

Effects of Cardiopulmonary Bypass on Renal Perfusion, Filtration, and Oxygenation in Patients Undergoing Cardiac Surgery

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ABSTRACT

Background: Acute kidney injury is a common complication after cardiac surgery with cardiopulmonary bypass. The authors evaluated the effects of normothermic cardiopulmonary bypass on renal blood flow, glomerular filtration rate, renal oxygen consumption, and renal oxygen supply/demand relationship, *i.e.*, renal oxygenation (primary outcome) in patients undergoing cardiac surgery.

Methods: Eighteen patients with a normal preoperative serum creatinine undergoing cardiac surgery procedures with normothermic cardiopulmonary bypass ($2.5 \text{ l} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$) were included after informed consent. Systemic and renal hemodynamic variables were measured by pulmonary artery and renal vein catheters before, during, and after cardiopulmonary bypass. Arterial and renal vein blood samples were taken for measurements of renal oxygen delivery and consumption. Renal oxygenation was estimated from the renal oxygen extraction. Urinary *N*-acetyl- β -D-glucosaminidase was measured before, during, and after cardiopulmonary bypass.

Results: Cardiopulmonary bypass induced a renal vasoconstriction and redistribution of blood flow away from the kidneys, which in combination with hemodilution decreased renal oxygen delivery by 20%, while glomerular filtration rate and renal oxygen consumption were unchanged. Thus, renal oxygen extraction increased by 39 to 45%, indicating a renal oxygen supply/demand mismatch during cardiopulmonary bypass. After weaning from cardiopulmonary bypass, renal oxygenation was further impaired due to hemodilution and an increase in renal oxygen consumption, accompanied by a seven-fold increase in the urinary *N*-acetyl- β -D-glucosaminidase/creatinine ratio.

Conclusions: Cardiopulmonary bypass impairs renal oxygenation due to renal vasoconstriction and hemodilution during and after cardiopulmonary bypass, accompanied by increased release of a tubular injury marker. (**ANESTHESIOLOGY 2017; 126:205-13**)

ACUTE kidney injury (AKI) is a prevalent complication after cardiac surgery with cardiopulmonary bypass (CPB). The incidence of post-cardiac surgery AKI ranges between 15% and 30%, depending on the complexity of the procedure.¹⁻⁴ Dialysis-dependent AKI, occurring in 2 to 5% of cardiac surgery patients, carries a mortality between 50% and 80%^{5,6} and is associated with high hospital costs.⁷ Indeed, even minor elevations in serum creatinine after cardiac surgery are an independent risk factor for increased morbidity and mortality.^{6,8,9}

Renal ischemia has been considered an important pathway in the development of post-cardiac surgery AKI.^{10,11} In general, CPB perfusion flow rates of 2.0 to $2.4 \text{ l} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$ ^{10,12,13} or 2.5 to $3 \text{ l} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$ ^{14,15} at a mean perfusion pressure of 50 to 75 mmHg are considered adequate to maintain systemic oxygen delivery. In humans, however, little is known about the effects of

What We Already Know about This Topic

- Dialysis-dependent acute kidney injury, occurring in 2 to 5% of cardiac surgery patients, carries a mortality between 50% and 80% and is associated with high hospital costs. Indeed, even minor elevations in serum creatinine after cardiac surgery are an independent risk factor for increased morbidity and mortality.
- This study evaluated the effects of normothermic cardiopulmonary bypass on renal blood flow, glomerular filtration rate, renal oxygen consumption, and renal oxygen supply/demand relationship (primary outcome) in patients undergoing cardiac surgery.

What This Article Tells Us That Is New

- Cardiopulmonary bypass impairs renal oxygenation due to renal vasoconstriction and hemodilution during and after cardiopulmonary bypass, accompanied by an increase in *N*-acetyl- β -D-glucosaminidase.

This article is featured in "This Month in Anesthesiology," page 1A. Corresponding article on page 199. This article has a video abstract. Preliminary data from this study were presented orally at the 30th annual meeting of the European Society of Cardiothoracic Anesthesiologists, Gothenburg, Sweden, June 25, 2015.

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CPB on renal blood flow (RBF), the major determinant of renal oxygen delivery (RDO₂). Andersson *et al.*¹⁶ showed that RBF was positively correlated to mean arterial pressure, during hypothermic (28°C), nonpulsatile CPB, suggesting an impairment of renal autoregulation. Thus, hypotension during CPB might cause a low RDO₂ increasing the risk of AKI.¹⁷ A decreased RDO₂ may also be caused by hemodilution because of priming the CPB circuit with cell-free solution, usually a crystalloid. It has been shown that the degree of hemodilution^{10,12,13,17–20} and a decreased systemic oxygen delivery²⁰ are independent risk factors for the development of postoperative AKI.

