Is Kidney Function Altered by the Duration of Cardiopulmonary Bypass?

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Background. **Cardiopulmonary bypass (CPB) is considered responsible for kidney damage. By using sensitive markers of kidney damage we assessed whether the length of CPB influences kidney function.**

Methods. **In a prospective study, 50 consecutive cardiac operation patients with CPB times of less than 70 minutes were compared with 50 consecutive patients showing CPB times of more than 90 minutes. Aside from creatinine clearance and fractional excretion of sodium, urine concentrations of N-acetyl-β-D-glucosaminidase, α_1-microglobulin, glutathione transferase-π, and glutathione transferase-α were measured after induction of anesthesia at the end of the operation, and on the first and second postoperative days in the intensive care unit.**

Results. **CPB times were 58 ± 12 minutes and 116 ± 18 minutes, respectively. Hemodynamics, volume replacement, and use of catecholamines during cardiopulmonary bypass (CPB) were without significant differences between groups. Concentrations of all kidney-specific proteins increased significantly after CPB, showing the highest significant increases in the CPB more than 90 minutes group (eg, glutathione transferase-α CPB > 90 minutes from 3.0 ± 1.0 to 12.9 ± 2.9 μg/L; glutathione transferase -α CPB < 70 minutes from 2.4 ± 0.5 to 5.5 ± 1.2 μg/L). By the second postoperative day, urine concentrations of kidney-specific proteins had returned to almost baseline in the CPB less than 70 minutes patients, but remained slightly elevated in the other group.**

Conclusions. **Patients with CPB times more than 90 minutes showed more pronounced kidney damage than patients with CPB times less than 70 minutes as assessed by sensitive kidney-specific proteins. Whether patients with preexisting renal dysfunction undergoing prolonged CPB times would profit from renal protection strategies needs to be elucidated.**

(Ann Thorac Surg 2003;75:906–12)

An incidence of acute renal failure (ARF) requiring dialysis of 0.7% to 5% has been demonstrated in patients undergoing cardiac operations [1–3]. Nondialysis dependent, more moderate kidney function alterations have been reported to occur with a frequency rate of up to 30% after cardiac operation using CPB [4, 5]. Mortality rate of patients with ARF is very high, ranging from 28% to 63% [1, 3]. 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 cause of renal dysfunction in cardiac operation patients is multifactorial. Postoperative changes in kidney function have been reported as more likely in patients older than 65 years after valve operation or after prolonged CPB times [6]. CPB per se has often been considered to be responsible for renal damage [7]. The unphysiologic, nonpulsatile flow during CPB, activation of inflammatory cascades, and coagulation abnormalities may be reasons for changes in kidney function. Patients who develop perioperative oliguric ARF without preexisting renal dysfunction is rare. Subclinical alterations in renal function detected by sensitive markers of tubular damage have been reported in the absence of overt changes in laboratory markers of kidney function, such as creatinine concentration and creatinine clearance [3, 8, 9]. The present study was designed to evaluate whether duration of CPB time is an important factor that influences kidney function assessed by sensitive markers of renal integrity.

Material and Methods

After approval by the ethic committee of the hospital, written informed consent was obtained from all patients. Fifty consecutive patients undergoing adult cardiac operations with CBP times less than 70 minutes and 50 consecutive patients with CPB times more than 90 minutes were prospectively studied. Renal insufficiency (serum creatinine > 2.0 mmoL/dL), liver insufficiency (aspartate aminotransferase > 40 U/L, alanine aminotransferase > 40 U/L), insulin-dependent diabetes mellitus, and use of corticosteroids were defined as exclusion criteria to participate in the study.

Standardized general anesthesia using weight-related doses of sufentanil, midazolam, and pancuronium bromide were used. Cardiopulmonary bypass was per-

Accepted for publication Oct 1, 2002.

