Article

Incidence, risk factors and prognosis of changes in serum creatinine early after aortic abdominal surgery

ELLENBERGER, Christoph, *et al*.

Abstract

To determine the incidence, risk factors, and prognostic implications of serum creatinine changes following major vascular surgery.

Reference

UNIVERSITÉ
DE GENÈVE

ORIGINAL

Christoph Ellenberger
Alexandre Schweizer
John Diaper
Afksendiyos Kalangos
Nicolas Murith
Gregory Katchatourian
Aristote Panos
Marc Licker

Incidence, risk factors and prognosis of changes in serum creatinine early after aortic abdominal surgery

C. Ellenberger · A. Schweizer · J. Diaper ·
M. Licker (✉)
University Hospital, Anesthetics and
Critical Care,
rue Micheli-Ducrest, 1211 Genève 14,
Switzerland
e-mail: marc-joseph.licker@hcuge.ch
Tel.: +41-22-3727439
Fax: +41-22-3727690

A. Kalangos · N. Murith ·
G. Katchatourian · A. Panos
University Hospital, Department of
Cardiovascular Surgery,
1211 Geneva 14, Switzerland

Abstract *Objective:* To determine the incidence, risk factors, and prognostic implications of serum creatinine changes following major vascular surgery. *Design:* Observational study. *Settings:* University hospital. *Patients:* Cohort of 599 consecutive patients undergoing elective abdominal aortic surgery. *Interventions:* Review of prospectively collected data from 1993 to 2004. *Measurements and results:* The receiver-operator characteristic (ROC) curve analysis was used to detect the best threshold for postoperative elevation in serum creatinine (Δ Creat) in relation to major complications. A cut-off value of +0.5 mg/dl was selected to define renal dysfunction ($RD_{0.5}$ group, $n = 91$; no $RD_{0.5}$, $n = 508$) that was associated with higher mortality (7.7% in $RD_{0.5}$ group vs 1.4% in no $RD_{0.5}$ group, $P < 0.05$), rate of admission to the ICU (34% vs 13%, $P < 0.05$), and incidence of cardiovascular (9% vs 4%, $P < 0.05$), respiratory (21% vs 7%, $P < 0.05$), surgical (24% vs 10%, $P < 0.05$), and septic complications (9% vs 3%, $P < 0.05$). After multivariate analysis with logistic regression, renal dysfunction was independently related to low preoperative creatinine clearance [< 40 ml/min; odds ratio (OR) 1.5, 95% confidence interval (CI) 1.1–3.9], prolonged renal ischemic time (> 40 min; OR, 3.8, 95% CI, 1.9–7.2), blood transfusion (> 5 units; OR, 1.9, 95% CI 1.2–6.1), and rhabdomyolysis (OR, 3.6, 95% CI 1.7–7.9). *Conclusions:* Postoperative $RD_{0.5}$ (Δ Creat > 0.5 mg/dl) occurs in 15% of vascular patients and carries a bad prognosis. Preoperative renal insufficiency and factors related to the complexity of surgery are the main predictors of renal dysfunction.

Keywords Abdominal vascular surgery · Renal failure · Renal dysfunction

Introduction

Acute changes in renal function are common after cardiac and major vascular surgery [1]. Depending on its definition, at least 1–28% of patients develop a transient or permanent decline in renal function following elective open abdominal aortic repair [2, 3, 4, 5, 6, 7]. Acute renal failure is less frequent (1–5%), except after ruptured aneurysm, and it exerts a profound impact on mortality (up to 50%) and medical resource utilization [1, 2, 3, 4, 5, 6, 7, 8, 9, 10].

The mechanisms of perioperative renal dysfunction (RD) are multifactorial, being related to renal ischemia, circulatory failure, and nephrotoxic agents as well as the neuroendocrine and inflammatory stress response to surgery [11, 12]. Hemorrhagic shock, the need for suprarenal clamping, atheroma or fat embolism, free radicals, and vasoconstrictive mediators/drugs may all contribute to acute tubular necrosis, delayed apoptosis, and, in turn, to multiple organ dysfunction and death [11, 12, 13]. Although various pharmacological agents (mannitol, calcium-channel antagonists, dopaminergic agonists, loop

diuretics, and angiotensin-converting enzyme inhibitors) have been tested to optimize renal perfusion and tubular function, none have been shown to provide any clinical benefit compared with conventional approaches targeting normovolemia with adequate cardiac output [14, 15].

Currently, the lack of uniform criteria to define RD and retrospective data collection make the existing literature almost unusable to analyze the prognostic implications of mild-to-moderate renal insufficiency in vascular surgical patients. Hence, the purposes of this observational study were to describe the pattern of changes in serum creatinine (Δ Creat), to define RD with regard to incremental morbidity and to identify the risk factors for RD after elective major vascular surgery.

Methods

With institutional review board approval, all patients who underwent "open" surgery for aortic abdominal aneurysm (AAA) or aortic occlusive disease (AOD) between 1 January 1993 and 31 December 2004 were prospectively entered into a computerized database. Patients with thoracoabdominal aneurysms ($n = 31$), suprarenal aortic occlusive disease ($n = 19$), endovascular procedures ($n = 34$), urgent/emergent surgery ($n = 186$), and previous renal failure ($n = 3$) were all excluded.

