative serum creatinine values. Patients with large decreases (ΔCrea < -0.3 mg/dl) showed a progressively increasing 30-d mortality (16 of 199 [8%]). Mortality was lowest (47 of 2195 [2.1%]) in patients in whom serum creatinine decreased to a maximum of -0.3 mg/dl; mortality increased to 6% in patients in whom serum creatinine remained unchanged or increased up to 0.5 mg/dl. Mortality (65 of 200 [32.5%]) was highest in patients in whom creatinine increased ≥ 0.5 mg/dl. For all groups, increases in mortality remained significant in multivariate analyses, including postoperative renal replacement therapy. After cardiac and thoracic aortic surgery, 30-d mortality was lowest in patients with a slight postoperative decrease in serum creatinine. Any even minimal increase or profound decrease of serum creatinine was associated with a substantial decrease in survival.

Acute renal failure (ARF) develops in 5 to 30% of patients who undergo cardiac surgery and is associated with a more complicated clinical course and with an excessive mortality of up to 80% (1–4). Actually, development of ARF was identified as the strongest risk factor for death with an odds ratio of 7.9 in patients who undergo cardiac surgery (1). Certainly, ARF presents an indicator for the severity and/or complicated course of disease; thus, perioperative patients with renal dysfunction are at a higher risk of dying. However, recently, is was shown convincingly that ARF acts as a risk factor for a grim prognosis independent of the severity of the underlying disease: that patients do not die with but rather from ARF (5,6).

Received October 27, 2003. Accepted March 13, 2004.

Correspondence to Dr. Andrea Lassnigg, Department of Cardiothoracic Anesthesia and Intensive Care Medicine, University Hospital of Vienna, Waehringer Guertel 18-20, A-1090 Vienna, Austria. Phone: +43-1-40400-4109; Fax: +43-1-40400-6404; E-mail andrea.lassnigg@univie.ac.at

1046-6673/1506-1597
Journal of the American Society of Nephrology

DOI: 10.1097/01.ASN.0000130340.93930.DD

Nevertheless, it remains unknown whether not only manifest ARF but also more subtle changes in postoperative renal function might predict outcome in surgical patients. In patients with contrast-induced nephropathy, renal impairment as defined by an increase of 25% to at least 2 mg/dl in serum creatinine was associated with an odds ratio of 5.5 for death (7). Thus, the aim of the present investigation was to determine the consequences of small changes in serum creatinine within 48 h after surgery on 30-d and late mortality, independent of other established perioperative risk indicators.

Materials and Methods

Between January 1 and December 31, 2001, 4374 patients underwent open-heart surgery at the Department of Cardiothoracic Surgery, University Hospital Vienna, Austria, as recorded in the prospectively collected database of the Department of Cardiothoracic and Vascular Anesthesia. For this analysis, we included adult patients (>18 yr) who were scheduled for cardiac surgery with cardiopulmonary bypass (CPB), coronary artery bypass grafting (CABG) with or without CBP, and thoracic aortic surgery with CPB. The following interventions were not included: transplant surgery, scheduled insertion of a cardiac assist device, operation on the descending aorta, thromboendarterectomy of the pulmonary arteries, and congenital heart disease. Exclu-

sion criteria were death within 48 h after the operation ($n = 86$), incomplete patient data ($n = 91$), and preexisting renal dysfunction requiring renal replacement therapy (RRT; $n = 46$) or a baseline serum creatinine >4 mg/dl ($n = 33$).

Surgery on CPB was performed according to institutional standards: crystalloid priming with 20 g of mannitol and 1,000,000 KIU of aprotinin added, membrane oxygenator, intermittent ante- and retrograde blood cardioplegia, and normothermic or hypothermic CPB, depending on indications and surgical preferences. The primary outcome was mortality after the operation and its relation to the difference between baseline serum creatinine before surgery and the maximal serum creatinine values (ΔCrea) within 48 h after surgery. Mortality was separately evaluated for the early phase within 30 d of surgery and for all patients who survived 30 d after surgery. The relation of the extent of early postoperative ΔCrea and the need for RRT during the entire postoperative course was also analyzed. RRT was included as an independent risk indicator in the multivariate model. In addition, the number of patients who had ARF at any postoperative time point and received RRT was analyzed in a patient flow diagram.

Demographic Data, Data Acquisition of Preoperative Risk Indicators, and Follow up

Preoperative patient data were collected prospectively at the time of premedication. Specifically, parameters that represented established risk indicators for mortality after cardiac and thoracic aortic surgery, according to the logistic EuroSCORE (Appendix 1) (8,9), were recorded. Additional risk indicators were weight, stable angina, congestive heart failure, diabetes, hypertension with appropriate therapy <140/90 mmHg, poorly controlled hypertension >140/90 mmHg, nicotine abuse, and therapy with diuretics and/or angiotensin-converting enzyme inhibitors.

At the end of the follow-up period (December 31, 2001), the prospectively collected data from the clinical database were combined with the database from the central laboratory and the hospital central database, the latter holding information from the Federal Austrian Statistical Office on any patient's death in Austria. We had a complete follow-up from all included patients.