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Published by Elsevier Science Inc

0003-4975/03/$30.00
PII S0003-4975(02)04559-9

Table 1. Demographic Data and Data From the Perioperative Period

	Cardiopulmonary Bypass > 90 Min (n = 50)	Cardiopulmonary Bypass < 70 Min (n = 50)
Age in years (range)	67.9 ± 3.3 (59–73)	64.7 ± 3.9 (61–75)
Weight (kg)	79.7 ± 11.1	78.2 ± 10.6
Height (cm)	169 ± 9	166 ± 10
Gender (F/M)	22/28	20/30
Type of surgery		
- CABG (including re-CABG)	38	40
- CABG + AVR	7	7
- CABG + MVR	5	3
Preoperative medication		
- Beta-blocker	44	45
- ACE inhibitors	23	21
- Nitrates	23	26
- AT_1-inhibitors	12	13
Time (mins)		
- Anesthesia (range)	275 ± 55 (188–299)*	209 ± 38 (176–293)
- CPB (range)	116 ± 18 (92–149)*	58 ± 12 (30–70)
- Cross clamp (range)	79 ± 14 (60–119)*	34 ± 8 (24–53)
Survivors	48	50

*Significant difference between the groups.

ACE = angiotensin converting enzyme; AT = angiotensin; AVR = aortic valve replacement; CABG = coronary artery bypass grafting; CPB = cardiopulmonary bypass; F = female; M = male; MVR = mitral valve replacement.

formed using a nonpulsatile pump and a membrane oxygenator (Optima XP, Stöckert Instrumente, Munich, Germany). The (nonheparinized) circuit was primed with 1,000 mL of Ringer's solution plus 500 mL of a synthetic colloid (either gelatin or a modern, third generation hydroxyethyl starch preparation [6%, 130/0.4]. Standard high-dose aprotinin regimen was used in all patients.

Temperature was kept at mild hypothermia (bladder temperature > 33°C) and a flow of 2.4 L/min · m^2 was used. Mean arterial blood pressure was kept between 50 and 70 mm Hg by adding bolus of norepinephrine when necessary. To maintain filling volume of the extracorporeal circuit, colloids (gelatin or hydroxyethyl starch preparation 130/0.4) and Ringer's lactate were added. When hemoglobin was less than 7 g/dL, packed red blood cells were given. During weaning off bypass, pump blood was infused to keep pulmonary capillary wedge pressure between 10 and 14 mm Hg. After CPB, the blood from the CPB circuit was salvaged by a cell saving system and re-transfused after sternal closure. Shed mediastinal blood was not re-transfused postoperatively. All patients were transferred to the intensive care unit and controlled mechanical ventilation was continued during at least the following 4 hours. Tracheal extubation was performed when hemodynamics were stable for at least one-half hour, temperature was more than 36°C, and the patient breathed spontaneously reaching adequate blood gases.

In the intensive care unit, colloids (gelatin or hydroxyethyl starch preparation 130/0.4) and crystalloids (Ringer's lactate) was given to keep pulmonary capillary wedge pressure or central venous pressure between 10 to 14 mm Hg. Packed red blood cells were given when hemoglobin was less than 9 g/dL, fresh frozen plasma was given only to maintain sufficient hemostasis (when aPTT was > 70 seconds, fibrinogen was < 2 g/dL, antithrombin III was < 40%, and bleeding occurred). Epinephrine was used when mean arterial blood pressure was less than 60 mm Hg and cardiac index was less than 2.5 L/min·m^2 in spite of sufficient volume infusion (target for cardiac index, 2.5 to 3.5 L·min^{-1}·m^{-2}). Norepinephrine was administered when systemic vascular resistance was less than 600 dyne·sec·cm^{-5} and mean arterial blood pressure was less than 60 mm Hg (target for systemic vascular resistance, 600 to 1,000 dyne·sec·cm^{-5}). The patients were managed by physicians who were not involved in the study and were blinded to the patients in the groups.

Measurements

Heart rate, mean arterial blood pressure, pulmonary artery pressure, pulmonary capillary wedge pressure, central venous pressure, and cardiac output (thermodilution technique using pulmonary artery catheter) were monitored and derived by hemodynamic measurements were calculated (systemic vascular resistance, cardiac index).

Creatinine, hemoglobin, blood gases, and electrolytes were measured from arterial blood samples or urine specimen using standard laboratory techniques. Creatinine clearance and fractional sodium clearance were calculated by standard formulae.

