INFOGRAPHICS IN ANESTHESIOLOGY

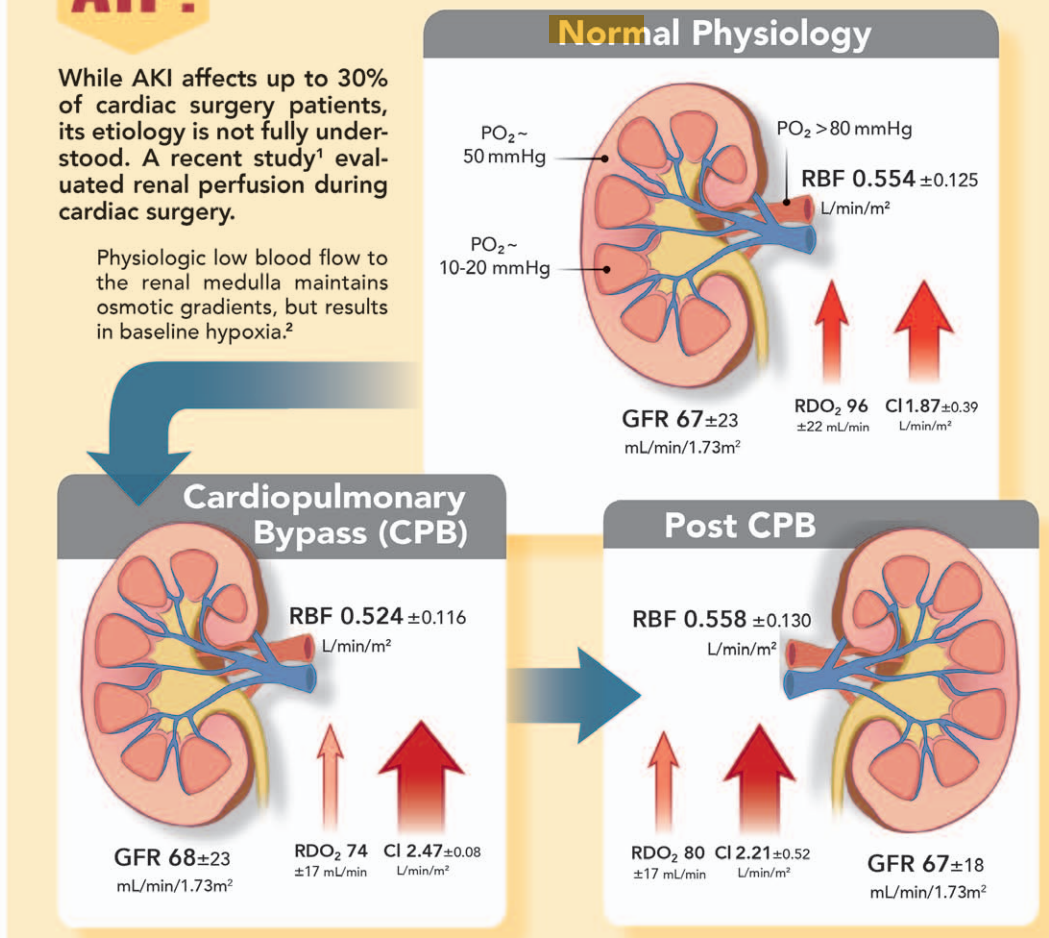
Complex Information for Anesthesiologists Presented Quickly and Clearly

ANESTHESIOLOGY

Into Thin Air: Cardiopulmonary Bypass, Renal Oxygenation, & Acute Kidney Injury

While AKI affects up to 30% of cardiac surgery patients, its etiology is not fully understood. A recent study[1] evaluated renal perfusion during cardiac surgery.

Physiologic low blood flow to the renal medulla maintains osmotic gradients, but results in baseline hypoxia.[2]



During CPB, systemic blood flow increases while renal blood flow is constant. Although renal function is maintained, hemodilution and vasoconstriction reduce renal oxygen delivery.

After CPB, renal oxygen delivery remains low while oxygen extraction increases. This renal oxygenation impairment is accompanied by a 7x rise in urinary NAG, a tubular injury marker.

CPB impairs renal oxygenation and is associated with a rise in a tubular injury marker.

AKI = acute kidney injury; CI = cardiac index; CPB = cardiopulmonary bypass; GFR = glomerular filtration rate; NAG = N-acetyl-β-dglucosaminidase; RBF = renal blood flow; RDO_2 = renal oxygen delivery.

Infographic created by Jonathan P. Wanderer, Vanderbilt University School of Medicine, and James P. Rathmell, Brigham and Women's Health Care/Harvard Medical School; illustration by Annemarie Johnson, Vivo Visuals. Address correspondence to Dr. Wanderer: jonathan.p.wanderer@vanderbilt.edu.