The major determinant of renal oxygen consumption (RVO₂) is the metabolic work of tubular sodium reabsorption.^{21–25} Tubular transport processes are highly load-dependent, and there is a close relationship between glomerular sodium filtration, renal sodium reabsorption, and RVO₂.^{23–25} The effect of normothermic CPB on glomerular filtration rate (GFR), the major determinant of RVO₂, has not previously been described.

The renal oxygen extraction (RO₂Ex) is approximately 10% after uncomplicated cardiac surgery,^{23–28} suggesting a favorable global renal oxygen supply/demand relationship. However, the renal medulla borders on hypoxia already under normal conditions. This is caused by high medullary utilization of oxygen and a relative low perfusion, evidenced by a tissue P_{O₂} of 10 to 20 mmHg in the outer medulla compared with 50 mmHg in the renal cortex.²⁹ The outer portion of the renal medulla is therefore particularly sensitive to impaired RDO₂ and is prone to injury, as commonly assessed *via* renal tubular injury markers.³⁰

To increase our understanding of the renal effects of cardiac surgery with normothermic CPB, we measured RBF and oxygen delivery, GFR and RVO₂ as well as the renal oxygen supply/demand relationship, before, during, and after open cardiac surgery utilizing CPB. We used an indwelling renal vein catheter and the infusion clearance technique³¹ for intraoperative assessment of RBF and GFR by renal extractions of *para*-aminohippuric acid (PAH) and 51 chromium-ethylenediamine tetraacetic acid (⁵¹Cr-EDTA; GE Healthcare Limited, United Kingdom), respectively. The primary endpoint of the current study was changes in renal oxygenation, expressed as changes in RO₂Ex. We tested the hypothesis that normothermic CPB induces an impaired RDO₂, causing a renal oxygen supply/demand mismatch.

Materials and Methods

Patients

The study protocol was approved by the Gothenburg Regional Ethics Committee, Gothenburg, Sweden (<http://www.epn.se>), and written informed consent was obtained from all patients on the day before surgery. The study was registered in ClinicalTrials.gov (identifier NCT02405195). Date of registration: March 27, 2015. Principal investigator: Lukas Lannemyr. The inclusion criteria were (1) age greater than 18 yr, (2) preoperative left ventricular ejection fraction greater than or equal to 50%,

(3) preoperative normal renal function (preoperative serum creatinine less than 110 μM for men and less than 90 μM for women), (4) elective, open cardiac surgery with CPB, and (5) an expected time on CPB exceeding 60 min. The exclusion criteria were (1) CPB time less than 60 min, (2) unsuccessful catheterization of the renal vein, (3) contraindication to radiocontrast, (4) cardiac transplantation, and (5) thoracic aortic surgery.

Premedication consisted of oxazepam (10 mg) and oxycodone (10 mg). Anesthesia was induced by fentanyl (5 to 10 μg/kg) and propofol (1 to 1.5 mg/kg), and intubation was facilitated by rocuronium (0.6 mg/kg). Before and after CPB, anesthesia was maintained with sevoflurane (0.5 to 2.5%) in a 50% O₂/air mixture. During CPB, anesthesia was maintained with an intravenous infusion of propofol (2.5 to 4 mg · kg⁻¹ · hr⁻¹).

CPB

The CPB circuit consisted of a Primox[®] or Inspire 8[®] oxygenator (Sorin Group, Italy), an HVR Hard-shell reservoir (Sorin Group), a Sorin Adult[®] tubing system, a Stöckert S5[®] heart–lung machine, and a Stöckert Heater Cooler System 3T[®] (Stöckert Instrumente, Germany). The priming solution consisted of 1,200 ml acetated Ringer's solution and 10,000 IU heparin. Mannitol or hydroxyethyl starch was not used in the pump prime, and neither of these fluids was delivered during or after CPB. Furthermore, loop-diuretics or albumin was not used before, during, or after CPB. After heparinization with 400 IU/kg, the patients were cannulated in the aortic root followed by venous mono- or bicaval cannulation depending on the surgical procedure. Activated clotting time was kept more than 480 s during CPB. Nonpulsatile CPB was performed at a target flow of 2.5 l · min⁻¹ · m⁻², a target hematocrit of 25 to 35%, and a target body temperature of 35 to 36°C. Before weaning from CPB, the patients were rewarmed to a target body temperature of 36.0 to 36.5°C. Mean arterial pressure was maintained at 60 to 80 mmHg using vasopressor (norepinephrine) or vasodilator (nitroprusside) therapy when necessary. Cold, hyperkalemic blood cardioplegia was given at an induction dose of 800 to 1,000 ml followed by subsequent doses when deemed necessary by the surgeon. Alpha-stat pH management was used during CPB. After weaning from CPB, the heparin was antagonized by protamine sulfate (4 mg/kg).