A minimum delay of 72 h was imposed between angiography and surgery. All patients had a balanced anesthetic regimen (opiates and inhaled isoflurane) and were equipped with five-lead ECG, an invasive arterial line and a central venous catheter. Transesophageal echocardiography (TEE) or a pulmonary artery catheter (PAC) was used in patients with pulmonary hypertension (mean pulmonary artery pressure ≥ 30 mmHg), a left ventricular ejection fraction less than 40% and/or a history of congestive heart failure ($n = 102$). The surgeon performed a midline incision in 545 patients and a retroperitoneal approach in 72 patients.

Regarding perioperative medical management, a protocol-driven approach was targeted to provide organ protection by controlling body homeostasis, fluid balance and oxygen transport parameters. For instance, prophylactic antibiotics (cefazoline 2 g/8 h) were given for 48 h and body normothermia was maintained with a forced-air warming device and by heating intravenous fluids. Vasoactive drugs (nitroglycerine, ephedrine, and phenylephrine) were administered to control blood pressure, particularly following aortic clamping/unclamping. A blood salvage device was routinely used and homologous red blood cell concentrates were administered to keep the hemoglobin level ≥ 80–90 g/l. Postoperatively, all patients were managed for 24 h in the postanesthesia care unit (PACU) or in the intensive care unit (ICU); betablockers were routinely given to keep the heart rate below 70 beats/min. Non-steroidal anti-inflammatory drugs

were not given within the first 24 h, in hemodynamically unstable patients, and in those with preoperative renal insufficiency.

Data collection and outcome assessment

Case information spanning 60 perioperative variables was entered into a continually updated registry. Demographic data, comorbid conditions, and current medical treatments were all prospectively collected at the time of the preoperative consultation and after reviewing medical files. The surgical approach and the anesthetic management were described in terms of duration (surgery, anesthesia, aortic cross-clamping, renal ischemia, postoperative ventilation), arterial grafting, fluid balance (diuresis, crystalloids, colloids, and blood products), type of vasoactive drugs, and time to extubation.

Laboratory data included serial measurements of blood gases, hemoglobin, creatinine, and the highest value of troponin I or creatine phosphokinase (CPK) and its isoenzyme CPK-MB. The difference between the highest/lowest serum creatinine value measured within the first 72 h and the baseline preoperative value (Δ Creat) was calculated for each patient and expressed in percentage (%) or absolute value (mg/dl). Serum creatinine concentration was measured using the Jaffe method on a Hitachi 747 analyzer (Roche, Basel, Switzerland). Intra- and interseries precisions were 0.7% and 2.3%, respectively; interassay coefficient of variation was 1.5% at a concentration of 0.9 mg/dl serum creatinine. The patient's baseline glomerular filtration rate was estimated by the Cockcroft–Gault formula and adjusted for 1.73 m^2 of body surface area [16].

Patient's clinical status, ECG, chest X-rays, and laboratory data were daily examined and, complications were categorized as being related to surgery, sepsis, rhabdomyolysis, or the cardiac and respiratory systems (see Appendix 1). In addition, the Sequential Organ Failure Assessment (SOFA) score was calculated [17] and mortality was defined as any death occurring during the hospital stay or within 30 days following surgery.

Statistical analysis

Data are presented as mean (± standard deviation), median (range), absolute numbers or percentages. An internal audit of 80 randomly selected cases was performed to test the completeness and accuracy of the database. The receiver-operator characteristic (ROC) curve analysis was used to detect the best threshold for Δ Creat (in % or mg/dl) to predict the occurrence of major complications (death and/or cardiovascular and respiratory complications). Differences between the two groups (reference

group and RD$_{0.5}$ group) were examined using unpaired Student's *t*-test or Mann–Whitney test for continuous variables and Fisher's exact test for proportions. For time-trends analysis, three consecutive 4-year-periods were considered, a χ^2 test for linear trend analyses (extension of Mantel) was applied followed by Duncan's multiple range test. Potential risk factors for RD were identified by univariate analysis, and those with a *P* value less than 0.25 were entered in a forward multivariate logistic regression model. To avoid multi-colinearity, only one variable in a set of variables with a correlation coefficient greater than 0.5 was used in the multivariate analysis. Adjusted odd ratios (OR) with 95% confidence intervals (CI) were calculated.

Results

From 1993 to 2004, 615 patients underwent elective infra-renal aortic surgery and completed data were obtained in 599 cases ($n = 235$ AOD and $n = 364$ AAA) with a reporting accuracy of 95%. Overall, the 30-day mortality rate was 2.3% (1.3% in patients with AOD and 3.0% among those with AAA) and 28% of patients presented at least one major postoperative complication. The incidence of renal failure requiring hemodialysis was 1.3% ($n = 8$), in all cases more than 72 h after the intervention.

Incidence of renal dysfunction and major complications

Within the first 72 h after surgery, serum creatinine concentrations decreased, remained stable, or increased by no more than 0.25 mg/dl in 74% of cases; a minor increase (0.26–0.5 mg/dl) was observed in 11% of cases; and moderate-to-large increases in Δ Creat (> 0.5 mg/dl) occurred in 15% of cases (Fig. 1). The incidence of persistent elevation of creatinine at hospital discharge and the worst SOFA score increased along with the severity of RD; of note, 19.5% of the patients with Δ Creat > 1.5 mg/dl required hemodialysis.