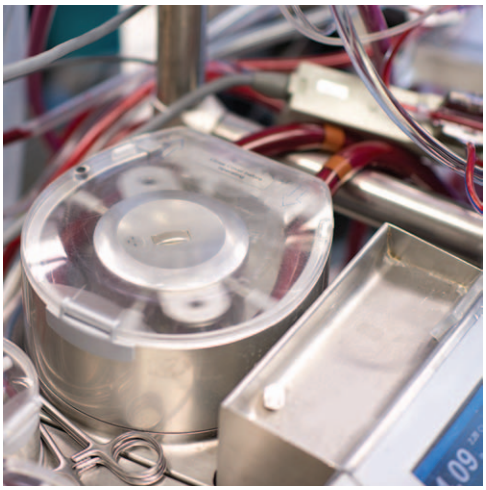
1. Lannemyr L, Bragadottir G, Krumbholz V, Redfors B, Sellgren J, Ricksten S-E. Effects of cardiopulmonary bypass on renal perfusion, filtration, and oxygenation in patients undergoing cardiac surgery. ANESTHESIOLOGY 2017;126:205–13

2. Brezis M, Rosen S. Hypoxia of the renal medulla—its implications for disease. N Engl J Med 1995; 332:647–55

Renal Oxygen Flux during Cardiopulmonary Bypass; Tubular Damage to Preserve Glomerular Filtration—What's a Kidney to Do?

Frederic T. Billings IV, M.D., M.Sc., Yandong Jiang, M.D., Ph.D., Andrew D. Shaw, M.B., F.R.C.A.

ONE quarter of cardiac surgery patients continue to suffer from postoperative acute kidney injury (AKI) despite the advances in perioperative patient management that have reduced mortality and shortened the duration of hospitalization. The majority of these cardiac surgery patients receive cardiopulmonary bypass (CPB) during surgery. CPB fundamentally alters systemic perfusion by providing nonpulsatile blood flow, induces myocardial and pulmonary ischemia, and elicits a significant neurohormonal and inflammatory response. Despite these severe physiologic derangements, the specific effects of CPB on individual and collective organ function remain unclear. In fact, the severity of major organ injury after surgical coronary revascularization appears to be similar in patients randomly assigned to on- or off-pump surgery.[1] It is within this context that Lannemyr *et al.*[2] now provide evidence that renal oxygenation is altered during and after CPB, perhaps providing a partial explanation of how CPB contributes to kidney injury.



"…renal oxygenation is altered during and after cardiopulmonary bypass, perhaps providing a partial explanation of how cardiopulmonary bypass contributes to kidney injury."

Lannemyr *et al.*[2] measured arterial oxygen content, mixed venous oxygen content, cardiac output, renal vein oxygen content, renal blood flow, glomerular filtration, sodium reabsorption, and a urinary marker of tubular injury before, during, and after CPB. They demonstrate that renal oxygen delivery is reduced during CPB and that renal oxygen consumption is increased after CPB. While they do not provide proof, these findings strongly suggest that CPB induces renal hypoxia that itself leads to kidney injury. Lannemyr *et al.*[2] employ an array of proven experimental methods to provide these data including the measurement of renal perfusion and glomerular filtration using infusions of *para*-aminohippuric acid and ^{51}chromium-ethylenediamine tetraacetic acid, insertion of renal vein catheters for effluent sampling, and assessments of urinary sodium and a urinary biomarker of kidney injury. We congratulate these physician-scientists for completing these complex experiments in patients presenting for major surgery and providing these rich data.

During CPB, renal oxygen delivery declined (primarily a result of hemodilution), but renal blood flow, glomerular filtration, and sodium reabsorption were maintained. Systemic oxygen delivery, on the other hand, did not decline during CPB, a result of increasing arterial flow to 2.5 $l \cdot min^{-1} \cdot m^{-2}$ on the CPB machine. The discrepancy between renal and systemic oxygen delivery during CPB could be interpreted as redistribution of blood flow away from the kidneys but more likely reflects appropriate maintenance of renal function (preserved tubuloglomerular feedback); since arteriolar resistance, renal blood flow, and glomerular filtration rate are a function of sodium chloride delivery to the macula densa, not hypoxia.[3] Nonetheless, the kidneys may have been hypoxic during CPB since the rate of oxygen consumption persisted, but oxygen delivery declined.

After CPB, renal oxygenation further declined. Oxygen delivery remained diminished, once again largely due to the

Image: J. P. Rathmell.

Corresponding article on page 205.

Accepted for publication September 22, 2016. From the Department of Anesthesiology, Vanderbilt University Medical Center, Nashville, Tennessee.

 Anesthesiology 2017; 126:199-201

decreased blood oxygen carrying capacity of diluted blood, but oxygen extraction increased by 35%. This change in consumption provides the best evidence that CPB is associated with impaired renal oxygenation. The decreased delivery and increased consumption resulted in an oxygen extraction ratio 78% above baseline. Simple diffusion kinetics support the notion that kidneys may be hypoxic at this time, in particular the renal medulla, which maintains a low oxygen tension and is prone to ischemic injury.[4] Indeed, the extent of renal oxygen extraction correlated with the extent of urinary excretion of the tubular injury marker *N*-acetyl-β-D-glucosaminidase (NAG). Kidney oxygenation, however, is complex. Although the kidneys require approximately 20% of the body's cardiac output to maintain glomerular filtration and waste excretion, they only consume 5% of the body's oxygen. A significant portion of oxygen delivered to the kidneys is shunted away from tubule and collecting system capillary beds.[5] This shunt maintains diffusion gradients for solute reabsorption and may protect tissues from oxidation but increases susceptibility to hypoxia. From the current study, we do not know if this shunt was altered, nor do we learn if the kidneys were actually hypoxic during or after CPB. We only know that renal oxygen supply and consumption were altered compared to baseline and that increased renal oxygen extraction after CPB was associated with increased urinary NAG concentrations. It is interesting to note that renal blood flow (*para*-aminohippuric acid clearance), glomerular filtration (^{51}chromium-ethylenediamine tetraacetic acid clearance), and sodium reabsorption did not change despite the changes in renal oxygenation and despite the evidence of renal injury, specifically a seven-fold increase in urinary NAG and a dissociation between sodium reabsorption and oxygen consumption. Similar to the findings during CPB, the kidneys appear to preserve renal function post CPB but may render themselves hypoxic in the process. It is unclear why oxygen extraction increases. The notion of sodium leak and reabsorption is provocative and could be tested using a diuretic with a similar sampling schedule. Damaged cellular machinery responsible for oxygen consumption, adenosine triphosphate production, and sodium chloride transport could also explain the increased oxygen consumption to maintain sodium reabsorption as could a shift from the more energy efficient paracellular sodium transport to the less efficient transcellular transport.[6]