Urine concentrations of N-acetyl-β-D-glucosaminidase (β-NAG: analyzed by a spectrophotometric method; Hoffmann La-Roche, Basel, Switzerland; normal values

in healthy volunteers, 0 to 7 U/L), α_1-microglobulin (analyzed by immunonephelometry, Behring Werke; Marburg, Germany; normal values in healthy volunteers, < 14 mg/L), glutathione transferase-π (GST-π) (measured by enzyme immunoassay with Nephkit-π, Biotrin International; Sinsheim-Reihen, Germany; normal values in healthy volunteers, 12 to 15 μg/L), and glutathione transferase-α (GST-α) (analyzed by enzyme immunoassay using Nephkit-α, Biotrin International; Sinsheim-Reihen, Germany, normal values in healthy volunteers, 3.5 ± 11.1 μg/L) were additionally measured. All measurements were carried out after induction of anesthesia (T0), at the end of operation (T1), at the first postoperative day (T2), and at the second postoperative day (T3) in the intensive care unit.

Statistics

The number of patients required in each group was determined using a power analysis according to data obtained from a previous study on the release patterns of urinary α-glutathione-S-transferase [10]. Although there is no generally accepted normal range for this biochemical marker during cardiopulmonary bypass, we felt that a 50% increase of urinary GST-α excretion from base line might be of clinical importance. The approximate standard deviation of urinary GST-α excretion has been found to be 22 μg per day. The alpha error was set at 0.05 (two-sided), and the type II error was set at 0.2. Based on this assumption, a minimum of 44 patients per group were required. Assuming a 15% subject drop out rate, the sample size was increased to 50 patients per study group.

All data are expressed as mean and standard deviation unless otherwise indicated. An SPSS PC+ software package was used for statistical analyses (V 4.0. SPSS, Inc, Chicago, IL). All categorical variables were tested by the χ^2 test. All normally distributed data (tested by the Kolmogorov-Smirnov test) were analyzed using the student's t test. One-way and two-way analysis of variance with repeated measures and post hoc Scheffé's test were used to determine the effects of group, time, and group–time interaction. The Mann–Whitney U test or the Kruskal-Wallis test was used when appropriate. A p value less than 0.05 was considered significant.

Table 2. Fluid Input and Output (Cumulative)

	Until End of Operation	Until First Postoperative Day	Until Second Postoperative Day
Ringer's lactate (mL)			
CPB > 90 min	2770 ± 450	4940 ± 410	6130 ± 370
CPB < 70 min	2490 ± 380	4800 ± 470	5600 ± 480
Colloids (mL)			
CPB > 90 min			
Gelatin (n = 26)	1260 ± 270	2990 ± 340	3670 ± 260
HES 130/0.4 (n = 24)	930 ± 190	2350 ± 410	3050 ± 290
CPB < 70 min			
Gelatin (n = 28)	1100 ± 150	2950 ± 290	3550 ± 350
HES 130/0.4 (n = 22)	890 ± 290	2150 ± 240	2800 ± 250
Blood loss (mL)			
CPB > 90 min	690 ± 140	1070 ± 220	1190 ± 230
CPB < 70 min	640 ± 180	950 ± 250	1050 ± 210
Urine output (mL)			
CPB > 90 min	1150 ± 390	5550 ± 570	8160 ± 1540
CPB < 70 min	1330 ± 480	5900 ± 440	8240 ± 1390
Blood/blood products (cumulative data)			
PRBC (no. of pts./ total no. of units per group)			
CPB > 90 min	18[a]/30[a]	25[a]/62[a]	31[a]/70[a]
CPB < 70 min	15/32	20/40	20/42
FFP (no. of pts/ total no. per group)			
CPB > 90 min	9[a]/24[a]	11/34[a]	11/36[a]
CPB < 70 min	4/14	9/21	9/21

[a] $P < 0.05$ different to the other group.

Mean ± standard deviation.

CPB = cardiopulmonary bypass; FFP = fresh frozen plasma; HES = hydroxyethylstarch; no. = number; PRBC = packed red blood cells; pts = patients.

Results

CPB lasted for 58 ± 12 minutes and 116 ± 18 minutes, respectively (Table 1). All demographic data, type of operation, and preoperative medication of the two groups were without statistical differences (Table 1). Use of crystalloids and colloids also was without significant differences between the two groups (Table 2). In the group of patients undergoing CPB, more than 90 minutes significantly more patients needed significantly more units of packed red blood cells and fresh frozen plasma (Table 2). The number of patients who needed catecholamines during CPB (norepinephrine) and in the postoperative period (epinephrine, norepinephrine, dobutamine) was similar in both groups (Table 3).