Intraoperative Parameters and Complications

For the procedure itself, urgent surgery, durations of anesthesia and surgery, CPB and aortic cross-clamp time, deep hypothermic cardiac arrest time, and various fluid components that were given to the patients and urinary output were entered into the analysis. The need for inotropic support, complications (*e.g.*, unplanned insertion of an intra-aortic balloon pump, unscheduled insertion of an assist device [left ventricular assist device or extracorporeal membrane oxygenation]), and emergency resternotomies were also recorded. In cases of scheduled reoperation (*e.g.*, a second aortic valve replacement) the most recent procedure was taken into account. We also recorded the need for postoperative renal replacement therapy. In total, we included 31 variables as potential confounders.

Risk Indicators and Outcome Variables

Baseline creatinine value was defined as the value recorded just before surgery. In case of a reoperation within 14 d after the first intervention, the value before the first operation was used. Maximal serum creatinine was the highest available value within 48 h after the patient was admitted to the postoperative intensive care unit (ICU). Serum creatinine values were taken after admission to the ICU and repeated at least once every 24 h. On the basis of these values, the difference between the highest serum creatinine value and the baseline value (ΔCrea) was calculated for each patient. Serum creatinine concentration was measured using the Jaffe method on a Hitachi 747 analyzer (Roche, Basel, Switzerland). According to the manufacturer, its intraseries precision of creatinine measurement was 0.7%; the interseries precision was 2.3% with human serum specimens. Our hospital laboratory had an interassay coefficient of variation of 1.5% at a concentration of 0.9 mg/dl serum creatinine.

Statistical Analyses

We performed univariate and multivariate Cox regression analyses (PROC PHREG SAS 8.01, Cary, NC) censoring for stay in hospital after December 31, 2001. A separate analysis for 30-d mortality and late mortality was performed. The analysis of late mortality included all patients who survived day 30 after surgery.

In the first step, we determined the relation between the changes in serum creatinine and mortality, when divided by steps of 0.1 mg/dl. The U-shaped profile was assessed by relating mortality to changes in serum creatinine expressed as a polynomial from the first to the third orders. The changes in serum creatinine were divided into four groups: (*1*) large decreases, group Δ−− (∞, −0.3) mg/dl; (*2*) small decreases, group Δ− (−0.3, 0) mg/dl served as the reference group; (*3*) small increases, group Δ+ (0, 0.5) mg/dl; and (*4*) large increases, group Δ++ (0.5, ∞) mg/dl.

In the second step, the univariate analysis, we analyzed 31 pre-, intra-, and postoperative variables and their effect on mortality. In the third step, all 26 risk indicators that were significant ($P < 0.01$) in the univariate analysis were analyzed with the four groups of serum creatinine change to identify those risk indicators that contribute to mortality, independent of the serum creatinine changes. In the final, fourth step, the multivariate analysis, we included the four groups of serum creatinine change and only those 20 risk indicators that were significantly related to mortality independent of serum creatinine changes in step 3. In addition, we checked whether forcing baseline creatinine up to the third order in the final model modifies the results for the U-shaped profile. Late mortality was analyzed with the same ΔCrea groups with steps 2 through 4. For comparison between individual ΔCrea groups, *t* test and χ^2 test were used (SAS 8.01). Data are presented as hazard ratio with 95% confidence intervals (CI).

Results

A total of 4118 patients (1446 women) with a mean age of 64 years (range, 18 to 92) were investigated (Table 1). Mean follow-up period was 28 mo (2 d to 61 mo; SD, 18 mo).

Change in Serum Creatinine/30-D Mortality

Overall, the early, 30-d mortality was 5.2% (212 of 4118 patients). The relation of mortality to change in serum creatinine is U-shaped (Figure 1) as confirmed by polynomial regression ($P < 0.0001$) of the second order.

The risk of death was lowest when serum creatinine fell ~20% below the baseline (group Δ−; Figure 1). Fifty-four percent of all patients are in this group with ΔCrea between −0.3 and 0 mg/dl (Figure 1). Patients with increases and large decreases in ΔCrea showed a progressively increasing 30-d mortality. Thirty-day mortality of the patients with ΔCrea values of −0.3 to −0.2 mg/dl was significantly different from that of the patients with ΔCrea of ∞ to −0.3 mg/dl (1.2 *versus* 8%). On the basis of this observation, decreases and increases were separated into four groups with cutoff values of −0.3 and

Table 1. Frequency of demographics and surgical characteristics according to 30-d mortality[a]

	N	Alive	Dead
Demographics			
no. of patients (*n*)		3906	212
male/female (*n*)		2548/1358	124/88
age (yr)		64 ± 13	69 ± 12
BMI		26.5 ± 4	25.7 ± 4
EuroSCORE		5.5 ± 3.1	8.4 ± 3.4
logistic EuroSCORE		7.1 ± 8.2	15.4 ± 14.1
Preoperative risk indicators			
LVEF <50%	2024	1964	60 (3%)
LVEF <30%	272	230	42 (15%)
angina stable	1287	1244	43 (3%)
congestive heart failure	656	589	67 (10%)
cardiogenic shock	98	78	20 (20%)
PAP_{syst} >60 mmHg	195	173	22 (11%)
diabetes	865	805	60 (7%)
COPD	457	420	37 (8%)
extracardiac arteriopathy	246	223	23 (9%)
Medication			
diuretics	1342	1241	101 (8%)
infection	47	39	8 (17%)
Surgical characteristics			
anesthesia (min)		315 ± 79	380 ± 138
surgery (min)		224 ± 72	284 ± 132
CPB (min)		100 ± 60	139 ± 87
aortic cross-clamp (min)		62 ± 38	73 ± 47
urgent surgery	477	420	57 (12%)
emergent surgery	227	198	29 (13%)
CABG-CPB	1608	1546	62 (4%)
off pump CABG	415	407	8 (2%)
combined procedure	590	537	53 (9%)
valve surgery	1296	1222	74 (6%)
TAA surgery	209	194	15 (7%)
reoperation	382	345	37 (19%)
revision ≤48 h	129	109	20 (16%)
revision >48 h	304	273	31 (10%)
IABP after CPB	115	84	31 (27%)
inotropics after CPB	1478	1338	140 (10%)