Systemic Hemodynamics

Arterial blood pressure was measured continuously with a radial or femoral artery catheter. A pulmonary artery thermodilution catheter (Baxter Healthcare Corporation, USA) was inserted through either the left subclavian vein or the right jugular internal vein and placed in the pulmonary artery after induction of anesthesia. The arterial blood pressure, heart rate, central venous pressure, and the pulmonary artery pressure were continuously measured. Measurements

of thermodilution cardiac output were performed in triplicate and indexed to the body surface area (BSA) for cardiac index (CI). The pulmonary artery wedge pressure was measured intermittently. The oxygen content of the arterial blood (CaO_2 , ml/l) was calculated as $1.34 \times \text{hemoglobin (g/l)} \times \text{arterial oxygen saturation (\%)} \times 0.01 + (0.23 \text{ ml O}_2/\text{l/mmHg} \times \text{PaO}_2 \text{ (mmHg)})$. Systemic vascular resistance index (SVRI), stroke volume index, systemic oxygen delivery index, and systemic oxygen consumption index (VO_2I) were calculated according to standard formulas.

Measurements of Renal Variables

A 7.5-Fr CCO Pulmonary Artery Catheter® (Edwards Lifesciences Corporation, USA) ($n = 13$) or a 8-Fr catheter (Webster laboratories, USA; $n = 5$) was inserted in the left renal vein *via* the right femoral vein under fluoroscopic guidance. The catheter was placed in the central portion of the renal vein, and its position was verified by venography using ultralow doses of iohexol (Omnipaque® 300 mg I/mL; GE Healthcare, Sweden). Since the cross-sectional area of the renal vein is approximately 25 times the cross-sectional area of the renal vein catheter, the risk of the catheter to partially occlude the vein is minimal. After the collection of blood and urine blanks, an intravenous priming dose of $^{51}\text{Cr-EDTA}$ and PAH (Merck, USA) was given, followed by infusion at a constant rate, individualized to BSA and preoperative serum creatinine. Serum concentrations of PAH and $^{51}\text{Cr-EDTA}$ activity were measured by a spectrophotometer (Beckman DU 530; Life Science UV/Vis, USA) and a well counter (Wizard 3™ 1480, Automatic Gamma Counter; Perkin Elma LAS, Finland), respectively. Renal plasma flow was calculated using the infusion clearance technique as the amount of infused PAH divided by the difference in arterial-renal vein PAH concentrations. Formulas for calculation of the various renal variables are described in table 1. All renal data were normalized to a BSA of 1.73 m^2 .

Urinary Measurements of N-acetyl- β -D-glucosaminidase

Urine was assayed for N-acetyl- β -D-glucosaminidase (NAG) by a spectrophotometric method (ABX Pentra 400; Horiba Medical, USA) using a commercially available kit (Roche Diagnostics GmbH, Germany) with an intraassay coefficient of variation of 4.6 to 10.4% and a lower limit of detection of 0.30 U/l. The urinary NAG/creatinine ratio was calculated.

Experimental Procedure

Measurements of systemic and renal variables were conducted, and blood and urine samples were obtained before CPB (baseline), 30 and 60 min after the start of CPB, and at 30 and 60 min after weaning from CPB.

Statistical Analysis

To detect a relative change of 30% in RO_2Ex during CPB (the primary outcome variable), 15 patients were needed at a power of 80% and a two-sided significance level of

Table 1. Formulas for Calculation of Renal Variables

Variable	Formula
RPF	Amount of PAH infused/([PAH arterial] – [PAH renal vein])
RBF	Amount of PAH infused/([PAH arterial] – [PAH renal vein]) / (1 – hematocrit)
FF	(RPF \times [$^{51}\text{Cr-EDTA}$ arterial] – [RPF – urine flow] \times [$^{51}\text{Cr-EDTA}$ renal vein]) / RPF \times ($^{51}\text{Cr-EDTA}$ arterial)
GFR	FF \times RPF
Renal vascular resistance	(MAP – CVP) / RBF
Renal oxygen consumption	RBF \times (CaO_2 – CrvO_2)
Renal oxygen delivery	RBF \times CaO_2
Renal oxygen extraction	(CaO_2 – CrvO_2) / CaO_2
Renal sodium filtration	GFR \times [Na^+] _s
Renal sodium excretion	Urine flow \times [Na^+] _u
Renal sodium reabsorption	(GFR \times [Na^+] _s) – (urine flow \times [Na^+] _u)

$^{51}\text{Cr-EDTA}$ = 51 chromium-ethylenediaminetetraacetic acid; CVP = central venous pressure; CaO_2 and CrvO_2 = arterial and renal vein oxygen contents; FF = filtration fraction; GFR = glomerular filtration rate; MAP = mean arterial pressure; [Na^+]_s = serum sodium concentration; [Na^+]_u = urine sodium concentration; PAH = *para*-aminohippuric acid; RBF = renal blood flow; RPF = renal plasma flow.