Hemodynamics were comparable in both groups throughout the entire study period (Table 4). None of the patients suffered from ARF requiring dialysis. Two patients of the CPB more than 90 minutes died (1 after 17 days, 1 after 10 days) due to multi-organ failure.

Creatinine clearance was normal in all patients at base line and remained almost normal without group differences during the entire study period (Fig 1). Fractional excretion of sodium was also normal at base line and increased significantly in both groups with the significant higher increase in the group with CPB more than 90 minutes (Fig 1). β-NAG and α_1-microglobulin urine concentrations were also within normal range at base line (Fig 2). In both groups they increased significantly after CPB showing the highest increase in the CPB more than 90 minutes patients. On the second postoperative there were still significant group differences (α_1-

Table 3. Use of Catecholamines

	Until End of Operation	At the First Postoperative Day	At the Second Postoperative Day
Norepinephrine (no. of patients/range)			
CPB > 90 min	45/3–10 μg/kg	22/2–11 μg/kg/min	6/2–8 μg/kg/min
CPB < 70 min	43/4–13 μg/kg	20/3–12 μg/kg/min	4/2–6 μg/kg/min
Epinephrine (no. of patients/range [μg/kg/min])			
CPB > 90min	29[a]/4–24	17[a]/6–12	3/2–6
CPB < 70min	10/2–18	9/2–8	...
Dobutamine (no. of patients/range [μg/kg/min])			
CPB > 90min	14[a]/2–14	9/2–10	4/2–12
CPB < 70min	9/2–10	4/2–8	...

[a] $P < 0.05$ different to the other group.

CPB = cardiopulmonary bypass; no. = number.

microglobulin CPB > 90 minutes, 18.2 ± 2.9 mg/L vs 8.5 ± 2.0 mg/L in the CPB < 70 minutes group).

GST-α and GST-π urine concentrations were within the normal range in both groups at baseline (Fig 3). They increased in both groups, with the highest significant increase in the patients with CPB more than 90 minutes (GST-α CPB > 90 minutes, from 3.0 ± 1.0 to 12.9 ± 2.9 μg/L; GST-α CPB < 70 minutes, from 2.4 ± 0.5 to 5.5 ± 1.2 μg/L).

Comment

Despite improvements in surgical techniques, CPB equipment and anesthesia management, postoperative kidney dysfunction is still a challenging problem in cardiac operations [11]. We measured kidney-specific proteins because standard markers of renal damage such as creatinine and creatinine clearance are not sensitive enough to detect discrete changes in renal function [3, 8, 9]. To detect subclinical and transient renal dysfunction after CPB we measured N-acetyl-β-glucosaminidase (a sensitive marker of proximal lysosomal tubular damage) [12, 13] and α_1-microglobulin, which is filtered at the glomerulus and reabsorbed (95%) at the proximal tubule and is a marker for proximal tubular damage even when no histologic damage is seen [14]. We also measured urine concentrations of GST enzymes that appeared to be more specific for renal tubular injury than other proteins found in the urine [15]. GST-α is considered a marker of proximal tubular cell injury [16], whereas GST-π indicates distal tubular damage [17]. We measured both isoenzymes of GST because they differ with regard to size and charge. Some filtration of the α-form might be seen, but hardly any filtration of the negatively charged π-enzyme through the glomerulus take place [18]. We distinguished patients with CPB times of less than 70 minutes