[a] Values are expressed as mean ± SD: BMI, body mass index; EuroSCORE, European system for cardiac operative risk evaluation; LVEF, left ventricular ejection fraction; PAP_{syst}, systolic pulmonary artery pressure; COPD, chronic obstructive pulmonary disease; CRF, chronic renal failure; CPB, cardiopulmonary bypass; CABG, coronary artery bypass grafting; TAA, thoracic aortic; IABP, intra-aortic balloon pump.

0.5 mg/dl ΔCrea, a frequent threshold for acute renal injury (10), for the multivariate analysis (Figure 2). In the univariate analysis, we found that the other three ΔCrea groups had significant increases in mortality risk as compared with group Δ− and that 26 additional variables were related to mortality. In step 3, after adjustment for ΔCrea groups, the number of independent risk indicators for mortality decreased to 20 and finally to 6 significant indicators after multivariate analysis (Table 2).

By repeating the analysis in the 3381 patient with a baseline serum creatinine <1.3 mg/dl, we were able to confirm our initial results for all patients with an increased ΔCrea. The hazard ratio (HR) for group Δ++ increased (as compared with the values for all patients; Table 2) to 7.09 (95% CI, 4.3 to 11.7) and for group Δ+ to 2.04 (95% CI, 1.32 to 3.16).

Demographic characteristic and perioperative risk indicators in group Δ−− were different from the adjacent group Δ− for five of six risk indicators that were significantly related to 30-d mortality in the multivariate analysis. Patients in group Δ−− had the highest preoperative serum creatinine concentrations (1.67 *versus* 1.11 mg/dl in group Δ−; $P < 0.0001$) and a higher predicted mortality (logistic EuroSCORE, 11.7 *versus*

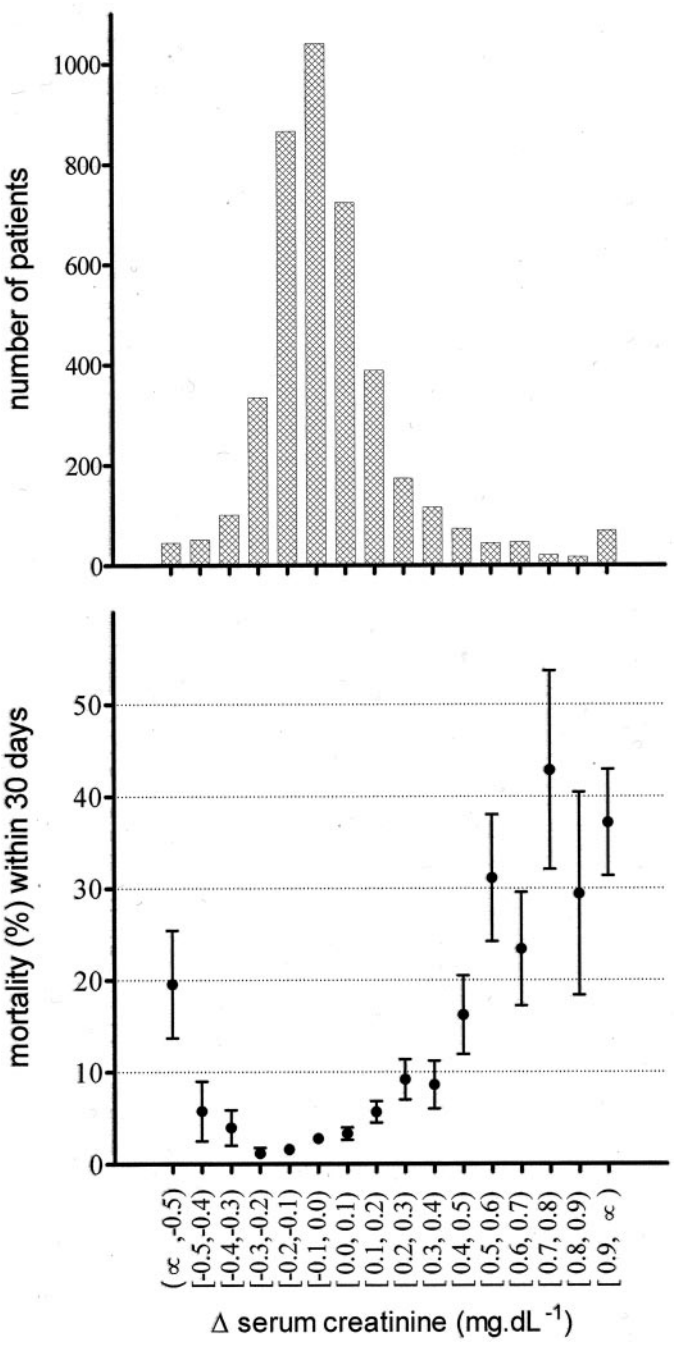

Figure 1. Thirty-day mortality and change in serum creatinine (ΔCrea) within 48 h after cardiac surgery. Distribution of ΔCrea (top) and mortality rates calculated for intervals of ΔCrea 0.1 mg/dl. Data are presented as mean ± SEM.