0.05, at a SD of 0.040 (paired design), based on data from a recent study.²⁷ We aimed to compile approximately 18 to 20 patients who could be analyzed. We know from our previous experiences with this technique that we need to include 30 to 50% more patients to compensate for dropouts. Data were analyzed by repeated-measures ANOVA. A significant ANOVA was followed by a Bonferroni–Holm *post hoc* test for comparison of baseline (pre-CPB) values *versus* data from subsequent measuring points. Data obtained after CPB (30 and 60 min) were pooled. A within-subject correlation was performed to correlate NAG/creatinine ratio to RO_2Ex . Data are presented as mean \pm SD. A $P < 0.05$ (two-tailed) was considered significant. Predictive Analytics Software Statistics 18.0 (SPSS Inc., USA) was used for statistical analyses.

Results

Informed consent was obtained from 28 patients the day before surgery. The clinical trial profile is shown in fig. 1. Surgery was cancelled or postponed in four patients; two patients were considered noneligible by the surgeon; in one patient, the CPB time was shorter than 60 min; and in three patients, catheterization of the renal vein was unsuccessful. Thus, the study protocol was completed in 18 patients. Patient characteristics are described in table 2.

Effects of CPB on Systemic Hemodynamics, Arterial Oxygen Content, and Systemic Oxygen Delivery Index

CI before CPB was 1.87 ± 0.39 . Mean systemic perfusion flow rate during CPB was 2.47 ± 0.08 at 30 min and $2.49 \pm 0.08 \text{ l} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$ at 60 min (table 3). Systemic perfusion flow thus increased by 32 to 33% ($P < 0.05$ and

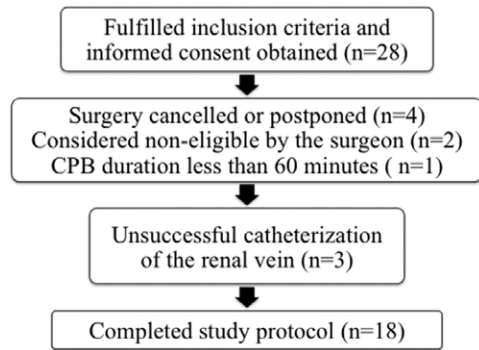


Fig. 1. Clinical trial profile. CPB = cardiopulmonary bypass.

Table 2. Patient Characteristics

No. of Patients (n)	18
Male gender, n (%)	16 (89)
Age, yr	70 ± 7
Body surface area, m ²	1.95 ± 0.20
Left ventricular ejection fraction, %	58 ± 5
Hypertension, n (%)	10 (56)
Preoperative serum creatinine, μM	87 ± 11
ACE inhibitor, n (%)	12 (67)
β-Adrenergic inhibitor, n (%)	12 (67)
Calcium channel antagonists, n (%)	2 (11)
Loop diuretics, n (%)	9 (50)
Valve surgery, n (%)	9 (50)
CABG plus valve surgery, n (%)	9 (50)
Cardiopulmonary bypass time, min	132 ± 31
Aortic cross-clamp time, min	103 ± 24

Values are mean ± SD.

ACE inhibitor = angiotensin converting enzyme inhibitor; CABG = coronary artery bypass grafting.

Table 3. Systemic Variables

	Pre-CPB	30-min CPB	60-min CPB	Post-CPB	P Value (ANOVA)
MAP, mmHg	76 ± 12	75 ± 10	73 ± 10	70 ± 7	0.16
CI or perfusion flow rate, l · min ⁻¹ · m ⁻²	1.87 ± 0.39	2.47 ± 0.08*	2.49 ± 0.08*	2.21 ± 0.52†	< 0.001
SVRI, dynes × s · cm ⁻⁵ · m ⁻²	2,909 ± 724	2,463 ± 396‡	2,402 ± 405†	2,308 ± 520†	0.003
MPAP, mmHg	26 ± 8	NA	NA	24 ± 4	0.38
PCWP, mmHg	18 ± 6	NA	NA	13 ± 3‡	0.030
CVP, mmHg	11 ± 4.0	-1 ± 4*	-1 ± 4*	9 ± 3	< 0.001
Hematocrit	0.37 ± 0.05	0.31 ± 0.04*	0.30 ± 0.04*	0.31 ± 0.04*	< 0.001
Serum hemoglobin, g/l	125 ± 3	102 ± 3*	100 ± 3*	103 ± 3*	< 0.001
CaO ₂ , ml/l	171 ± 19	141 ± 18*	138 ± 16*	139 ± 17*	< 0.001
DO ₂ I, ml · min ⁻¹ · m ⁻²	319 ± 59	346 ± 45	343 ± 38	305 ± 78	0.038
VO ₂ I, ml · min ⁻¹ · m ⁻²	74 ± 17	81 ± 11	81 ± 11	89 ± 16‡	0.007
SvO ₂ , %	75 ± 6	76 ± 4	76 ± 3	67 ± 5*	< 0.001
Temp, °C	35.7 ± 0.41	35.6 ± 0.32	35.7 ± 0.43	36.4 ± 0.39*	< 0.001
Norepinephrine, μg · kg ⁻¹ · min ⁻¹	0.020 ± 0.011	0.017 ± 0.007	0.020 ± 0.009	0.076 ± 0.030	0.046

Values are mean ± SD. Bonferroni-Holm adjustment for multiple comparisons was used.