Table 4. Hemodynamics in the Two Groups

		Before Operation	At End of Operation	First Postoperative Day	Second Postoperative Day
MAP (mm Hg)	CPB > 90 min	72.2 ± 5.9	78.4 ± 6.9	80.6 ± 10.1	65.8 ± 7.7
	CPB < 70 min	74.4 ± 6.6	80.4 ± 8.8	78.7 ± 11.1	63.2 ± 7.7
HR (min^{-1})	CPB > 90 min	56.4 ± 5.9	92.6 ± 12.1	89.4 ± 11.1	86.3 ± 7.9
	CPB < 70 min	59.6 ± 8.8	90.6 ± 13.5	85.3 ± 7.8	87.4 ± 8.9
PAP (mm Hg)	CPB > 90 min	20.3 ± 3.2	25.5 ± 3.3	22.3 ± 4.4	26.9 ± 3.3
	CPB < 70 min	18.5 ± 3.3	23.8 ± 4.0	20.8 ± 5.3	23.5 ± 4.1
PCWP (mm Hg)	CPB > 90 min	13.0 ± 2.2	15.3 ± 3.3	12.0 ± 2.1	...
	CPB < 70 min	11.9 ± 2.1	13.3 ± 2.2	10.9 ± 2.3	...
CVP (mm Hg)	CPB > 90 min	9.9 ± 1.9	12.2 ± 2.4	10.9 ± 2.2	10.5 ± 2.3
	CPB < 70 min	10.9 ± 2.0	11.9 ± 1.9	10.1 ± 2.1	9.8 ± 2.1
CI ($L \cdot min \cdot m^2$)	CPB > 90 min	2.05 ± 0.2	2.67 ± 0.2	2.77 ± 0.3	...
	CPB < 70 min	2.22 ± 0.2	2.72 ± 0.2	2.91 ± 0.4	...
SVR ($dyne \cdot sec \cdot cm^{-5}$)	CPB > 90 min	1318 ± 196	1099 ± 271	1226 ± 164	...
	CPB < 70 min	1349 ± 154	1070 ± 221	1091 ± 188	...

Mean ± standard deviation.

CI = cardiac index; CPB = cardiopulmonary bypass; CVP = central venous pressure; HR = heart rate; MAP = mean arterial blood pressure; PAP = pulmonary artery pressure; PCWP = pulmonary capillary wedge pressure; SVR = systemic vascular resistance.

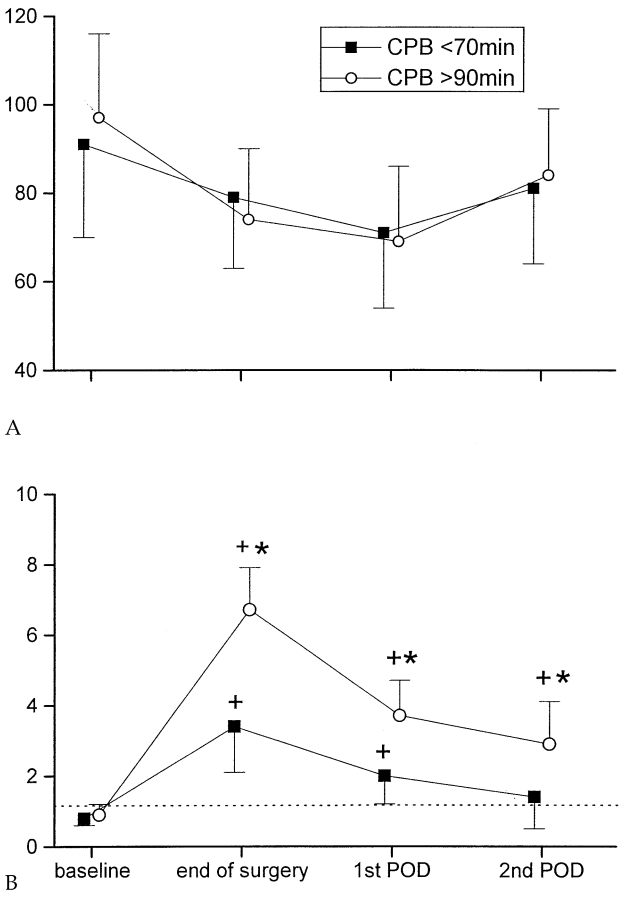

Fig 1. Changes in (A) creatinine clearance (normal value, 70 to 110 mL/min) and (B) fractional excretion of sodium (normal value, < 1%) in the two groups. $^{+}$p *less than 0.05 different to baseline data;* *p *less than 0.05 different to the other group;* dashed line *indicates normal range. (*CPB = *cardiopulmonary bypass;* POD = *postoperative day.)*

and more than 90 minutes, because in a prospective study of patients undergoing CPB times more than 100 minutes, a greater rise in gut permeability was demonstrated [19]. Moreover it has been shown that inflammatory response was relatively small in CPB times of less than 70 minutes and increased significantly beyond 80 minutes of CPB times [20].

