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

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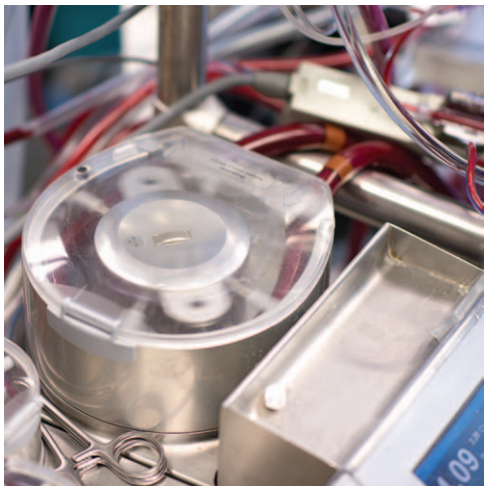
ONE quarter of cardiac surgery patients continue to suffer from postoperative acute kidney injury (AKI) despite the advances in perioperative patient management that have reduced mortality and shortened the duration of hospitalization. The majority of these cardiac surgery patients receive cardiopulmonary 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.

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

 Anesthesiology 2017; 126:199-201

<zdoi;10.1097/ALN.0000000000001462>

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.

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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.)

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