Based on the frequency distribution of Δ Creat and its relationship with the worst non-renal SOFA score, a cut-off value of +0.5 mg/dl was selected to identify RD$_{0.5}$ (reference group, $n = 508$; RD$_{0.5}$ group $n = 91$). The area under the ROC curve was significantly better with a cut-off value of +0.5 mg/dl than with +20% Δ Creat; this model demonstrated a good model calibration and discriminatory power (0.79, 95% CI 0.74–0.84 vs 0.65, 95% CI 0.60–0.70 with a Δ Creat cut-off value of 20%). Compared with the reference group, patients with RD$_{0.5}$ required more frequent admission to the ICU and presented higher incidences of surgical, cardiovascular, respiratory and septic complications (Table 1). Seven of the 91 patients with RD$_{0.5}$ died (7.7% vs 1.4% in the reference group, $P < 0.05$) and mortality rate further increased in those who experienced an-

other organ dysfunction ($n = 49$; 12.2% vs 2.4% in isolated RD, $P < 0.05$).

Over the 12-year period, there was no change in the incidence of postoperative RD$_{0.5}$ (1993–1996: 14%, 1997–2000: 16%, 2001–2004: 15%).

Intraoperative hemodynamic monitoring with PAC/TEE did not influence either the occurrence of RD$_{0.5}$ (18.5% vs 14.5% without PAC/TEE, n.s.) or the incidence of cardiovascular and respiratory complications (5.6% vs 3.3% and 8.3% vs 7.1%, respectively; n.s.).

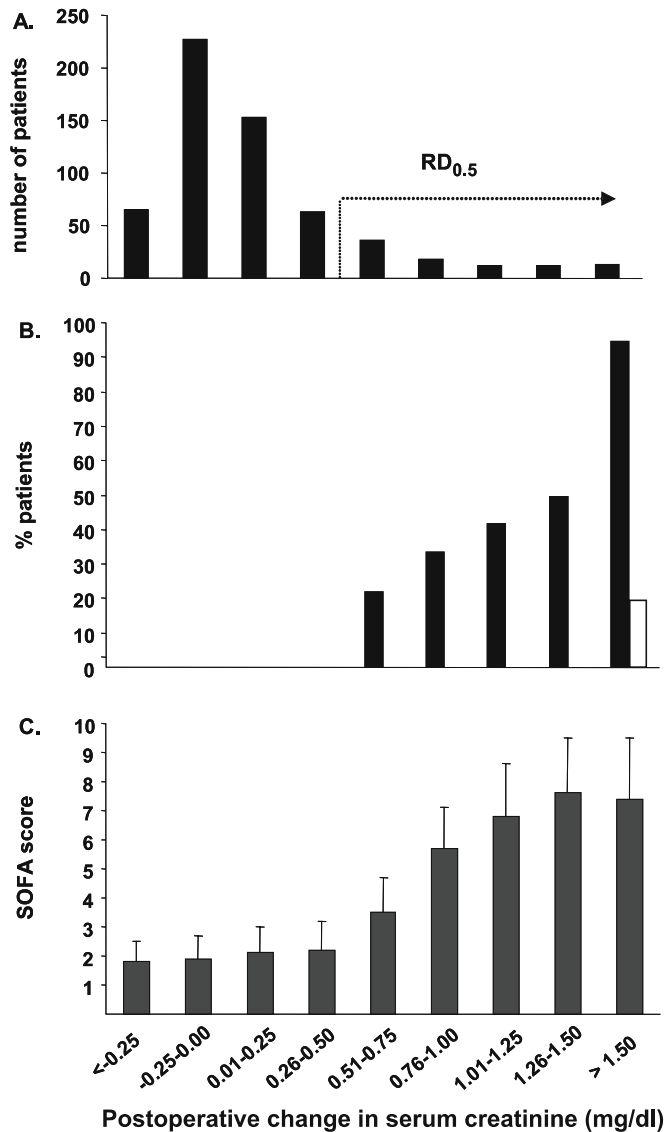**Fig. 1** **a** Frequency distribution of postoperative serum creatinine changes among patients undergoing aortic abdominal surgery. **b** Proportion of patients with persistent elevation in serum creatinine at hospital discharge (■) and those requiring hemodialysis (□) **c** Relationship between postoperative changes in serum creatinine and the Sequential Organ Failure Assessment (*SOFA*) score.