*P < 0.001 vs. baseline. †P < 0.01. ‡P < 0.05.

CaO₂ = arterial oxygen content; CI = cardiac index; CPB = cardiopulmonary bypass; CVP = central venous pressure; DO₂I = systemic oxygen delivery index (ml · min⁻¹ · m⁻²); MAP = mean arterial pressure; MPAP = mean pulmonary artery pressure; NA = not applicable; PCWP = pulmonary capillary wedge pressure; SvO₂ = mixed venous oxygen saturation; SVRI = systemic vascular resistance index (dynes × s · cm⁻³ · m⁻²); Temp = body temperature; VO₂I = systemic oxygen consumption (ml · min⁻¹ · m⁻²).

P < 0.001), and SVRI decreased by 15 to 17% (P < 0.05 and P < 0.01) during CPB, compared with pre-CPB values, while mean arterial pressure (MAP) was not significantly changed. Hematocrit, serum hemoglobin, and CaO₂ decreased by 16 to 20% (P < 0.001) during CPB. In spite of this, Systemic Oxygen Delivery Index (DO₂I), if anything, increased (8%), due to the increase in systemic perfusion flow rate during CPB (fig. 2). Body temperature and VO₂I were not significantly affected during CPB.

After CPB, CI was higher (18%; P < 0.01), SVRI was lower (-21%; P < 0.01), while MAP was not different from the pre-CPB values. After CPB, hematocrit, serum hemoglobin, and CaO₂ were lower (16 to 19%; P < 0.001) when compared with the pre-CPB values. After CPB, body temperature and VO₂I (20%, P < 0.05) were significantly higher when compared with the pre-CPB values.

Two patients received nitroprusside during the trial to maintain MAP less than 80 mmHg. Twelve patients required norepinephrine to maintain a target MAP between 60 and 80 mmHg. The dose of norepinephrine was not changed during CPB. After CPB, the dose of norepinephrine was significantly higher when compared with the pre-CPB dose. No other inotropic or vasoactive agents were used in the current study.

Effects of CPB on Renal Variables

During CPB, renal vascular resistance (RVR) increased by 15 to 23% (ANOVA, P < 0.005) with no change in RBF (table 4). Thus, as systemic perfusion flow increased, the relationship between RBF and perfusion flow, the RBF/CI ratio, decreased by 25 to 29% (P < 0.01 and 0.001), suggesting a redistribution of blood flow away from the kidneys during CPB. Hemodilution, in combination with a maintained RBF, caused an

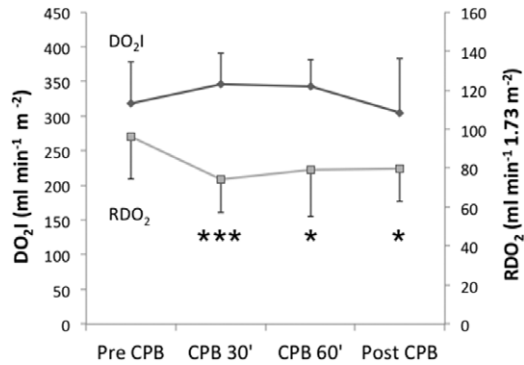


Fig. 2. The effects of cardiopulmonary bypass (CPB) on systemic oxygen delivery index (DO₂I) and renal oxygen delivery (RDO₂) before (Pre-CPB), 30 min (CPB 30') and 60 min (CPB 60') after initiation of CPB, and after end of CPB (Post-CPB). ****P* < 0.001, **P* < 0.05 versus baseline (Pre-CPB).

18 to 23% decrease in RDO₂ (*P* < 0.05 and *P* < 0.001; fig. 2). GFR, filtration fraction, sodium filtration, sodium reabsorption, and urine flow were not affected by CPB. RVO₂ was not affected, while RO₂Ex increased by 33 to 44% (*P* < 0.05) during CPB (fig. 3). Neither arterial PAH concentration nor renal PAH extraction was changed during CPB.

After CPB, RDO₂ was still lower (–17%; *P* < 0.05), while RBF and RVR were not different from the pre-bypass values. After CPB, GFR, filtration fraction, sodium filtration, sodium reabsorption, and urine flow did not differ from baseline. After CPB, RVO₂ was higher (50%; *P* < 0.05) compared with baseline, and RO₂Ex increased further and was 78% higher (*P* < 0.001) than the baseline value (fig. 3). After CPB, arterial PAH concentration and renal PAH extraction did not differ from baseline.