6.5 in group Δ−; $P < 0.0001$). Preoperative diuretic treatment was also significantly more common (49 *versus* 30% in group Δ−; $P < 0.0001$), a higher rate of an intra-aortic balloon pumps were inserted (4 *versus* 1.3% in group Δ−; $P < 0.05$), and the need for inotropic support was 47 *versus* 31% in group Δ− ($P < 0.0001$). Group Δ−− had 50% more packed red blood cells transfused ($P < 0.0001$), and in the multivariate analysis, which contained all patients, mortality remained significantly correlated to the use of packed red blood cells.

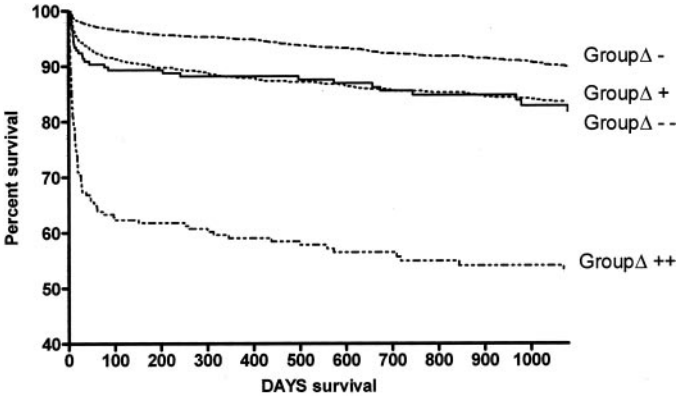

Figure 2. Kaplan-Meier plot for the four ΔCrea groups.

After forcing preoperative serum creatinine up to the third order into the final model, the hazard ratio associated with group Δ−− remained always significant and did not decrease by >10%. A total of 236 (5.7%) patients received postoperative RRT, 60 of them in group Δ++ and 176 in the other groups (Figure 3).

Late Mortality

At the end of the follow-up period (mean, 28 mo; SD, 18 mo; range, 2 d to 61 mo), 3549 (86%) patients were still alive. A total of 357 patients died after 30 d, 26 in group Δ++ and 331 in the other groups (NS). The ΔCrea groups as defined in the 30-d mortality analysis were not significantly associated with mortality after 30 d. Using Cox regression analysis, 10 risk indicators significantly increased the risk for late death independent of other variables (Table 3).

Discussion

In this prospective cohort study, we found that patients with a mild fall in serum creatinine of −0.1 to −0.3 mg/dl within 48 h after surgery had the lowest mortality rate of 2.1%. Any deviation from this large group, representing more than half of all patients, was accompanied by a substantial increase in the hazard of death. A small increase in serum creatinine (0 to 0.5 mg/dl) was already associated with a nearly threefold increase in 30-d mortality, whereas a larger increase of ≥0.5 mg/dl, typically defined as acute renal injury (10–12), was associated with a >18-fold increase in 30-d mortality. This relation is maintained after including multiple risk indicators in multivariate analysis. Surprising is that a group of patients with a larger postoperative fall in serum creatinine had an elevated risk of dying. In contrast to early mortality, late mortality was not related to early postoperative changes in serum creatinine: if a patient survived the immediate postoperative course, then alterations of perioperative serum creatinine had no further effect on long-term prognosis.

During cardiac surgery, a slight fall in serum creatinine is the expected reaction to hemodilution, volume therapy, and blood loss (13). A relevant hemodilution is seen in patients who undergo CPB. In the case of an increased postoperative serum creatinine, this hemodilution must be counteracted by a

Table 2. Thirty-day mortality[a]