In previous studies, Ricksten *et al.*[7] demonstrated a near-linear relationship between renal oxygen consumption and sodium reabsorption. The tubules must reabsorb the sodium chloride filtered by the glomeruli to prevent massive natriuresis and dehydration. The glomeruli and vasa recta comprise a unique vascular system in the renal cortex and medulla—two capillary beds in series in which the former is relatively hyperoxic and the latter relatively hypoxic—and the differential perfusion of these vascular beds (shunt or lack of) dictates tubular hypoxia despite the kidneys' generous blood supply. Increased renal perfusion may increase glomerular filtration and tubular hypoxia if a favorable balance between cortical and medullary perfusion is not maintained. The current study demonstrated that a total decrement in renal oxygenation is associated with renal injury but did not provide data related to the differential perfusion or oxygenation of the renal cortex, corticomedullary junction, and medulla.

In addition, since the biggest changes in renal oxygenation and those most likely to cause hypoxia (*i.e.*, increased renal oxygen extraction) occur after rather than during CPB, the renal injury could be the result of CPB-induced neurohormonal activation, oxidative damage, renal inflammation, and hemoglobinemia rather than CPB-induced perfusion effects. If CPB-induced alterations in perfusion cause renal hypoxia, then the termination of CPB should restore, *not further impair*, oxygenation. Indeed, the proportion of blood flow to the kidneys was 17.1% before CPB but only 14.6% after CPB despite decreased oxygen delivery and increased consumption. Additional assessments of urinary and renal vein (based on the excellent opportunity to sample a proximal fluid using the current experimental design) biomarkers of AKI could provide opportunity to further assess the associations between renal oxygenation and kidney injury, and a larger study might allow one to compare kidney oxygenation, function, and injury data to clinical AKI.

The current study confirms that renal hypoxia during and after CPB is associated with kidney injury, but it remains unclear if treatments to improve renal oxygenation will be effective or if they will reduce kidney injury. The methodology employed by Lannemyr *et al.*[2] provides a comprehensive framework to conduct subsequent mechanistic studies into the pathophysiology of kidney injury and an opportunity to measure the effects of preventive strategies on these mechanisms. Tissue oxygenation remains one of the greatest responsibilities of anesthesiologists during surgery, and the control of renal ischemia, reperfusion, oxidative stress, and oxygen utilization should provide opportunities to decrease kidney injury after major surgery and improve the quality of patient care.

Acknowledgments

The authors acknowledge Guatam Bhave, M.D., Ph.D., Division of Nephrology and Hypertension, Department of Medicine, Vanderbilt University Medical Center, Nashville, Tennessee, for providing an additional review of our editorial.

Research Support

Supported by grant nos. K23GM102676 (Dr. Billings) and R01GM112871 (Dr. Billings) from the National Institutes of Health, Bethesda, Maryland.

Competing Interests

The authors are not supported by, nor maintain any financial interest in, any commercial activity that may be associated with the topic of this article.

Correspondence

Address correspondence to Dr. Billings: frederic.t.billings@vanderbilt.edu

References

1. Lamy A, Devereaux PJ, Prabhakaran D, Taggart DP, Hu S, Paolasso E, Straka Z, Piegas LS, Akar AR, Jain AR, Noiseux N, Padmanabhan C, Bahamondes JC, Novick RJ, Vaijyanath P, Reddy S, Tao L, Olavegogeascoechea PA, Airan B, Sulling TA, Whitlock RP, Ou Y, Ng J, Chrolavicius S, Yusuf S; CORONARY Investigators: Off-pump or on-pump coronary-artery bypass grafting at 30 days. N Engl J Med 2012; 366:1489–97
2. Lannemyr L, Bragadottir G, Krumbholz V, Redfors B, Sellgren J, Ricksten S-E: Effects of cardiopulmonary bypass on renal perfusion, filtration, and oxygenation in patients undergoing cardiac surgery. Anesthesiology 2017; 126:205–13
3. Rose BD, Post TW: Clinical Physiology of Acid-Base and Electrolyte Disorders: Renal Circulation and Glomerular Filtration Rate. 5th edition. New York, McGraw-Hill, Medical Pub. Division, 2001, pp 21–70
4. Brezis M, Rosen S: Hypoxia of the renal medulla–Its implications for disease. N Engl J Med 1995; 332:647–55
5. Evans RG, Gardiner BS, Smith DW, O'Connor PM: Intrarenal oxygenation: Unique challenges and the biophysical basis of homeostasis. Am J Physiol Renal Physiol 2008; 295:F1259–70
6. Pei L, Solis G, Nguyen MT, Kamat N, Magenheimer L, Zhuo M, Li J, Curry J, McDonough AA, Fields TA, Welch WJ, Yu AS: Paracellular epithelial sodium transport maximizes energy efficiency in the kidney. J Clin Invest 2016; 126:2509–18
7. Ricksten SE, Bragadottir G, Redfors B: Renal oxygenation in clinical acute kidney injury. Crit Care 2013; 17:221