Table 1 Postoperative outcome according to presence or absence of renal dysfunction

	Reference group N = 508		RD group N = 91	
Mortality, n pts (%)	7	(1.4)	8	(8.8)*
Intensive Care Unit, n pts (%)				
Primary admission	65	(12.8)	31	(34.1)*
Re-admission	15	(2.9)	6	(6.6)
Duration, days, mean (SD)	2.0	(1.3)	3.1	(2.4)*
Hospital Stay (duration), mean (SD)	12.7	(3.1)	17.8	(9.3)*
Surgical complications, n pts (%)				
Re-operation	44	(8.7)	19	(22.1)*
Wound infection	17	(3.3)	3	(3.4)
Cardiovascular complications, n pts (%)				
Arrhytmia	13	(2.6)	7	(7.7)*
Myocardial infarction	13	(2.6)	6	(6.6)*
Heart failure	12	(2.4)	8	(8.8)*
Stroke	3	(0.6)	2	(2.2)
Respiratory complications, n pts (%)				
Postoperative Ventilation > 12 hrs	4	(0.8)	6	(6.6)*
Atelectasis	27	(5.3)	14	(15.4)*
Bronchopneumonia	19	(3.7)	4	(4.4)
Sepsis, n pts (%)	9	(1.8)	8	(8.8)*
Maximal SOFA score, mean (SD)	1.9	(1.2)	6.1	(2.3)*

* RD, renal dysfunction defined by an increase in serum creatine > 0.5 mg/dl

Table 2 Preoperative risk factors of postoperative renal dysfunction

	Reference group N = 508	RD group N = 91	Univariate Analysis OR (95% CI)	P value	Multivariate Analysis OR (95% CI)	P value
Age (yrs), mean (SD)	66 (11)	69 (8)				
> 70 yrs, n pts (%)	189 (37)	45 (51)	1.6 (1.04–3.8)	0.031	n.s.	
Gender						
Male, n pts (%)	430 (84)	80 (91)				
BMI (kg/m^2), mean (SD)	25 (4)	26 (4)				
Smoking, n pts (%)						
Current	345 (68)	66 (72)				
Ex-smoker	102 (20)	16 (17)				
Prior PTCA/CABGS, n pts (%)	66 (13)	20 (22)	1.8 (0.98–3.1)	0.054	n.s.	
Co-morbidities, n pts (%)						
Hypertension	295 (58)	63 (69)	1.7 (1.1–2.9)	0.028	n.s.	
Coronary Artery Disease	36 (183)	40 (44)	2.4 (1.2–3.8)	0.009	n.s.	
Heart Failure	36 (7)	16 (17)	2.9 (1.2–5.8)	0.004	n.s.	
Hypercholesterolemia	223 (45)	39 (43)				
Diabetes mellitus	76 (15)	16 (17)				
Arrythmia	46 (9)	9 (10)				
Conduction blockade	40 (8)	11 (12)	1.9 (1.1–4.3)	0.021	n.s.	
Stroke	15 (3)	6 (5)				
COPD	56 (11)	18 (20)	2.1 (1.0–3.4)	0.034	n.s.	
Preop medications, n pts (%)						
Beta-blockers	202 (20)	34 (37)	2.8 (1.3–4.7)	< 0.001	n.s.	
Calcium channel blockers	117 (23)	17 (19)				
ACE Inhibitors/All Antagonists	152 (30)	38 (42)	2.2 (1.1–4.1)	0.015	n.s.	
Nitrates	56 (11)	12 (13)				
Diuretics	81 (16)	23 (25)	1.8 (1.1–3.1)	0.027	n.s.	
Anti-platelets	142 (28)	23 (25)				
Laboratory data						
Hemoglobin (g/L), mean (SD)	142 (20)	138 (19)				
Ccreat (ml/min/1.73 m^2), mean (SD)	77 (20)	61 (21)*				
Ccreat < 40 ml/min, n pts (%)	20 (4)	37 (41)*	2.2 (1.2–3.9)	0.006	1.5 (1.1–3.9)	0.028

RD, renal dysfunction; BMI, body mass Index; PTCA, percutaneous coronary angioplasty; CABGS, coronary artery bypass graft surgery; COPD, Chronic Obstructive Pulmonary disease; ACE, angiotensin-converting enzyme inhibitors; All, angiotensin II; Ccreat, creatinine clearance

* Independent risk factor of renal dysfunction

Table 3 Perioperative management and postoperative renal dysfunction

	Reference group N = 508	RD group N = 91	Univariate Analysis OR (95% CI)	P value	Multivariate Analysis OR (95% Cl)	P value
Intraoperative period						
AAA/AOD (n)	296/212	68/23	2.1 (1.2–4.8)	0.006	n.s.	
Fluids (ml.kg^{-1}.h^{-1}), mean (SD)						
Crystalloids	16.5 (4.8)	16.2 (5.1)				
Colloids	4.1 (2.2)	4.0 (1.6)				
Diuresis (ml.kg^{-1}.h^{-1})	22 (1.4)	1.6 (1.8)	1.5 (0.9–6.8)	0.092	n.s.	
Duration (min), mean (SD)						
Surgery	271 (71)	307 (101)	1.6 (1.1–5.2)	0.031	n.s.	
Aortic clamping	71 (26)	80 (28)	1.9 (1.1–3.2)	0.019	n.s.	
Renal ischemia	6 (8)	24 (15)*	5.2 (3.2–9.6)	<0.001	3.8 (1.9–6.2)	<0.001
Vasoactive drugs						
Ephedrine (mg), mean (SD)	13 (12)	21 (13)				
Phenylephrine (mcg), mean (SD)	448 (401)	744 (503)				
Vasopressors, n pts (%)	10 (50)	19 (17)*	1.5 (1.1–2.7)	0.056	n.s.	
Postoperative period (24 h)						
Fluids (ml.kg^{-1}.h^{-1}), mean (SD)	2.4 (0.6)	2.3 (0.5)				
Diuresis (ml.kg^{-1}.h^{-1})	1.4 (0.7)	1.1 (0.8)				
PaO$_2$/FIO$_2$ at POD1 (mmHg), mean (SD)	315 (49)	306 (51)				
Hemoglobin at POD1 (g/L), mean (SD)	111 (16)	115 (18)				
Homologous transfusion						
Patients, n pts (%)	186 (37)	52 (57)				
Erythrocytes concentrates, mean (SD)	2.6 (2.1)	3.7 (3.1)*	2.4 (1.4–5.8)	0.004	1.9 (1.2–6.7)	0.021
Fresh Frozen Plasma, mean (SD)	2.5 (1.0)	3.1 (2.3)				
Ventilation > 12 hrs, n pts (%)	4 (0.8)	6 (6.6)	2.5 (1.2–9.1)	0.026	n.s.	
Rhabdomyolysis, n pts (%)	14 (2.8)	16 (17.6)*	4.1 (2.8–10.4)	<0.001	3.6 (1.7–6.9)	<0.001