The RVO₂/mM sodium reabsorbed was 0.9 ± 0.3 ml/mM before CPB and increased by 55% to 1.4 ± 0.4 ml/mM after CPB (*P* < 0.01).

Table 4. Renal Variables

	Pre-CPB	30-min CPB	60-min CPB	Post-CPB	<i>P</i> Value (ANOVA)
Renal perfusion pressure, mmHg	66 ± 11	76 ± 12*	75 ± 12*	61 ± 7	< 0.001
RBF, ml · min ⁻¹ · 1.73 m ⁻²	554 ± 126	524 ± 116	564 ± 162	558 ± 130	0.638
RVR, mmHg · ml ⁻¹ · min ⁻¹	0.127 ± 0.036	0.156 ± 0.044	0.146 ± 0.055	0.116 ± 0.038	0.005
RBF/CI	0.30 ± 0.06	0.21 ± 0.05†	0.23 ± 0.06‡	0.26 ± 0.09	< 0.001
RDO ₂ , ml/min	96 ± 22	74 ± 17†	79 ± 24*	80 ± 17*	0.001
GFR, ml · min ⁻¹ · 1.73 m ⁻²	67 ± 23	68 ± 23	70 ± 19	67 ± 18	0.972
Filtration fraction	0.20 ± 0.07	0.20 ± 0.06	0.19 ± 0.07	0.18 ± 0.06	0.794
Sodium filtration, mM/min	8.6 ± 3.8	9.5 ± 3.2	8.9 ± 3.2	9.1 ± 3.0	0.674
Sodium reabsorption, mM/min	8.4 ± 3.7	9.3 ± 3.1	8.7 ± 3.1	8.9 ± 2.8	0.889
Urine flow, ml/min	2 ± 0.4	2 ± 0.5	1 ± 0.2	3 ± 0.7	0.177
RVO ₂ , ml/min	8 ± 3	9 ± 3	9 ± 3	12 ± 4*	0.017
RO ₂ Ex	0.09 ± 0.03	0.12 ± 0.05*	0.13 ± 0.06*	0.16 ± 0.05†	< 0.001
Arterial PAH concentration	0.282 ± 0.073	0.266 ± 0.069	0.261 ± 0.069	0.274 ± 0.075	0.248
PAH extraction	0.76 ± 0.13	0.75 ± 0.17	0.74 ± 0.13	0.71 ± 0.11	0.692

Values are mean ± SD. Bonferroni–Holm adjustment for multiple comparisons was used.

**P* < 0.05. †*P* < 0.001 vs. baseline. ‡*P* < 0.01.

CPB = cardiopulmonary bypass; GFR = glomerular filtration rate; PAH = *para*-aminohippuric acid; RBF = renal blood flow; RBF/CI = renal blood flow divided by cardiac index; RDO₂ = renal oxygen delivery; RO₂Ex = renal oxygen extraction; RVO₂ = renal oxygen consumption; RVR = renal vascular resistance.

Eleven of 18 patients (61%) increased their serum creatinine, 1 to 2 days postoperatively, compared with the baseline serum creatinine. Four patients (22%) developed postoperative AKI according to the Kidney Disease Improving Global Outcomes criteria³² (Acute Kidney Injury Network stage 1, *n* = 3; Acute Kidney Injury Network stage 3, *n* = 1).

Effects of CPB on Renal Release of the Injury Marker NAG

The urinary NAG/creatinine ratio increased significantly already 30 min after the start of CPB (*P* < 0.05), with a peak, seven-fold increase 30 to 60 min after the end of CPB (*P* < 0.01). The urinary NAG/creatinine ratio was normalized 24 h after CPB. Urinary NAG/creatinine correlated to RO₂Ex (*r* = 0.57; *P* < 0.001; fig. 4).

Discussion

In the current study, we evaluated the effects of CPB on renal perfusion, filtration, and oxygenation in patients undergoing cardiac surgery. The main findings were that despite a maintained systemic oxygen delivery during CPB, the renal oxygen supply/demand relationship was impaired, expressed as an increase in RO₂Ex. Furthermore, renal oxygenation was even further deteriorated after the end of CPB. Finally, the significant positive correlation between NAG release and RO₂Ex during and after CPB suggests that renal hypoxia may have a causative role for the release of tubular injury markers and later postoperative AKI.

