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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 duration of hospitalization. The majority of these cardiac surgery patients receive cardiopulmonary bypass (CPB) during surgery. CPB fundamentally alters systemic perfusion by providing non-pulsatile blood flow, induces myocardial and pulmonary ischemia, and elicits a significant neuro-hormonal and inflammatory response. Despite these severe physiological derangements, the specific effects of CPB on individual and collective organ function remain unclear. In fact, the severity of major organ injury following 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 and colleagues now provide evidence that renal oxygenation is altered during and following CPB, perhaps providing a partial explanation of the way in which CPB contributes to kidney injury.²

Lannemyr *et al* 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 prior to, during, and following CPB. They demonstrate that renal oxygen delivery is reduced during CPB, and that renal oxygen consumption is increased following 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* 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 (PAH) and Cr-EDTA, 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 cardiac output to 2.5 l/min/m² on the CPB machine. The discrepancy between renal and systemic oxygen delivery during CPB could be interpreted as redistribution of blood flow

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away from the kidneys but more likely reflects appropriate maintenance of renal function (preserved tubuloglomerular feedback); since arteriolar resistance, renal blood flow, and GFR 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.

Following CPB, renal oxygenation further declined. Oxygen delivery remained diminished, once again largely due to the decreased blood oxygen carrying capacity secondary to hemodilution, 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 tubular 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 present study we don't know if this shunt was altered nor do we learn if the kidneys were actually hypoxic during or following CPB. We only know that renal oxygen supply and consumption were altered compared to baseline and that increased renal oxygen extraction following CPB was associated with increased urinary NAG concentrations. It's interesting to note that renal blood flow (PAH clearance), glomerular filtration (Cr-EDTA clearance), and sodium reabsorption did not change despite the changes in renal oxygenation and despite the evidence of renal injury, specifically a 7-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 re-absorption is provocative and could be tested using a diuretic with a similar sampling schedule. Damaged cellular machinery responsible for oxygen consumption, ATP 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 prior studies Ricksten *et al* demonstrated a near linear relationship between renal oxygen consumption and sodium reabsorption.⁷ 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 neuro-hormonal 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% prior to CPB but only 14.6% following 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 oxygenation, functional, and injury data to clinical AKI.

The current study confirms that renal hypoxia during and following 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 and colleagues 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 following major surgery and improve the quality of patient care.

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