AAA, aortic abdominal aneurysm; AOD, aortic occlusive disease; PaO$_2$/FIO$_2$, oxygenation index; POD1, postoperative day 1; ephedrine > 20 mg and/or phenylephrine > 600 mcg; * lndependent risk factor of renal dysfunction

Risk factors for renal dysfunction

Patient characteristics and perioperative management are described in Tables 2 and 3. The development of RD$_{0.5}$ was more frequently associated with advanced age (> 70 years), low creatinine clearance, use of chronic cardiac medications (beta-blockers, diuretics or ACE inhibitors/angiotensin II antagonists) and the presence of hypertension, coronary artery disease, heart failure, electrical conduction blockade, aortic aneurysm, cerebrovascular disease and COPD. Among the perioperative events, rhabdomyolysis, the duration of surgery, aortic cross-clamping and renal ischemia, as well as the need for homologous transfusions, vasoactive drugs (ephedrine, phenylephrine) and postoperative ventilation differed significantly between patients with and without RD$_{0.5}$.

Using multivariate regression analysis, the development of RD$_{0.5}$ was found to be related to four independent risk factors: preoperative renal insufficiency (creatinine clearance < 40 ml/min), renal ischemic time > 40 min, the need for transfusion (> 5 units), and rhabdomyolysis. The relationship between the duration of renal ischemia and postoperative elevation in serum creatinine is illustrated in Fig. 2.
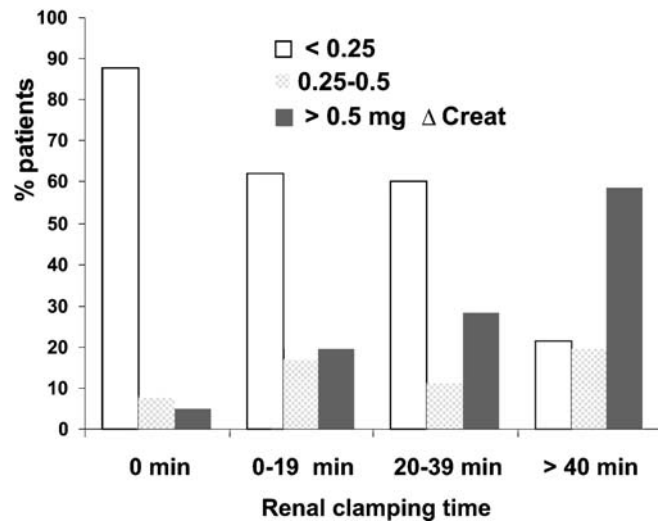

Fig. 2 Relationship between the duration of renal ischemia and changes in serum creatinine level within the first 72 h after vascular surgery

Discussion

In this 12-year cohort study, postoperative renal dysfunction occurred in 15% of 599 consecutive patients undergoing aortic reconstructive surgery. Renal dysfunction was defined by changes in serum creatinine exceeding 0.5 mg/dl ($RD_{0.5}$) that was associated with a 5 times greater mortality rate and more frequent episodes of sepsis, cardiopulmonary dysfunction and surgical complications. Importantly, baseline renal impairment, the duration of renal ischemia, the need for transfusion and rhabdomyolysis were all predictive of $RD_{0.5}$. Although our results do not provide any pathophysiologic insights, it is tempting to speculate that $RD_{0.5}$-associated impairments in volume load excretion, electrolyte regulation, and platelet function contributed to the increased morbidity and mortality.

Given its nonlinear relationship with glomerular filtration and its low diagnostic sensitivity, change in serum creatinine (Δ Creat) largely underestimates the occurrence of renal functional impairment, particularly in patients with normal or borderline renal function [18]. Nevertheless, monitoring serum creatinine is a practical approach for assessing short-term alteration in renal function, reflecting reduced renal creatinine clearance, increased creatinine formation, or both [16, 19]. Compared with inuline clearance – the reference method for glomerular filtration – serum creatinine has been shown to be a valid indicator of early postischemic renal dysfunction and a predictor of postoperative complications [20]. In previous studies, preset levels of relative/absolute increase in serum creatinine were used as biological criteria for perioperative RD [2, 3, 4, 5, 6, 7]. Instead of arbitrarily defining RD, we examined the relationship between serious adverse events and Δ Creat within the first 3 postoperative days and we found that a Δ Creat of 0.5 mg/dl was the best criterion to discriminate two populations of patients with different postoperative outcome. After cardiac surgery and thoracic aortic aneurysm, similar cut-off values for Δ Creat (+20%, +0.5–1 mg/dl) have also been shown to detect mild-to-moderate renal impairment that was predictive of increased mortality, prolonged hospital stay, and poor quality of life [21, 22, 23, 24].