The impaired renal oxygenation during CPB was caused by a decreased RDO₂ at a maintained level of RVO₂. The reduced RDO₂ was mainly attributable to a reduced arterial oxygen content due to hemodilution. The RBF remained unchanged despite an increase of more than 30% in the systemic perfusion flow rate during CPB. Thus, CPB seemed to redistribute blood flow away from the kidneys, as reflected by the 25 to 30% fall in the RBF/CI ratio. In the current

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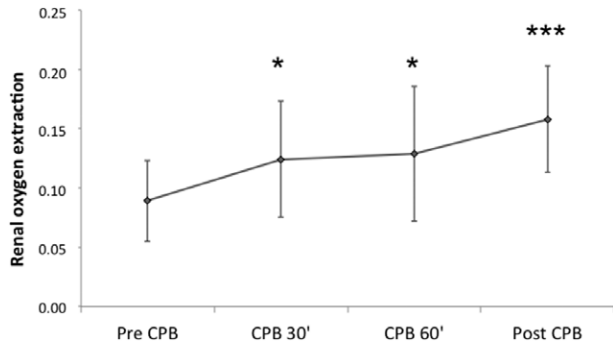


Fig. 3. The effects of cardiopulmonary bypass (CPB) on renal oxygen extraction before (Pre-CPB), 30 min (CPB 30'), and 60 min (CPB 60') after initiation of CPB, and after end of CPB (Post-CPB). * $P < 0.05$, *** $P < 0.001$ versus baseline (Pre-CPB).

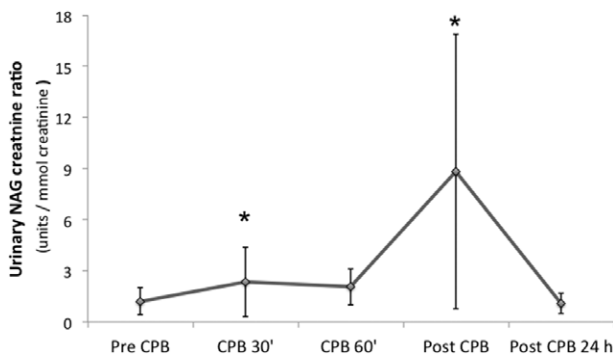


Fig. 4. The effects of cardiopulmonary bypass (CPB) on the urinary *N*-acetyl- β -D-glucosaminidase (NAG)/creatinine ratio before (Pre-CPB), 30 min (CPB 30') and 60 min (CPB 60') after initiation of CPB, and after end of CPB (Post-CPB). * $P < 0.05$ versus baseline (Pre-CPB).

study, one would have expected that RBF should have increased due to hemodilution-induced decrease in blood viscosity and a well-maintained renal perfusion pressure during CPB. On the other hand, RVR increased, which could be explained by the previously described neuroendocrine response to CPB with increases in norepinephrine, vasopressin, and angiotensin II.^{33–38}

Our group has repeatedly shown in postoperative patients that the major determinant of RVO_2 is GFR. An increase in glomerular sodium filtration will increase the tubular sodium load and sodium reabsorption, which will increase RVO_2 .^{23–25} In the current study, GFR was not changed, which could explain the lack of change in RVO_2 during CPB. The oncotic pressure most likely decreased during CPB with the crystalloid prime. One would therefore have expected an increase in GFR, particularly as renal perfusion pressure, if anything, was increased. However, the increased renal perfusion pressure was counteracted by an increase in RVR, involving mainly the preglomerular arterioles, as indicated by the unchanged filtration fraction.

The renal oxygen supply/demand mismatch starting already during CPB was further aggravated after CPB, as shown by a nearly 80% increase in RO_2Ex . The increase in

RVO_2 after CPB could not be attributed to an increase in GFR and tubular reabsorption, since neither of these variables differed from baseline. One obvious explanation is the higher body temperature seen after CPB (36.4° vs. 35.7°C), which increased VO_2I . On the other hand, the increase in RVO_2 was considerably higher than the increase in VO_2I (45% vs. 20%). Another explanation could be the finding that after CPB, the oxygen consumption per millimole of reabsorbed sodium was 55% higher than before, indicating a shift in the relationship between sodium reabsorption and RVO_2 . Such an increased oxygen utilization for tubular sodium transport has previously been described in patients with post-cardiac surgery AKI.²⁶ Efficient vectorized sodium reabsorption is dependent on polarized tubular cells and intact tight junctions. Ischemic tubular damage has been shown to depolarize tubular cells and disrupt tight junctions.^{39–42} Thus, reabsorbed sodium ions may leak back to the tubular lumen to be reabsorbed again, which might explain the high oxygen utilization per millimole net sodium reabsorbed, as seen in the current study. This might, in turn, be caused by tubular injury/dysfunction, as also manifested by the release of renal injury marker NAG.

Ranucci *et al.*¹⁰ have shown that during moderate hypothermic (32° to 34°C) CPB, a hematocrit less than 26% and a systemic oxygen delivery less than $272 \text{ ml} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$ were independent risk factors for the development of AKI. They concluded that their data support the hypothesis that renal ischemia during CPB could explain AKI after cardiac surgery with CPB.¹⁰ In the current study, CPB was performed at a higher body temperature (35° to 36°C). The systemic oxygen delivery was maintained at 340 to $350 \text{ ml} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$, and the hematocrit was approximately 30%, both considerably higher than the renal ischemia threshold values suggested by Ranucci *et al.*¹⁰ Furthermore, systemic oxygen delivery was 10% higher than that of the pre-bypass level. We therefore believe that CPB was safely performed in the current study with respect to systemic oxygen delivery, as mixed venous oxygen saturation was well maintained.