ANESTHESIOLOGY REFLECTIONS FROM THE WOOD LIBRARY-MUSEUM

An Inebriated *Sleeping Faun*: From Hosmer to Guinness and Then Around the World

Considered the leading American sculptress of the nineteenth century, Harriet Goodhue Hosmer (1830 to 1908) apprenticed in Rome with a master Neoclassicist from Wales named John Gibson. She produced the clay model for her *Sleeping Faun* in 1864, and her mentor Gibson pronounced it "worthy to be an antique." Rather than imitating classical renderings of a faun as a half-human, half-goat follower of the Greco-Roman god of goatherds, Hosmer chiseled marble versions of her faun with pointed ears as the only goat-like feature. Asleep in a drunken stupor, her faun has dropped grapes and a panpipe at the base of the tree stump on which he is sprawled. A little Satyr is tying to that stump the tiger's skin draped around the inebriated faun. In 1865, the original *Sleeping Faun* marble was purchased by a philanthropic brewer from Dublin named… Sir Benjamin Guinness. Marble copies of her *Sleeping Faun* (a *ca.* 1870 copy, *above*) now grace museum galleries worldwide. (Copyright © the American Society of Anesthesiologists' Wood Library-Museum of Anesthesiology.)

George S. Bause, M.D., M.P.H., Honorary Curator and Laureate of the History of Anesthesia, Wood Library-Museum of Anesthesiology, Schaumburg, Illinois, and Clinical Associate Professor, Case Western Reserve University, Cleveland, Ohio. UJYC@aol.com.

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

Lukas Lannemyr, M.D., Gudrun Bragadottir, M.D., Ph.D., Vitus Krumbholz, M.D., Bengt Redfors, M.D., Ph.D., Johan Sellgren, M.D., Ph.D., Sven-Erik Ricksten, M.D., Ph.D.

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 l · min^{-1} · 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 l · min^{-1} · m^{-2} [10,12,13] or 2.5 to 3 l · min^{-1} · 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.

Submitted for publication April 11, 2016. Accepted for publication October 27, 2016. From the Department of Anesthesiology and Intensive Care Medicine at the Sahlgrenska Academy, University of Gothenburg, Sahlgrenska University Hospital, Gothenburg, Sweden.

 Anesthesiology 2017; 126:205-13

CPB on renal blood flow (RBF), the major determinant of renal oxygen delivery (RDO_2). 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 RDO_2 increasing the risk of AKI.[17] A decreased RDO_2 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 delivery[20] are independent risk factors for the development of postoperative AKI.

The major determinant of renal oxygen consumption (RVO_2) 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 RVO_2.[23–25] The effect of normothermic CPB on glomerular filtration rate (GFR), the major determinant of RVO_2, has not previously been described.

The renal oxygen extraction (RO_2Ex) 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_{O_2} 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 RDO_2 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 RVO_2 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 technique[31] for intraoperative assessment of RBF and GFR by renal extractions of *para*-aminohippuric acid (PAH) and 51 chromium-ethylenediamine tetraacetic acid (^{51}Cr-EDTA; GE Healthcare Limited, United Kingdom), respectively. The primary endpoint of the current study was changes in renal oxygenation, expressed as changes in RO_2Ex. We tested the hypothesis that normothermic CPB induces an impaired RDO_2, 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% O_2/air mixture. During CPB, anesthesia was maintained with an intravenous infusion of propofol (2.5 to 4 $mg \cdot kg^{-1} \cdot hr^{-1}$).

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 $l \cdot min^{-1} \cdot m^{-2}$, 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 × hemoglobin (g/l) × arterial oxygen saturation (%) × 0.01 + (0.23 ml O_2/l/mmHg × Pao_2 (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}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}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 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 ± SD. A $P < 0.05$ (two-tailed) was considered significant. Predictive Analytics Software Statistics 18.0 (SPSS Inc., USA) was used for statistical analyses.

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 × [^{51}Cr-EDTA arterial] – [RPF – urine flow] × [^{51}Cr-EDTA renal vein])/RPF × (^{51}Cr-EDTA arterial)
GFR	FF × RPF
Renal vascular resistance	(MAP – CVP)/RBF
Renal oxygen consumption	RBF × (Cao_2 – $CrvO_2$)
Renal oxygen delivery	RBF × Cao_2
Renal oxygen extraction	(Cao_2 – $CrvO_2$)/Cao_2
Renal sodium filtration	GFR × $[Na^+]_s$
Renal sodium excretion	Urine flow × $[Na^+]_s$
Renal sodium reabsorption	(GFR × $[Na^+]_s$) – (urine flow × $[Na^+]_u$)

^{51}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.

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 ± 0.08 $l \cdot min^{-1} \cdot m^{-2}$ at 60 min (table 3). Systemic perfusion flow thus increased by 32 to 33% ($P < 0.05$ and

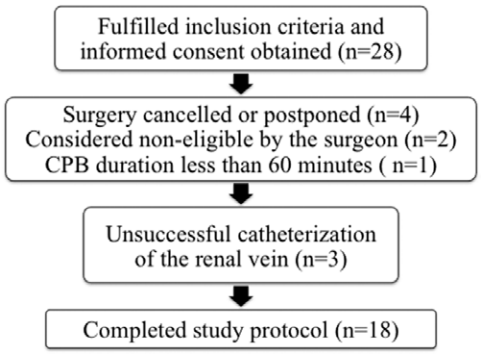


Fig. 1. Clinical trial profile. CPB = cardiopulmonary bypass.