In this single-center study, standardization of perioperative interventions probably contributed to lowering the risk of $RD_{0.5}$, for instance by avoiding nephrotoxic agents (e.g., non-steroidal anti-inflammatory drugs, radiological contrast agents, antibiotics) and by stabilization of the hemodynamic condition [14]. Among preoperative variables, a low creatinine clearance (< 40 ml/min) was the only predictor of $RD_{0.5}$. Consistent with this finding, Powell and Johnston reported a twofold incidence of renal dysfunction in patients with preoperative serum creatinine exceeding 2 mg/dl or when the estimated creatinine clearance was below 40–45 ml/min [4, 25]. Conceptually, the ongoing renal pathophysiological processes render the residual nephrons more vulnerable to subsequent hypoxemic, ischemic, hypotensive, inflammatory, and/or nephrotoxic insults leading to further deterioration of the filtering, concentrating, and reabsorbing capacities of the kidney [12, 26, 27].

Although advanced age and cardiovascular diseases (e.g., hypertension, heart failure, coronary artery disease, conduction blockade) were more prevalent in the $RD_{0.5}$ group, they were not considered as independent risk factors of RD. Population based studies suggest that these clinical markers simply parallel the age-related reduction in functioning nephron mass and/or reflect the progression of renal vascular atheromatosis and glomerular sclerosis [28].

Not surprisingly, the main determinant of postoperative creatinine levels was the duration of renal ischemia. Suprarenal aortic clamping was deemed necessary in about 20% of our patients, and atheromatous debris could be dislodged from the aortic intima with subsequent embolization within the renal vasculature. While the risk for $RD_{0.5}$ was low for renal ischemia time shorter than 20 min, renal clamping time exceeding 40 min was associated with a 60% occurrence of $RD_{0.5}$. Consistent with these observations, a "safe" renal ischemia time between 45 min and 60 min has been supported by previous experimental and clinical investigations [3, 8, 29, 30]. In a review of 60 patients following aortic reconstruction, Wahlberg et al. reported a tenfold risk of postoperative elevation of creatinine when the suprarenal aortic clamping time was greater than 50 min [31]. Likewise, Kudo et al. demonstrated a positive correlation between the duration of renal ischemia and postoperative creatinine elevation, 45 min clamping time being considered the upper limit of "tolerable" renal ischemia [8].

Among clinical and biological markers reflecting the extent of surgical trauma and procedural complexity, rhabdomyolysis and bleeding, expressed by transfusion requirement, were identified as the sole independent predictors of postoperative $RD_{0.5}$. In a similar surgical population, Bertrand et al. found a 25% incidence of acute renal failure in a subset of patients who experienced rhabdomyolysis (compared with less than 1% in those without rhabdomyolysis) and there was a close association between the occurrence of rhabdomyolysis (9%) and longer clamping time, marked intraoperative bleeding, and the need for visceral artery reimplantation [32]. Altogether, circulating hypovolemia and the cytotoxic and vasoconstrictive effects of myoglobin are considered the triggering factors leading to a reduced glomerular filtration rate as a result of renal hypoperfusion associated with acute tubular necrosis and apoptosis [33].

We are mindful of several limitations of this observational study. First, although more than 60 items were prospectively collected at one center, the criteria and potential risk factors of RD were investigated a posteriori, precluding control of several confounding variables and

the generalization of the results to other institutions. Selection bias and length bias were unavoidable; for instance, the surgeon's choice to select an "open" or endovascular approach has changed over this 12-year period, being determined by the recent availability of this noninvasive technique, the patient's comorbidities, and the morphologic features of the aorta, as well as the operator's learning curve. Although our logistic regression analysis adheres to sample size recommendations for 10 or more outcome events per risk factor, external validation is needed that would entail a large multicenter database [34].

Second, analysis of several potential risk factors such as the presence of cardiac insufficiency, diabetes, or cirrhosis, chronic use of beta-blockers, angiotensin-converting inhibitors, or angiotensin blockers and intraoperative interventions (e.g., renal vein ligation, arterial grafting), was inconclusive due to incomplete data and the small number of patients in these categories (type II error, false negative results) [35].

Third, elevated serum creatinine levels persisted at hospital discharge in 40% of our surgical patients and additional cases of mild-to-moderate renal impairments were probably undetected given the low diagnostic sensitivity of Δ Creat [19, 20]. Hence, follow-up studies using sensitive biological markers of glomerular and tubular injuries are needed to examine whether perioperative elevation in creatinine represents a transient functional impairment or a permanent loss of nephrons evolving towards progressive renal failure.