To our knowledge, this is the first study measuring tubular biomarkers systematically and repeatedly both during and immediately after CPB. NAG is a lysosomal enzyme produced predominantly in the proximal tubules. Due to its high molecular weight (130 to 140 kDa), it is not subject to glomerular filtration. NAG is a sensitive marker of tubular damage, and increased urinary excretion is associated with tubular necrosis in cardiac surgery.³⁰ In the current study, the impaired renal oxygenation during CPB was accompanied by a release of NAG, suggesting ischemic tubular damage. Indeed, already 30 min after the start of CPB, we found a significant increase in the urinary NAG/creatinine ratio with a maximal seven-fold increase seen after the end of CPB.

For the detection of early AKI after cardiac surgery, urinary, plasma, and serum markers for tubular injury have been utilized. In a recent survey of 28 studies on cardiac surgery patients, Ho *et al.*⁴³ found that intraoperative

measurements of urine, plasma, or serum biomarkers were performed in only four studies with sample collection immediately after CPB. In these studies, intraoperative discrimination by NAG to detect AKI was as good, or even better, than neutrophil gelatinase-associated lipocalin (NGAL) and kidney injury marker 1: the intraoperative performance (area under the receiver operating characteristic curve) of the biomarkers to detect postoperative AKI was 0.61 to 0.71 for NAG and 0.59 to 0.61 for NGAL. One major problem with NGAL, considered the most promising biomarker of AKI, is that NGAL assays measure different NGAL forms originating from various cell types including leukocytes. Systemic inflammation, commonly seen in cardiac surgery with CPB, may therefore contribute to a nonrenal release and glomerular filtration of NGAL, thus decreasing its specificity for detection of AKI in cardiac surgery.⁴⁴

Our results are supported by previous experimental investigations (pigs, rats) in which the effects of CPB on medullary and cortical tissue P_{O_2} were studied.^{45,46} In those studies, a low medullary P_{O_2} were evident already before initiation of CPB. Medullary P_{O_2} further declined during CPB, particularly at low levels of hemoglobin, and was only partially restored after cessation of CPB.^{45,46}

Our findings are in line with a recent study, in which we evaluated the differential systemic and renal effects of a crystalloid or colloid fluid, when used for plasma volume expansion in post-cardiac surgery patients.²⁷ Both fluids increased CI and RBF but neither of them improved RDO_2 , as they both induced hemodilution. Furthermore, the crystalloid caused an impairment of renal oxygenation due to an increase in RVO_2 , which was not met by an increase in RDO_2 . These data are compatible with previous animal studies, in which a crystalloid was used for plasma volume expansion.^{47–49}

We used the so-called constant infusion clearance technique, in which renal clearance of PAH is calculated from the arterial serum level of PAH and the infusion rate of PAH.^{50–53} This technique for estimation of RBF, corrected for renal extraction of PAH, has been validated in cardiac surgery patients against standard urinary clearance for PAH.³¹ It was found to have a high reproducibility and a high level of agreement with the urinary clearance reference method. The requirements for infusion clearance technique are that the test substance (*e.g.*, PAH) is rapidly equilibrated after the start of infusion, not metabolized and only excreted by the kidney. Furthermore, there should be an equilibrium between rate of infusion and rate of excretion, as indicated by stable serum concentrations of the test substance. In the current study, the arterial PAH concentrations did not change significantly during the procedure, suggesting that these requirements were met.

This study has some limitations. The use of vasopressors may have influenced renal vascular tone and RDO_2 . Twelve patients required norepinephrine during CPB to maintain a MAP between 60 and 80 mmHg. One could argue that the

use of norepinephrine in the majority of the patients (67%) could have contributed to the increase in renal vascular tone and impaired oxygen delivery during and after CPB. We believe that this is less likely, as we have previously shown in post-cardiac surgery patients with AKI that restoration of MAP from 60 to 75 mmHg increased RDO_2 and GFR and improved renal oxygenation.⁵⁴ Furthermore, the switch from sevoflurane to propofol during CPB could have influenced renal vascular tone and RDO_2 . However, experimental studies have shown that propofol does not affect RBF or RVR.^{55,56}

Conclusions

In the current study, we evaluated the renal effects of CPB in patients undergoing open cardiac surgery. The major finding was that despite a 33% increase in systemic perfusion flow rate during CPB, a renal oxygen supply/demand mismatch developed. This was most likely caused by renal vasoconstriction, which in combination with hemodilution decreased RDO_2 by 20% during CPB. This impairment in renal oxygenation was accompanied by a release of a tubular injury marker and was further aggravated after weaning from CPB.

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Competing Interests

The authors declare no competing interests.

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