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.

$P < 0.001$), 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 Cao_2 decreased by 16 to 20% ($P < 0.001$) during CPB. In spite of this, Systemic Oxygen Delivery Index (DO_2I), if anything, increased (8%), due to the increase in systemic perfusion flow rate during CPB (fig. 2). Body temperature and VO_2I 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 Cao_2 were lower (16 to 19%; $P < 0.001$) when compared with the pre-CPB values. After CPB, body temperature and VO_2I (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

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, $l \cdot min^{-1} \cdot m^{-2}$	1.87 ± 0.39	2.47 ± 0.08*	2.49 ± 0.08*	2.21 ± 0.52†	< 0.001
SVRI, dynes × $s \cdot cm^{-5} \cdot m^{-2}$	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_2I, $ml \cdot min^{-1} \cdot m^{-2}$	319 ± 59	346 ± 45	343 ± 38	305 ± 78	0.038
VO_2I, $ml \cdot min^{-1} \cdot m^{-2}$	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, $\mu g \cdot kg^{-1} \cdot min^{-1}$	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. †$P < 0.01$. ‡$P < 0.05$.

CaO_2 = arterial oxygen content; CI = cardiac index; CPB = cardiopulmonary bypass; CVP = central venous pressure; DO_2I = systemic oxygen delivery index ($ml \cdot min^{-1} \cdot m^{-2}$); MAP = mean arterial pressure; MPAP = mean pulmonary artery pressure; NA = not applicable; PCWP = pulmonary capillary wedge pressure; SvO_2 = mixed venous oxygen saturation; SVRI = systemic vascular resistance index (dynes × $s \cdot cm^{-3} \cdot m^{-2}$); Temp = body temperature; VO_2I = systemic oxygen consumption ($ml \cdot min^{-1} \cdot m^{-2}$).

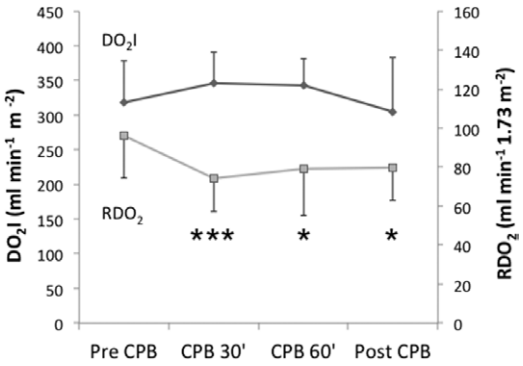


Fig. 2. The effects of cardiopulmonary bypass (CPB) on systemic oxygen delivery index (DO_2I) and renal oxygen delivery (RDO_2) before (Pre-CPB), 30 min (CPB 30′) and 60 min (CPB 60′) after initiation of CPB, and after end of CPB (Post-CPB). ***$P < 0.001$, *$P < 0.05$ *versus* baseline (Pre-CPB).

18 to 23% decrease in RDO_2 ($P < 0.05$ and $P < 0.001$; fig. 2). GFR, filtration fraction, sodium filtration, sodium reabsorption, and urine flow were not affected by CPB. RVO_2 was not affected, while RO_2Ex 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, RDO_2 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, RVO_2 was higher (50%; $P < 0.05$) compared with baseline, and RO_2Ex 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 RVO_2/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 ($P < 0.01$).

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 criteria[32] (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 RO_2Ex ($r = 0.57$; $P < 0.001$; 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 RO_2Ex. Furthermore, renal oxygenation was even further deteriorated after the end of CPB. Finally, the significant positive correlation between NAG release and RO_2Ex 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 RDO_2 at a maintained level of RVO_2. The reduced RDO_2 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

Table 4. Renal Variables

	Pre-CPB	30-min CPB	60-min CPB	Post-CPB	*P* 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_2Ex	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; RDO_2 = renal oxygen delivery; RO_2Ex = renal oxygen extraction; RVO_2 = renal oxygen consumption; RVR = renal vascular resistance.

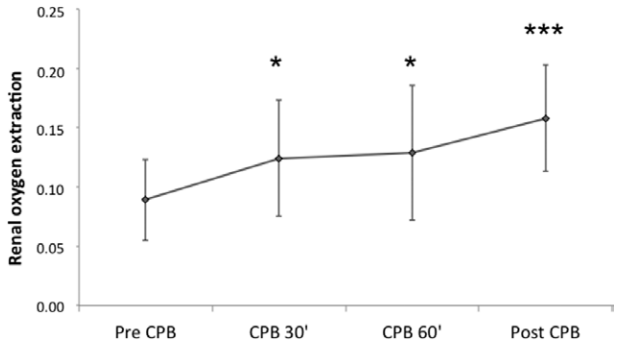


Fig. 3. The effects of cardiopulmonary bypass (CPB) on renal oxygen extraction before (Pre-CPB), 30 min (CPB 30′), and 60 min (CPB 60′) after initiation of CPB, and after end of CPB (Post-CPB). *$P < 0.05$, ***$P < 0.001$ *versus* baseline (Pre-CPB).