In summary, the likelihood of developing postoperative RD after major elective vascular surgery is mainly influenced by baseline renal functional reserve and by factors related to the complexity of the vascular intervention (renal ischemia, rhabdomyolysis and bleeding). These results highlight the importance of preoperative risk stratification, implementation of standardized perioperative protocols, and involvement of multidisciplinary specialized teams. Accordingly, reduction in postoperative RD should better be targeted in high-volume hospitals by sharing best practices of care between highly trained and experienced health care providers [36].

Appendix

Definitions of major non-fatal complications

Cardiovascular

1. Myocardial infarct: typical rise and fall of CPK (> 120 U/l) and CK-MB/CPK $\geq 6\%$ or troponin-I ≥ 1.5 ng/ml with at least one of the following criteria: ischemic symptoms, development of pathological Q waves on the ECG, ST segment elevation or depression (≥ 1 mm) or coronary artery intervention

2. Arrhythmias: supraventricular and ventricular tachyarrhythmias on ECG requiring anti-arrhythmic medications and/ or an electrical cardioversion

3. Congestive heart failure: need for sympathomimetic support, diuretics, or vasodilators consistent with clinical, hemodynamic (pulmonary artery pressure ≥ 15 mmHg), and radiological evidence of pulmonary congestion

Cerebral

Stroke: focal neurological deficit (transient or permanent)

Respiratory

1. Atelectasis: lobar collapse (chest X-rays), need for CPAP and/or bronchoscopy

2. Bronchopneumonia: temperature > 38°C, hyperleukocytosis (neutrophils), new lung infiltration (chest X-rays), positive culture (bronchial secretions or alveolar fluid)

3. Prolonged mechanical ventilation ≥ 24 h

Surgical

1. Re-operation for bleeding
2. Re-operation for ischemia

Sepsis

Systemic inflammatory response syndrome (SIRS) associated with an infection (positive culture of blood, urine, bronchoalveolar lavage fluid or other internal fluid specimen):

- Body temperature < 35.6° or > 38.3°C
- Tachycardia (> 90 beats/min)
- Ventilatory frequency > 20 bpm or $PaCO_2 < 4.3$ kPa
- White blood cells $> 12 \times 10^9$/l or $< 4 \times 10^9$/l, or 10% immature neutrophils

Rhabdomyolysis

Creatine phosphokinase (CPK) value > 1700 U/l, corresponding to the mean value +2 SD of maximum CPK value observed after peripheral vascular surgery in our institution, in the absence of myocardial infarct (see above).

References

1. Sear JW (2005) Kidney dysfunction in the postoperative period. Br J Anaesth 95:20–32

2. Hertzer NR, Mascha EJ, Karafa MT, O'Hara PJ, Krajewski LP, Beven EG (2002) Open infrarenal abdominal aortic aneurysm repair: the Cleveland Clinic experience from 1989 to 1998. J Vasc Surg 35:1145–1154

3. Breckwoldt WL, Mackey WC, Belkin M, O'Donnell TF Jr (1992) The effect of suprarenal cross-clamping on abdominal aortic aneurysm repair. Arch Surg 127:520–524

4. Powell RJ, Roddy SP, Meier GH, Gusberg RJ, Conte MS, Sumpio BE (1997) Effect of renal insufficiency on outcome following infrarenal aortic surgery. Am J Surg 174:126–130

5. Fleron MH, Weiskopf RB, Bertrand M, Mouren S, Eyraud D, Godet G, Riou B, Kieffer E, Coriat P (2003) A comparison of intrathecal opioid and intravenous analgesia for the incidence of cardiovascular, respiratory, and renal complications after abdominal aortic surgery. Anesth Analg 97:2–12

6. Ryckwaert F, Alric P, Picot MC, Djoufelkit K, Colson P (2003) Incidence and circumstances of serum creatinine increase after abdominal aortic surgery. Intensive Care Med 29:1821–1824

7. Prinssen M, Verhoeven EL, Buth J, Cuypers PW, van Sambeek MR, Balm R, Buskens E, Grobbee DE, Blankensteijn JD (2004) A randomized trial comparing conventional and endovascular repair of abdominal aortic aneurysms. N Engl J Med 351:1607–1618

8. Kudo FA, Nishibe T, Miyazaki K, Murashita T, Yasuda K, Ando M, Nishibe M (2004) Postoperative renal function after elective abdominal aortic aneurysm repair requiring suprarenal aortic cross-clamping. Surg Today 34:1010–1013

9. Braams R, Vossen V, Lisman BA, Eikelboom BC (1999) Outcome in patients requiring renal replacement therapy after surgery for ruptured and non-ruptured aneurysm of the abdominal aorta. Eur J Vasc Endovasc Surg 18:323–327

10. Sarac TP, Clair DG, Hertzer NR, Greenberg RK, Krajewski LP, O'Hara PJ, Ouriel K (2002) Contemporary results of juxtarenal aneurysm repair. J Vasc Surg 36:1104–1111

11. Aronson S, Blumenthal R (1998) Perioperative renal dysfunction and cardiovascular anesthesia: concerns and controversies J Cardiothorac Vasc Anesth 12:567–586

12. Lieberthal W, Nigam SK (2000) Acute renal failure. II Experimental models of acute renal failure: imperfect but indispensable. Am J Physiol Renal Physiol 278:F1–F12

