



## RESEARCH REPOSITORY

*This is the author's final version of the work, as accepted for publication following peer review but without the publisher's layout or pagination.*

*The definitive version is available at:*

<https://doi.org/10.1111/apha.12995>

Evans, R.G., Lankadeva, Y.R., Cochrane, A.D., Marino, B., Iguchi, N., Zhu, M.Z.L., Hood, S.G., Smith, J.A., Bellomo, R., Gardiner, B.S., Lee, C-J, Smith, D.W. and May, C.N. (2018) Renal haemodynamics and oxygenation during and after cardiac surgery and cardiopulmonary bypass. *Acta Physiologica*, 222 (3).

<http://researchrepository.murdoch.edu.au/id/eprint/39895/>

Copyright: © 2017 Scandinavian Physiological Society.  
It is posted here for your personal use. No further distribution is permitted.

Article type : Review Article

## Renal haemodynamics and oxygenation during and after cardiac surgery and cardiopulmonary bypass

Roger G. Evans<sup>1</sup> Yugeesh R. Lankadeva<sup>2</sup>, Andrew D. Cochrane<sup>3</sup>, Bruno Marino<sup>4</sup>,  
Naoya Iguchi<sup>2</sup>, Michael Z.L. Zhu<sup>3</sup>, Sally G. Hood<sup>2</sup>, Julian A. Smith<sup>3</sup>, Rinaldo Bellomo<sup>5</sup>, Bruce S.  
Gardiner<sup>6,7</sup>, Chang-Joon Lee<sup>6,7</sup>, David W. Smith<sup>7</sup> and Clive N. May<sup>2</sup>

<sup>1</sup>Cardiovascular Disease Program, Biomedicine Discovery Institute and Department of  
Physiology, Monash University, Melbourne, Australia.

<sup>2</sup>Florey Institute of Neuroscience and Mental Health, University of Melbourne, Australia.

<sup>3</sup>Department of Cardiothoracic Surgery, Monash Health and Department of Surgery  
(School of Clinical Sciences at Monash Health), Monash University, Melbourne, Australia.  
Departments of <sup>4</sup>Perfusion Services and <sup>5</sup>Intensive Care, Austin Hospital, Australia.

<sup>6</sup>School of Engineering and Information Technology, Murdoch University, Perth, Australia.

<sup>7</sup>Faculty of Engineering and Mathematical Sciences, The University of Western Australia,  
Perth, Australia.

**Short title:** Renal oxygenation during and after cardiac surgery

**Author for correspondence:**

Dr Roger Evans  
Department of Physiology  
26 Innovation Walk, Monash University, Victoria 3800, Australia  
Tel: 61 3 9905 1466  
Fax: 61 3 9905 2566  
Email: Roger.Evans@monash.edu

This article has been accepted for publication and undergone full peer review but has not  
been through the copyediting, typesetting, pagination and proofreading process, which may  
lead to differences between this version and the Version of Record. Please cite this article as  
doi: 10.1111/apha.12995

This article is protected by copyright. All rights reserved.

## Abstract

Acute kidney injury (AKI) is a common complication following cardiac surgery performed on cardiopulmonary bypass (CPB) and has important implications for prognosis. The aetiology of cardiac surgery-associated AKI is complex, but renal hypoxia, particularly in the medulla, is thought to play at least some role. There is strong evidence from studies in experimental animals, clinical observations and computational models, that medullary ischaemia and hypoxia occurs during CPB. There are no validated methods to monitor or improve renal oxygenation during CPB, and thus possibly decrease the risk of AKI. Attempts to reduce the incidence of AKI by early transfusion to ameliorate intra-operative anaemia, refinement of protocols for cooling and rewarming on bypass, optimisation of pump flow and arterial pressure, or the use of pulsatile flow, have not been successful to date. This may in part reflect the complexity of renal oxygenation, which may limit the effectiveness of individual interventions. We propose a multidisciplinary pathway for translation comprising three components. Firstly, large-animal models of CPB to continuously monitor both whole kidney and regional kidney perfusion and oxygenation. Secondly, computational models to obtain information that can be used to interpret the data and develop rational interventions. Thirdly, clinically feasible non-invasive methods to continuously monitor renal oxygenation in the operating theatre and to identify patients at risk of AKI. In this review we outline the recent progress on each of these fronts.