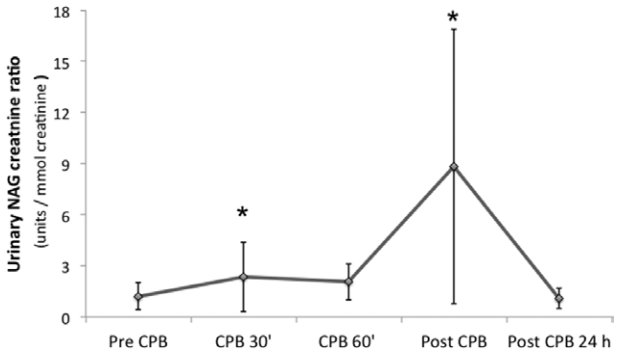


Fig. 4. The effects of cardiopulmonary bypass (CPB) on the urinary *N*-acetyl-β-D-glucosaminidase (NAG)/creatinine ratio before (Pre-CPB), 30 min (CPB 30′) and 60 min (CPB 60′) after initiation of CPB, and after end of CPB (Post-CPB). *$P<0.05$ *versus* baseline (Pre-CPB).

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 ml · min^{-1} · 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 ml · min^{-1} · 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.

Research Support

Supported by the Swedish State Support for Clinical Research (Gothenburg, Sweden; grant nos. ALFGBG431341 and ALFGBG446511) and The Gothenburg Medical Society (Gothenburg, Sweden; grant no. GLS503191).

Competing Interests

The authors declare no competing interests.

Correspondence

Address correspondence to Dr. Ricksten: Department of Anesthesiology and Intensive Care Medicine, Sahlgrenska Academy, University of Gothenburg, Sahlgrenska University Hospital Gothenburg, Blå Stråket 5, 413 45 Gothenburg, Sweden. sven-erik.ricksten@aniv.gu.se. This article may be accessed for personal use at no charge through the Journal Web site, www.anesthesiology.org.

References

1. Englberger L, Suri RM, Li Z, Casey ET, Daly RC, Dearani JA, Schaff HV: Clinical accuracy of RIFLE and Acute Kidney Injury Network (AKIN) criteria for acute kidney injury in patients undergoing cardiac surgery. Crit Care 2011; 15:R16
2. Heringlake M, Knappe M, Vargas Hein O, Lufft H, Kindgen-Milles D, Böttiger BW, Weigand MR, Klaus S, Schirmer U: Renal dysfunction according to the ADQI-RIFLE system and clinical practice patterns after cardiac surgery in Germany. Minerva Anestesiol 2006; 72:645–54
3. Mangano CM, Diamondstone LS, Ramsay JG, Aggarwal A, Herskowitz A, Mangano DT; The Multicenter Study of Perioperative Ischemia Research Group: Renal dysfunction after myocardial revascularization: Risk factors, adverse outcomes, and hospital resource utilization. Ann Intern Med 1998; 128:194–203
4. Robert AM, Kramer RS, Dacey LJ, Charlesworth DC, Leavitt BJ, Helm RE, Hernandez F, Sardella GL, Frumiento C, Likosky DS, Brown JR; Northern New England Cardiovascular Disease

Study Group: Cardiac surgery-associated acute kidney injury: A comparison of two consensus criteria. Ann Thorac Surg 2010; 90:1939–43