Variable	% *N*	Mean (SD)	Univariate Analysis		Adjusted for Crea Groups		Multivariate Analysis	
			HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Group Δ−−	5		3.95 (2.23–6.96)	0.0001	(−)		2.27 (1.28–4.03)	0.0052
Group Δ−	54		1		1		1	
Group Δ+	36		2.77 (1.94–3.95)	0.0001	(−)		1.92 (1.34–2.77)	0.0004
Group Δ++	5		18.64 (12.8–27.13)	0.0001	(−)		5.76 (3.86–8.61)	0.0001
Risk indicators								
BL serum creatinine (mg/dl)			2.78 (2.22–3.49)	0.0001	1.82 (1.42–2.33)	0.0001	NS	
Weight (pro 10 kg)		77 (14)	0.84 (0.76–0.92)	0.0003	0.81 (0.73–0.89)	0.0001	NS	
EuroSCORE[b] (mortality %)		7.6 (8.8)	1.05 (1.04–1.06)	0.0001	1.04 (1.03–1.05)	0.0001	NS	
log (EuroScore)			2.45 (2.12–2.82)	0.0001	2.07 (1.79–2.4)	0.0001	1.62 (1.4–1.89)	0.0001
angina stable	31		0.55 (0.4–0.77)	0.0005	NS		NS	
congestive heart failure	16		2.51 (1.88–3.36)	0.0001	1.89 (1.41–2.54)	0.0001	NS	
diabetes	21		1.50 (1.11–2.02)	0.0083	NS		NS	
hypertension (<140/90 mmHg)	42		0.69 (0.52–0.91)	0.0098	NS		NS	
hypertension (>140/90 mmHg)	10		NS		NS		NS	
smoker	14		0.42 (0.25–0.73)	0.0018	NS		NS	
Medication								
diuretics	33		1.92 (1.47–2.51)	0.0001	1.73 (1.32–2.27)	0.0001	1.57 (1.19–2.06)	0.0014
ACE inhibitors	43		NS		NS		NS	
Perioperative data								
anesthesia (h)		319 (84)	1.44 (1.35–1.53)	0.0001	1.27 (1.19–1.35)	0.0001	NS	
surgery (h)		227 (77)	1.47 (1.38–1.57)	0.0001	1.28 (1.2–1.37)	0.0001	NS	
CPB (h)		115 (54)	1.48 (1.37–1.61)	0.0001	1.33 (1.21–1.46)	0.0001	NS	
aortic cross-clamp (h)		72 (32)	1.51 (1.24–1.83)	0.0001	1.32 (1.1–1.58)	0.0033	NS	
DHCA (h)		30 (16)	3.39 (1.34–8.58)	0.0099	NS		NS	
urgent surgery	12		2.92 (2.16–3.96)	0.0001	1.99 (1.46–2.72)	0.0001	NS	
reoperation <1 mo	1.1		NS		NS		NS	
resternotomy ≤48 h	3.1		3.39 (2.14–5.38)	0.0001	1.95 (1.22–3.12)	0.0051	NS	
resternotomy >48 h	7.4		2.19 (1.49–3.20)	0.0001	NS		NS	
IABP after CPB	2.8		6.95 (4.75–10.18)	0.0001	3.78 (2.55–5.59)	0.0001	1.75 (1.17–2.63)	0.0068
inotropics after CPB	36		3.62 (2.73–4.81)	0.0001	2.74 (2.05–3.66)	0.0001	1.55 (1.15–2.10)	0.0044
urinary output (L)		0.7 (0.5)	NS		NS		NS	
crystalloids (L)		2.3 (1.1)	NS		NS		NS	
colloids (L)		0.6 (0.4)	1.79 (1.3–2.46)	0.0003	1.61 (1.19–2.17)	0.0021	NS	
EC (units)		1.5 (2)	1.27 (1.23–1.3)	0.0001	1.19 (1.15–1.22)	0.0001	1.10 (1.07–1.14)	0.0001
FFP (units)		0.7 (2)	1.19 (1.16–1.22)	0.0001	1.14 (1.11–1.17)	0.0001	NS	
platelets (units)		0.1 (0.3)	3.01 (2.55–3.55)	0.0001	1.91 (1.60–2.28)	0.0001	NS	
assist device	0.4		23.4 (12.38–44.24)	0.0001	9.78 (5.12–18.7)	0.0001	NS	
RRT	5.7		12.61 (9.57–16.61)	0.0001	6.95 (5.1–9.48)	0.0001	4.77 (3.53–6.45)	0.0001

[a] HR, hazard ratios; CI, confidence interval; BL, baseline; ACE, angiotensin-converting enzyme; DHCA, deep hypothermic cardiac arrest; EC, erythrocyte concentrate suspension; FFP, fresh frozen plasma; RRT, postoperative renal replacement therapy.

[b] Mortality according to the logistic model.

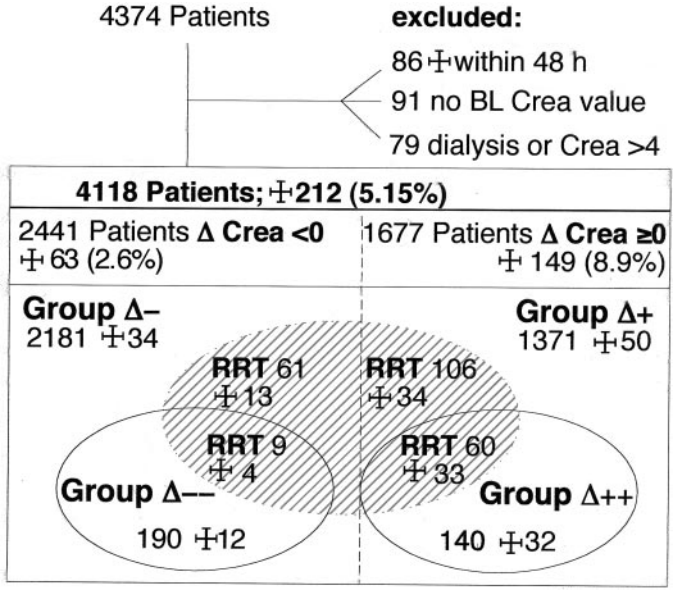

Figure 3. Group description and 30-d mortality. BL, baseline; RRT, renal replacement therapy. The four groups represent ΔCrea as follows: group Δ−− (∞, −0.3) mg/dl, $n = 199$; group Δ− (−0.3, 0) mg/dl, $n = 2242$; group Δ+ (0, 0.5) mg/dl, $n = 1477$; and group Δ++ (0.5, ∞) mg/dl, $n = 200$.

phase of reduced renal creatinine clearance or increased creatinine formation or both (12). Whether this reduced renal elimination is a consequence of decreased renal perfusion including perioperative fluid restriction, hypotension, compromised cardiac output, extreme hemodilution on CPB (13), and/or treatment with diuretics (11,14) is difficult to assess.