One major finding of the present study was that CPB altered kidney function in all our patients as seen by an increase in the fractional excretion of sodium in urine and by an increase in urine concentrations of kidney-specific proteins. Our results are in agreement with other studies also showing transient alterations in sensitive markers of kidney dysfunction in the absence of conventional markers of renal function abnormalities (eg, creatinine, creatinine clearance) [3, 21]. In addition, our study reveals that duration of CPB has a considerable negative influence on alterations of kidney function integrity. Our patients undergoing CPB more than 90 minutes always showed significantly higher urine levels of kidney-specific proteins than the group of patients with CPB times of less than 70 minutes, indicating considerable kidney damage. However, conventional measures of kidney function were without significant differences. Most changes in kidney function in the patients undergoing CPB more than 90 minutes were also seen on the second postoperative day, whereas in the other group urine concentrations of kidney-specific proteins have almost returned to normal base line values indicating normalization of kidney function.

The reason for the more pronounced alterations in kidney function after prolonged CPB cannot definitely be named from the present data. The worst situation is prolonged poor perfusion with hypoxemic blood through renal proximal tubules so that sodium transport is no longer possible, leading to a failure in cell wall integrity, cell swelling, and finally cell death. Gormley and colleagues [3] demonstrated that cardiac operations using CPB resulted in changes in plasma and urinary cytokine homeostasis that correlated with renal tubular dysfunc-

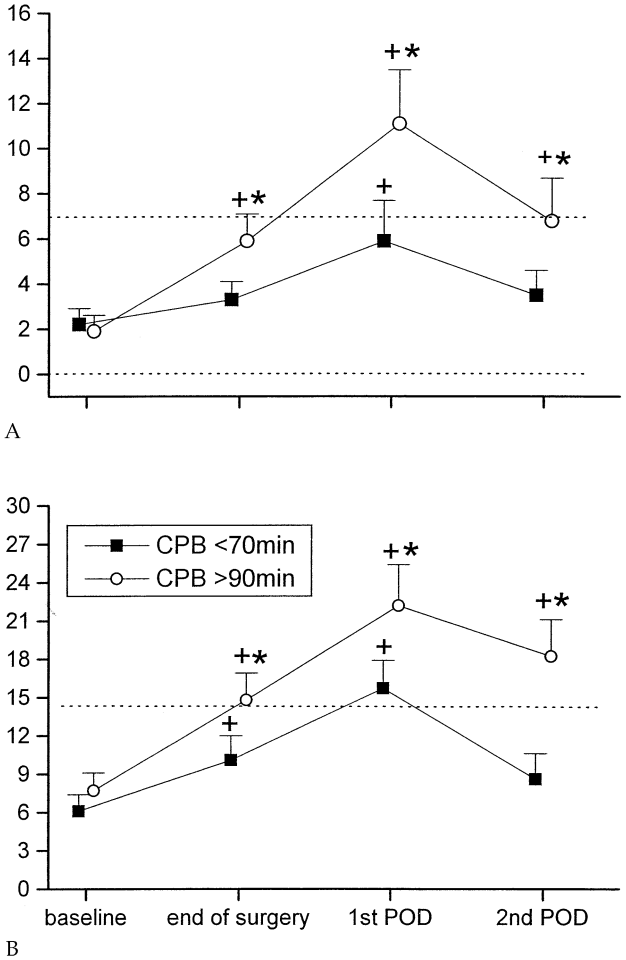

Fig 2. Changes in (A) N-acetyl-β-D-glucosaminidase (normal value, 0 to 7 U/L) and (B) α_1-microglobulin (normal value, < 14 mg/L) in the two groups. $^{+}$p *less than 0.05 different to baseline data;* *p *less than 0.05 different to the other group;* dashed lines *indicate normal range. (*CPB = *cardiopulmonary bypass;* POD = *postoperative day.)*