5. Chertow GM, Levy EM, Hammermeister KE, Grover F, Daley J: Independent association between acute renal failure and mortality following cardiac surgery. Am J Med 1998; 104:343–8
6. Lassnigg A, Schmidlin D, Mouhieddine M, Bachmann LM, Druml W, Bauer P, Hiesmayr M: Minimal changes of serum creatinine predict prognosis in patients after cardiothoracic surgery: A prospective cohort study. J Am Soc Nephrol 2004; 15:1597–605
7. Swaminathan M, Phillips-Bute BG, Patel UD, Shaw AD, Stafford-Smith M, Douglas PS, Archer LE, Smith PK, Mathew JP: Increasing healthcare resource utilization after coronary artery bypass graft surgery in the United States. Circ Cardiovasc Qual Outcomes 2009; 2:305–12
8. Liotta M, Olsson D, Sartipy U, Holzmann MJ: Minimal changes in postoperative creatinine values and early and late mortality and cardiovascular events after coronary artery bypass grafting. Am J Cardiol 2014; 113:70–5
9. Ryckwaert F, Boccara G, Frappier JM, Colson PH: Incidence, risk factors, and prognosis of a moderate increase in plasma creatinine early after cardiac surgery. Crit Care Med 2002; 30:1495–8
10. Ranucci M, Romitti F, Isgrò G, Cotza M, Brozzi S, Boncilli A, Ditta A: Oxygen delivery during cardiopulmonary bypass and acute renal failure after coronary operations. Ann Thorac Surg 2005; 80:2213–20
11. Ranucci M: Perioperative renal failure: Hypoperfusion during cardiopulmonary bypass? Semin Cardiothorac Vasc Anesth 2007; 11:265–8
12. Swaminathan M, Phillips-Bute BG, Conlon PJ, Smith PK, Newman MF, Stafford-Smith M: The association of lowest hematocrit during cardiopulmonary bypass with acute renal injury after coronary artery bypass surgery. Ann Thorac Surg 2003; 76:784–91; discussion 92
13. Karkouti K, Beattie WS, Wijeysundera DN, Rao V, Chan C, Dattilo KM, Djaiani G, Ivanov J, Karski J, David TE: Hemodilution during cardiopulmonary bypass is an independent risk factor for acute renal failure in adult cardiac surgery. J Thorac Cardiovasc Surg 2005; 129:391–400
14. Habib RH, Zacharias A, Schwann TA, Riordan CJ, Durham SJ, Shah A: Adverse effects of low hematocrit during cardiopulmonary bypass in the adult: Should current practice be changed? J Thorac Cardiovasc Surg 2003; 125:1438–50
15. von Heymann C, Sander M, Foer A, Heinemann A, Spiess B, Braun J, Krämer M, Grosse J, Dohmen P, Dushe S, Halle J, Konertz WF, Wernecke KD, Spies C: The impact of an hematocrit of 20% during normothermic cardiopulmonary bypass for elective low risk coronary artery bypass graft surgery on oxygen delivery and clinical outcome–a randomized controlled study [ISRCTN35655335]. Crit Care 2006; 10:R58
16. Andersson LG, Bratteby LE, Ekroth R, Hallhagen S, Joachimsson PO, van der Linden J, Wesslén O: Renal function during cardiopulmonary bypass: Influence of pump flow and systemic blood pressure. Eur J Cardiothorac Surg 1994; 8:597–602
17. Ranucci M, Pavesi M, Mazza E, Bertucci C, Frigiola A, Menicanti L, Ditta A, Boncilli A, Conti D: Risk factors for renal dysfunction after coronary surgery: The role of cardiopulmonary bypass technique. Perfusion 1994; 9:319–26
18. Fang WC, Helm RE, Krieger KH, Rosengart TK, DuBois WJ, Sason C, Lesser ML, Isom OW, Gold JP: Impact of minimum hematocrit during cardiopulmonary bypass on mortality in patients undergoing coronary artery surgery. Circulation 1997; 96(9 suppl):II–194–9
19. Habib RH, Zacharias A, Schwann TA, Riordan CJ, Engoren M, Durham SJ, Shah A: Role of hemodilutional anemia and transfusion during cardiopulmonary bypass in renal injury after coronary revascularization: Implications on operative outcome. Crit Care Med 2005; 33:1749–56
20. Kanji HD, Schulze CJ, Hervas-Malo M, Wang P, Ross DB, Zibdawi M, Bagshaw SM: Difference between pre-operative and cardiopulmonary bypass mean arterial pressure is independently associated with early cardiac surgery-associated acute kidney injury. J Cardiothorac Surg 2010; 5:71
21. Kiil F, Aukland K, Refsum HE: Renal sodium transport and oxygen consumption. Am J Physiol 1961; 201:511–6
22. Torelli G, Milla E, Faelli A, Costantini S: Energy requirement for sodium reabsorption in the *in vivo* rabbit kidney. Am J Physiol 1966; 211:576–80
23. Swärd K, Valsson F, Sellgren J, Ricksten SE: Differential effects of human atrial natriuretic peptide and furosemide on glomerular filtration rate and renal oxygen consumption in humans. Intensive Care Med 2005; 31:79–85
24. Bragadottir G, Redfors B, Nygren A, Sellgren J, Ricksten SE: Low-dose vasopressin increases glomerular filtration rate, but impairs renal oxygenation in post-cardiac surgery patients. Acta Anaesthesiol Scand 2009; 53:1052–9
25. Redfors B, Swärd K, Sellgren J, Ricksten SE: Effects of mannitol alone and mannitol plus furosemide on renal oxygen consumption, blood flow and glomerular filtration after cardiac surgery. Intensive Care Med 2009; 35:115–22
26. Redfors B, Bragadottir G, Sellgren J, Swärd K, Ricksten SE: Acute renal failure is NOT an "acute renal success"—A clinical study on the renal oxygen supply/demand relationship in acute kidney injury. Crit Care Med 2010; 38:1695–701
27. Skytte Larsson J, Bragadottir G, Krumbholz V, Redfors B, Sellgren J, Ricksten SE: Effects of acute plasma volume expansion on renal perfusion, filtration, and oxygenation after cardiac surgery: A randomized study on crystalloid *vs* colloid. Br J Anaesth 2015; 115:736–42
28. Singh P, Ricksten SE, Bragadottir G, Redfors B, Nordquist L: Renal oxygenation and haemodynamics in acute kidney injury and chronic kidney disease. Clin Exp Pharmacol Physiol 2013; 40:138–47
29. Brezis M, Rosen S: Hypoxia of the renal medulla—Its implications for disease. N Engl J Med 1995; 332:647–55
30. Han WK, Waikar SS, Johnson A, Betensky RA, Dent CL, Devarajan P, Bonventre JV: Urinary biomarkers in the early diagnosis of acute kidney injury. Kidney Int 2008; 73:863–9
31. Swärd K, Valsson F, Sellgren J, Ricksten SE: Bedside estimation of absolute renal blood flow and glomerular filtration rate in the intensive care unit: A validation of two independent methods. Intensive Care Med 2004; 30:1776–82
32. Kellum JA, Lameire N; KDIGO AKI Guideline Work Group: Diagnosis, evaluation, and management of acute kidney injury: A KDIGO summary (Part 1). Crit Care 2013; 17:204
33. Landymore RW, Murphy DA, Kinley E, Parrott J, Sai O, Quirbi AA: Suppression of renin production in patients undergoing coronary artery bypass. Ann Thorac Surg 1980; 30:558–63
34. Philbin DM, Levine FH, Kono K, Coggins CH, Moss J, Slater EE, Buckley MJ: Attenuation of the stress response to cardiopulmonary bypass by the addition of pulsatile flow. Circulation 1981; 64:808–12
35. Taylor KM, Bain WH, Russell M, Brannan JJ, Morton IJ: Peripheral vascular resistance and angiotensin II levels during pulsatile and non-pulsatile cardiopulmonary bypass. Thorax 1979; 34:594–8
36. Philbin DM, Levine FH, Emerson CW, Coggins CH, Buckley MJ, Austen WG: Plasma vasopressin levels and urinary flow during cardiopulmonary bypass in patients with valvular heart disease: Effect of pulsatile flow. J Thorac Cardiovasc Surg 1979; 78:779–83
37. Reves JG, Karp RB, Buttner EE, Tosone S, Smith LR, Samuelson PN, Kreusch GR, Oparil S: Neuronal and adrenomedullary catecholamine release in response to cardiopulmonary bypass in man. Circulation 1982; 66:49–55