13. Laukontaus SJ, Lepantalo M, Kantonen I, Pettila V (2005) Prediction of survival after 48-h of intensive care following open surgical repair of ruptured abdominal aortic aneurysm. Eur J Vasc Endovasc Surg 30:509–515

14. Zacharias M, Gilmore IC, Herbison GP, Sivalingam P, Walker RJ (2005) Interventions for protecting renal function in the perioperative period. Cochrane Database Syst Rev 3:CD003590

15. Tang IY, Murray PT (2004) Prevention of perioperative acute renal failure: what works? Best Pract Res Clin Anaesthesiol 18:91–111

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

17. Moreno R, Vincent JL, Matos R, Mendonca A, Cantraine F, Thijs L, Takala J, Sprung C, Antonelli M, Bruining H, Willats S (1999) The use of maximum SOFA score to quantify organ dysfunction/failure in intensive care. Results of a prospective, multicentre study. Working Group on Sepsis related Problems of the ESICM. Intensive Care Med 25(7):686–696

18. Charlson ME, MacKenzie CR, Gold JP, Shires DT (1989) Postoperative changes in serum creatinine. When do they occur and how much is important? Ann Surg 209(3):328–333

19. Van Den Noortgate NJ, Janssens WH, Delanghe JR, Afschrift MB, Lameire NH (2002) Serum cystatin C concentration compared with other markers of glomerular filtration rate in the old. J Am Geriatr Soc 50:1278–1282

20. Daniel JP, Chantrel F, Offner M, Moulin B, Hannedouche T (2004) Comparison of cystatin C, creatinine and creatinine clearance vs. GFR for detection of renal failure in renal transplant patients. Ren Fail 26(3):253–257

21. Lassnigg A, Schmidlin D, Mouhieddine M, Bachmann LM, Druml W, Bauer P, Hiesmayr M (2004) Minimal changes of serum creatinine predict prognosis in patients after cardiothoracic surgery: a prospective cohort study. J Am Soc Nephrol 15:1597–1605

22. Coselli JS, LeMaire SA, Conklin LD, Koksoy C, Schmittling ZC (2002) Morbidity and mortality after extent II thoracoabdominal aortic aneurysm repair. Ann Thorac Surg 73:1107–1116

23. Huynh TT, Miller CC, 3rd, Estrera AL, Sheinbaum R, Allen SJ, Safi HJ (2002) Determinants of hospital length of stay after thoracoabdominal aortic aneurysm repair. J Vasc Surg 35:648–653

24. Ryckwaert F, Boccara G, Frappier JM, Colson PH (2002) Incidence, risk factors, and prognosis of a moderate increase in plasma creatinine early after cardiac surgery. Crit Care Med 30:1495–1498

25. Johnston KW (1989) Multicenter prospective study of nonruptured abdominal aortic aneurysm. Part II. Variables predicting morbidity and mortality. J Vasc Surg 9:437–447

26. Bown MJ, Nicholson ML, Bell PR, Sayers RD (2001) Cytokines and inflammatory pathways in the pathogenesis of multiple organ failure following abdominal aortic aneurysm repair. Eur J Vasc Endovasc Surg 22:485–527

27. Thakar CV, Worley S, Arrigain S, Yared JP, Paganini EP (2005) Influence of renal dysfunction on mortality after cardiac surgery: modifying effect of preoperative renal function. Kidney Int 67:1112–1119

28. O'Brien MM, Gonzales R, Shroyer AL, Grunwald GK, Daley J, Henderson WG, Khuri SF, Anderson RJ (2002) Modest serum creatinine elevation affects adverse outcome after general surgery. Kidney Int 62:585–592

29. Jean-Claude JM, Reilly LM, Stoney RJ, Messina LM (1999) Pararenal aortic aneurysms: the future of open aortic aneurysm repair. J Vasc Surg 29:902–912

30. Krause SM, Walsh TF, Greenlee WJ, Ranaei R, Williams DL, Jr., Kivlighn SD (1997) Renal protection by a dual ETA/ETB endothelin antagonist, L-754,142, after aortic cross-clamping in the dog. J Am Soc Nephrol 8:1061–1071

31. Wahlberg E, Dimuzio PJ, Stoney RJ (2002) Aortic clamping during elective operations for infrarenal disease: the influence of clamping time on renal function. J Vasc Surg 36:13–18

32. Bertrand M, Godet G, Fleron MH, Bernard MA, Orcel P, Riou B, Kieffer E, Coriat P (1997) Lumbar muscle rhabdomyolysis after abdominal aortic surgery. Anesth Analg 85:11–15

33. Holt SG, Moore KP (2001) Pathogenesis and treatment of renal dysfunction in rhabdomyolysis. Intensive Care Med 27:803–811

34. Concato J, Feinstein AR, Holford TR (1993) The risk of determining risk with multivariate models. Ann Intern Med 118:201–210

35. Williams JL, Hathaway CA, Kloster KL, Layne BH (1997) Low power, type II errors, and other statistical problems in recent cardiovascular research. Am J Physiol 273:H487–H493

36. Urbach DR, Baxter NN (2004) Does it matter what a hospital is "high volume" for? Specificity of hospital volume-outcome associations for surgical procedures: analysis of administrative data. Qual Saf Health Care 13(5):379–383