An unexpected finding was the significant increase in mortality in the group with the most pronounced fall in postoperative serum creatinine of < -0.3 mg/dl. However, in this group, patients had higher preoperative serum creatinine and more preoperative comorbidities, preoperative diuretic treatment was more common, requirement for the use of an intraaortic balloon pump was more often, and the need for inotropic support was increased. Most important, in this group, volume replacement and or blood transfusions were much higher. Thus, besides the initially impaired renal function, these patients had a more complicated course of disease in which serum creatinine was more diluted by higher volume replacement and blood transfusions.

After multivariate analysis, the hazard ratio associated with group Δ−− decreased by nearly one half but remained significant. Thus, the 20 standard linear predictors as included in the stepwise proportional hazard model are not able to explain completely the U-shaped relationship between mortality and ΔCrea.

There is ample evidence that the evolution of an ARF confers an excessive risk of a grim prognosis. Certainly, ARF may serve as an indicator of the severity of disease and/or associated complications. Nevertheless, several studies have shown that ARF exerts a profound impact on prognosis independent of the severity of the condition (1,7). Also, the results of the multivariate mortality analysis in our cohort suggest that the high mortality rate in patients with acute renal injury cannot by explained by the underlying conditions alone. Renal injury itself further increases the risk of developing severe nonrenal complications that may lead to death (15,16). However, the data presented suggest that also small changes in serum creatinine without evolution of an acutely uremic condition can serve as a predictor of a poor prognosis, probably representing a sensitive marker of microcirculatory compromise.

Our observation period was 48 h to include the typical maximum increase in serum creatinine of the early postoperative period. Stafford Smith (17) found that serum creatinine typically peaks on the second day after CABG with CPB and in most cases returns to baseline by the fourth and fifth days.

We found that RRT after surgery is not limited to patients who had an early initial increase in serum creatinine, as only 25% of the patients who needed RRT had an early increase ≥0.5 mg/dl. A variety of postoperative events, which may occur at any time point later, (*e.g.*, sepsis, cardiopulmonary resuscitation), may cause ARF that required RRT. Elevated ΔCrea seems to be an indicator for risk of death independent of the need for RRT, suggesting that even mild changes in renal function have an effect on outcome. Our observation period ended after 48 h, so we did not evaluate the pattern of postoperative complications except the need for reoperation and the incidence of RRT representing those patients with the most severe impairment of renal function any time after the operation, *i.e.*, patients with manifest ARF requiring extracorporeal therapy.

In contrast to the pronounced effect on short-term survival, long-term outcome is not influenced by perioperative alterations in serum creatinine but rather by the extent and pattern of preexisting comorbidities. Thus, any increase but also a profound decrease in serum creatinine is harmful and augments the risk of perioperative death after cardiothoracic surgery. However, patients who survived the first 30 d had sufficient recovery of renal (and other organ) functions and regained the same long-term prognosis as patients without a temporary impaired renal function. Another reason for the "diluted" effect of ΔCrea on later mortality is that the high-risk patients usually die early within the first 30 d, and this leads to a remaining population with a lower risk profile.

Admittedly, the choice of the four Δ groups may seem arbitrary. Looking at the data of the patients with the largest decrease in serum creatinine (199 patients with > -0.3 mg/dl) makes this arbitrariness crucial: this group causes the U-shaped curve with its high mortality. The huge mortality difference between these patients (8%) and the adjacent group (1.2%), which represents 335 patients with a fall in serum creatinine of only 0.1 mg/dl less (−0.2 to −0.3 mg/dl), suggests the separation of a group with a large decrease in serum creatinine (group Δ−−). It is also noticeable that the risk increases