38. Nagaoka H, Innami R, Arai H: Effects of pulsatile cardiopulmonary bypass on the renin-angiotensin-aldosterone system following open heart surgery. Jpn J Surg 1988; 18:390–6
39. Molitoris BA, Chan LK, Shapiro JI, Conger JD, Falk SA: Loss of epithelial polarity: A novel hypothesis for reduced proximal tubule Na+ transport following ischemic injury. J Membr Biol 1989; 107:119–27
40. Molitoris BA: Na(+)-K(+)-ATPase that redistributes to apical membrane during ATP depletion remains functional. Am J Physiol 1993; 265(5 Pt 2):F693–7
41. Molitoris BA, Wagner MC: Surface membrane polarity of proximal tubular cells: Alterations as a basis for malfunction. Kidney Int 1996; 49:1592–7
42. Kwon O, Corrigan G, Myers BD, Sibley R, Scandling JD, Dafoe D, Alfrey E, Nelson WJ: Sodium reabsorption and distribution of Na+/K+-ATPase during postischemic injury to the renal allograft. Kidney Int 1999; 55:963–75
43. Ho J, Tangri N, Komenda P, Kaushal A, Sood M, Brar R, Gill K, Walker S, MacDonald K, Hiebert BM, Arora RC, Rigatto C: Urinary, plasma, and serum biomarkers' utility for predicting acute kidney injury associated with cardiac surgery in adults: A meta-analysis. Am J Kidney Dis 2015; 66:993–1005
44. Martensson J, Bellomo R: The rise and fall of NGAL in acute kidney injury. Blood Purif 2014; 37:304–10
45. Stafford-Smith M, Grocott HP: Renal medullary hypoxia during experimental cardiopulmonary bypass: A pilot study. Perfusion 2005; 20:53–8
46. Darby PJ, Kim N, Hare GM, Tsui A, Wang Z, Harrington A, Mazer CD: Anemia increases the risk of renal cortical and medullary hypoxia during cardiopulmonary bypass. Perfusion 2013; 28:504–11
47. Wan L, Bellomo R, May CN: A comparison of 4% succinylated gelatin solution *versus* normal saline in stable normovolaemic sheep: Global haemodynamic, regional blood flow and oxygen delivery effects. Anaesth Intensive Care 2007; 35:924–31
48. Legrand M, Mik EG, Balestra GM, Lutter R, Pirracchio R, Payen D, Ince C: Fluid resuscitation does not improve renal oxygenation during hemorrhagic shock in rats. Anesthesiology 2010; 112:119–27
49. Konrad FM, Mik EG, Bodmer SI, Ates NB, Willems HF, Klingel K, de Geus HR, Stolker RJ, Johannes T: Acute normovolemic hemodilution in the pig is associated with renal tissue edema, impaired renal microvascular oxygenation, and functional loss. Anesthesiology 2013; 119:256–69
50. Levinsky NG, Wilfred L: Clearance techniques, Handbook of Physiology. Edited by Orloff J, Berliner RW. Baltimore, Waverly Press, 1973, pp 103–17
51. Earle DP Jr, Berliner RW: A simplified clinical procedure for measurement of glomerular filtration rate and renal plasma flow. Proc Soc Exp Biol Med 1946; 62:262–4
52. Rose GA: Measurement of glomerular filtration rate by inulin clearance without urine collection. Br Med J 1969; 2:91–3
53. Cole BR, Giangiacomo J, Ingelfinger JR, Robson AM: Measurement of renal function without urine collection: A critical evaluation of the constant-infusion technic for determination of inulin and para-aminohippurate. N Engl J Med 1972; 287:1109–14
54. Redfors B, Bragadottir G, Sellgren J, Swärd K, Ricksten SE: Effects of norepinephrine on renal perfusion, filtration and oxygenation in vasodilatory shock and acute kidney injury. Intensive Care Med 2011; 37:60–7
55. Shiga Y, Minami K, Uezono Y, Segawa K, Nagaoka E, Shiraishi M, Noguchi T, Shigematsu A: Effects of the intravenously administered anaesthetics ketamine, propofol, and thiamylal on the cortical renal blood flow in rats. Pharmacology 2003; 68:17–23
56. Booke M, Armstrong C, Hinder F, Conroy B, Traber LD, Traber DL: The effects of propofol on hemodynamics and renal blood flow in healthy and in septic sheep, and combined with fentanyl in septic sheep. Anesth Analg 1996; 82:738–43