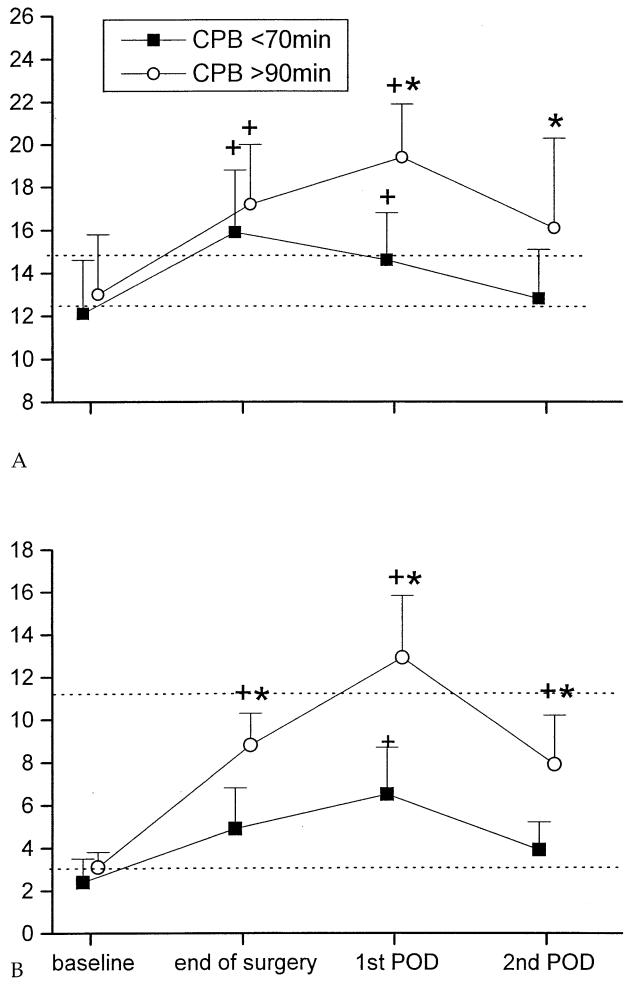

Fig 3. Changes in (A) glutathione transferase-π creatinine clearance (normal value, 12 to 15 μg/L) and (B) glutathione transferase-α (normal value, 3.5 ± 11.1 μg/L) in the two groups. $^{+}$p *less than 0.05 different to baseline data;* *p *less than 0.05 different to the other group;* dashed lines indicate *normal range.* (CPB = *cardiopulmonary bypass;* POD = *postoperative day.)*

tion. This dysfunction may be related to the renal filtration of proinflammatory mediators. The kidney is involved in controlling the proinflammatory response [22]; however, the kidney appears to be damaged by the proinflammatory response it is seeking to control [3]. As proinflammatory cytokine release is increased with duration of CPB [23] and adhesion of blood corpuscles to the endothelial vessel lining is increased [24] by the duration of CPB, this might be one explanation of the higher urine concentrations of kidney-specific proteins and the higher fractional excretion of sodium indicating tubular necrosis in our patients with CPB times more than 90 minutes. Others [25] found altered renal circulatory measurements during cardiac operations using hypothermic CPB (eg, renal plasma flow decreased during CPB), which may be associated with deteriorated renal function. All our patients received aprotinin; thus it unlikely that aprotinin is responsible for the differences in kidney damage between the two groups.

The importance of CPB on kidney function has been demonstrated by Ascione and colleagues [26] comparing off-pump coronary artery bypass operations with CPB-based cardiac operations in which the authors found increased urinary concentrations of kidney-specific proteins such as N-acetyl- β-D-glucosaminidase.

Preoperative renal function is one of the important predictors of postoperative development of ARF [27]. Preoperative creatinine levels of more than 160 mmoL/dL progressively increase the risk of development of ARF [28]. None of our patients suffered from manifest ARF in the postoperative period; however none of our patients showed impaired renal function at base line even when assessed by sensitive markers of kidney dysfunction. Kidney function alterations in our groups of patients with CPB times more than 90 minutes were only moderate and transient as seen by the reduction of urine concentrations already on the second postoperative day. It is tempting to speculate whether patients with preexisting renal dysfunction undergoing long-lasting CPB times have alterations in kidney function that would have been more pronounced.

It is summarized that in cardiac operation patients without preexisting renal function damage undergoing CPB times more than 90 minutes kidney function was significantly more altered than in patients with CPB times less than 70 minutes. Measuring urinary concentrations of sensitive kidney-specific proteins may be helpful in detecting patients at risk for development of ARF earlier than with conventional markers of renal dysfunction. Patients undergoing complex cardiac operations with prolonged CPB times may benefit the most from therapeutic interventions to prevent development of postoperative acute renal failure.

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