Table 3. Late mortality

Variable	Univariate Analysis		Adjusted for Crea-Groups		Multivariate Analysis	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Group Δ−−	NS		(−)		NS	
Group Δ−	1		1		1	
Group Δ+	1.56 (1.25–1.94)	0.0001	(−)		NS	
Group Δ++	2.89 (1.92–4.34)	0.0001	(−)		NS	
Risk indicators						
BL serum creatinine (mg/dl)	2.45 (2.01–2.99)	0.0001	2.45 (1.98–3.04)	0.0001	1.54 (1.19–1.99)	0.001
weight (pro 10 kg)	0.81 (0.75–0.87)	0.0001	0.8 (0.74–0.86)	0.0001	0.87 (0.8–0.95)	0.0009
EuroSCORE[a] (mortality %)	1.05 (1.04–1.05)	0.0001	1.05 (1.04–1.05)	0.0001	NS	
log (EuroScore)	2.07 (1.86–2.31)	0.0001	2.02 (1.81–2.26)	0.0001	1.69 (1.48–1.92)	0.0001
angina stable	0.72 (0.57–0.91)	0.0065	NS		NS	
congestive heart failure	2.11 (1.67–2.66)	0.0001	2.00 (1.58–2.52)	0.0001	NS	
diabetes	1.59 (1.26–2)	0.0001	1.55 (1.23–1.95)	0.0002	1.59 (1.25–2.01)	0.0002
hypertension (<140/90 mmHg)	NS		NS		NS	
hypertension (>140/90 mmHg)	NS		NS		NS	
smoker	NS		NS		NS	
Medication						
diuretics	1.93 (1.57–2.38)	0.0001	1.90 (1.54–2.33)	0.0001	1.28 (1.03–1.6)	0.0288
ACE inhibitors	NS		NS		NS	
Perioperative data						
anesthesia (h)	1.14 (1.06–1.22)	0.0003	1.11 (1.03–1.2)	0.0028	1.13 (1.04–1.22)	0.0035
surgery (h)	1.17 (1.08–1.27)	0.0001	1.14 (1.05–1.23)	0.0011	NS	
CPB (min)	1.13 (1.03–1.24)	0.0086	NS		NS	
aortic cross-clamp (h)	NS		NS		NS	
DHCA (h)	NS		NS		NS	
urgent surgery	NS		NS		NS	
reoperation <1 mo	NS		NS		NS	
resternotomy ≤48 h	2.51 (1.63–3.86)	0.0001	2.14 (1.38–3.31)	0.0007	1.85 (1.18–2.89)	0.0071
resternotomy >48 h	2.72 (2.01–3.68)	0.0001	2.39 (1.76–3.25)	0.0001	2.01 (1.45–2.77)	0.0001
IABP after CPB	3.53 (2.31–5.39)	0.0001	3.05 (1.99–4.68)	0.0001	1.61 (1.03–2.52)	0.0388
inotropics after CPB	2.29 (1.86–2.83)	0.0001	2.15 (1.74–2.66)	0.0001	1.34 (1.06–1.68)	0.0138
urinary output (L)	0.62 (0.47–0.81)	0.0005	0.66 (0.5–0.86)	0.0023	0.57 (0.43–0.77)	0.0002
crystalloids (L)	NS		NS		NS	
colloids (L)	NS		NS		NS	
blood (units)	1.18 (1.14–1.22)	0.0001	1.16 (1.12–1.21)	0.0001	NS	
FFP (units)	1.12 (1.08–1.16)	0.0001	1.09 (1.05–1.14)	0.0001	NS	
platelets (units)	1.92 (1.53–2.40)	0.0001	1.7 (1.35–2.14)	0.0001	NS	
assist device	7.42 (1.85–29.74)	0.0047	NS		NS	
RRT	3.69 (2.73–5)	0.0001	3.16 (2.31–4.33)	0.0001	2.36 (1.71–3.27)	0.0001

[a] Mortality according to the logistic model.

progressively for larger decrease in serum creatinine (Figure 1). We therefore do not believe that the presented selection of the four risk groups is the cause for the U-shaped mortality profile.

A general caveat in interpretation of study results based on large databases is that perhaps not all of the important outcome variables are either known or included in the multivariate analysis. The selected parameters were those cited in important experimental or clinical studies regarding renal injury mechanisms and/or outcome after cardiac surgery. However, including too many variables relative to the number of events may yield results that are potentially inaccurate (18) in studies that have fewer than 10 events per variable analyzed. In our study, the multivariate analysis for

30-d mortality contained 20 variables and 212 events; the multivariate analysis for late mortality contained 18 variables and 357 events. Logistic EuroSCORE contains a selection of parameters with a proven impact on early mortality in cardiac surgical patients and a properly published accuracy (8,9). Its inclusion as an entity helped restrain the number of variables necessary.

In conclusion, we found that even a minimal increase (but surprisingly also a profound decrease) in serum creatinine is associated with an augmented mortality. Our finding that even these subtle changes in renal function very early in the postoperative period seriously effect patients' outcome certainly has important clinical implications. In any patient in whom such small alterations of renal function—which usually have been perceived as fluctuations within the "normal range"—become evident, the clinician must be alerted and she or he must avoid any cause for further renal function impairment (11,14,19). It is this very early postoperative period when the prognosis of the patient is defined.

Appendix: multifactorial risk indices for the prediction of outcome after cardiac surgery[a]

EuroSCORE		Maximum Points
Age (yr)		
>60	1	
>64	2	
>69	3	
>74	4	
>79	5	
>84	6	
>89	7	7
Female gender	1	1
Emergency operation (same day)	2	2
Chronic pulmonary disease		
long-term use of either bronchodilators or steroids	1	1
Extracardiac arteriopathy		
claudication or carotid occlusion or stenosis ≥50% or previous or planned surgery of abdominal aorta, limb arteries or carotis	2	2
Neurological dysfunction (severely affecting ambulation or day-to-day function)	2	2
Previous cardiac surgery (requiring opening of the pericardium)	3	3
Serum creatinine >200 μmol/L	2	2
Active endocarditis		
still under antibiotics at time of surgery	3	3
Critical preoperative state		
any of the following:		
ventricular tachycardia/fibrillation		
aborted sudden death		
previous cardiac massage		
preoperative ventilation		
preoperative inotropics		
intra-aortic counterpulsation		
acute renal failure (anuria or oliguria <10 ml/h)	3	3
Unstable angina (requiring intravenous nitrates)	2	2
Left ventricular function		
EF 30–50%	1	
EF <30%	3	3
Recent myocardial infarction (<90 d)	2	2
Pulmonary hypertension (systemic PA pressure >60 mmHg)	2	2
Operation other than isolated CABG	2	2
Surgery on thoracic aorta		
ascending, arch, or descending	3	3
Postinfarct septal rupture	4	4
Maximum points		44

[a] CABG, coronary artery bypass graft; EF, ejection fraction; PA, pulmonary artery.

Acknowledgments

We thank all of the medical staff of the Department of Cardiothoracic and Vascular Anesthesia for contribution to the database.

References

1. Chertow GM, Levy EM, Hammermeister KE, Grover F, Daley J: Independent association between acute renal failure and mortality following cardiac surgery. *Am J Med* 104: 343–348, 1998
2. Hilberman M, Myers BD, Carrie BJ, Derby G, Jamison RL, Stinson EB: Acute renal failure following cardiac surgery. *J Thorac Cardiovasc Surg* 77: 880–888, 1979
3. Star RA: Treatment of acute renal failure. *Kidney Int* 54: 1817–1831, 1998
4. Zanardo G, Michielon P, Paccagnella A, Rosi P, Calo M, Salandin V, Da Ros A, Michieletto F, Simini G: Acute renal failure in the patient undergoing cardiac operation. Prevalence, mortality rate, and main risk factors. *J Thorac Cardiovasc Surg* 107: 1489–1495, 1994
5. Metnitz PG, Krenn CG, Steltzer H, Lang T, Ploder J, Lenz K, Le Gall JR, Druml W: Effect of acute renal failure requiring renal replacement therapy on outcome in critically ill patients. *Crit Care Med* 30: 2051–2058, 2002
6. Kellum JA, Angus DC: Patients are dying of acute renal failure. *Crit Care Med* 30: 2156–2157, 2002
7. Levy EM, Viscoli CM, Horwitz RI: The effect of acute renal failure on mortality. A cohort analysis. *JAMA* 275: 1489–1494, 1996
8. Roques F, Nashef SA, Michel P, Gauducheau E, de Vincentiis C, Baudet E, Cortina J, David M, Faichney A, Gabrielle F, Gams E, Harjula A, Jones MT, Pintor PP, Salamon R, Thulin L: Risk factors and outcome in European cardiac surgery: Analysis of the EuroSCORE multinational database of 19030 patients. *Eur J Cardiothorac Surg* 15: 816–822, 1999
9. Roques F, Michel P, Goldstone AR, Nashef SA: The logistic EuroSCORE. *Eur Heart J* 24: 881–882, 2003
10. Solomon R, Werner C, Mann D, D'Elia J, Silva P: Effects of saline, mannitol, and furosemide to prevent acute decreases in renal function induced by radiocontrast agents. *N Engl J Med* 331: 1416–1420, 1994
11. Lassnigg A, Donner E, Grubhofer G, Presterl E, Druml W, Hiesmayr M: Lack of renoprotective effects of dopamine and furosemide during cardiac surgery. *J Am Soc Nephrol* 11: 97–104, 2000
12. Singri N, Ahya SN, Levin ML: Acute renal failure. *JAMA* 289: 747–751, 2003
13. Swaminathan M, Phillips-Bute BG, Conlon PJ, Smith PK, Newman MF, Stafford-Smith M: The association of lowest hematocrit during cardiopulmonary bypass with acute renal injury after coronary artery bypass surgery. *Ann Thorac Surg* 76: 784–791, 2003
14. Mehta RL, Pascual MT, Soroko S, Chertow GM: Diuretics, mortality, and nonrecovery of renal function in acute renal failure. *JAMA* 288: 2547–2553, 2002
15. Anderson RJ, O'Brien M, MaWhinney S, VillaNueva CB, Moritz TE, Sethi GK, Henderson WG, Hammermeister KE, Grover FL, Shroyer AL: Renal failure predisposes patients to adverse outcome after coronary artery bypass surgery. VA Cooperative Study #5. *Kidney Int* 55: 1057–1062, 1999
16. Ryckwaert F, Boccara G, Frappier JM, Colson PH: Incidence, risk factors, and prognosis of a moderate increase in plasma creatinine early after cardiac surgery. *Crit Care Med* 30: 1495–1498, 2002
17. Stafford Smith M. Perioperative renal dysfunction: Implications and strategies for protection. In: *Perioperative Organ Protection*, edited by Newman MF, Richmond, VA, Society of Cardiovascular Anesthesiologists, 2003, pp 89–124
18. Peduzzi P, Concato J, Feinstein AR, Holford TR: Importance of events per independent variable in proportional hazards regression analysis. II. Accuracy and precision of regression estimates. *J Clin Epidemiol* 48: 1503–1510, 1995
19. Mehta RL, McDonald B, Gabbai F, Pahl M, Farkas A, Pascual MT, Zhuang S, Kaplan RM, Chertow GM: Nephrology consultation in acute renal failure: Does timing matter? *Am J Med* 113: 456–461, 2002