**Keywords:** Acute kidney injury, renal hypoxia, renal ischaemia, renal medulla.

## Introduction

The development of cardiopulmonary bypass (CPB), to allow cardiothoracic surgeons to operate on a motionless and bloodless field while the patient's cardiovascular system is sustained by a heart-lung machine, was one of the greatest medical breakthroughs of the 20<sup>th</sup> century. It makes the ~2 million coronary artery bypass graft procedures or valve replacement or repair procedures performed annually worldwide possible.<sup>1</sup> However, one of the major risks associated with on-pump cardiac surgery is acute kidney injury (AKI). Globally the incidence of AKI after cardiac surgery has been estimated at 22.3%, although it does vary according to the diagnostic criteria used.<sup>1</sup> When AKI is severe enough to require renal replacement therapy, as occurs in 1-2% of patients after CPB, mortality exceeds 35%.<sup>2</sup> But even mild AKI after CPB is associated with a more than 4-fold greater risk of in-hospital death and greater risk of extended hospitalisation.<sup>3</sup> Furthermore, there is now very strong evidence that even short or mild episodes of AKI are independently associated with a greatly increased risk of chronic kidney disease (CKD).<sup>4,5</sup>

Our efforts to prevent AKI associated with cardiac surgery are hampered by three major challenges. The first challenge is that we have little ability to predict which patients will develop AKI after cardiac surgery. Pre-operative risk scoring systems are available, but these only have limited predictive efficacy.<sup>6,7</sup> Secondly, we lack methods to monitor risk of AKI

Accepted Article

intra-operatively, prior to development of kidney injury. Urinary and plasma biomarkers have been developed that allow early detection of AKI.<sup>8</sup> However, at best these can predict AKI on arrival at the intensive care unit (i.e. after the operation),<sup>9</sup> and even then their predictive efficacy is rather low.<sup>10, 11</sup> The third challenge is that we have no effective interventions, either during the surgical procedure itself or once AKI has been diagnosed.<sup>12-16</sup> This suggests that continuous assessment of the kidney during surgery would be advantageous, as this is a promising time for an effective intervention.

There are also significant impediments to the development of interventions to prevent or ameliorate AKI associated with cardiac surgery. Patients undergoing cardiac surgery are, for the most part, critically ill. Therefore, the implementation of interventions with questionable efficacy is problematic. Cardiac surgery and CPB are also technically challenging to model in animals.<sup>17</sup> Thus, there are roadblocks in our ability to test new interventions both in pre-clinical and clinical settings. Another consequence of these impediments is that our understanding of the pathophysiology of cardiac surgery-associated AKI is poor, and so a rational basis for intervention is commensurately limited.

In this article we review the evidence that renal tissue hypoxia, particularly in the medulla is a likely important driver of AKI, including in the setting of cardiac surgery. We then consider how renal hypoxia could be targeted, both as a way of monitoring risk of AKI and as a therapeutic or management target.

### Renal Oxygenation

The oxygenation of all bodily tissues is determined by the balance between oxygen delivery and oxygen consumption. But in the kidney, this apparent simplicity is belied by the complexity of the determinants of oxygen delivery and oxygen consumption, particularly in the renal medulla.<sup>18</sup> In terms of oxygen delivery, we must consider the fact that the renal circulation is arranged in parallel with the non-renal circulations, that the medullary circulation is effectively arranged in parallel with the bulk of the cortical circulation,<sup>19</sup> and that there is likely some level of differential control of perfusion of the inner and outer medulla. So to understand the control of oxygen delivery to the medulla we must understand the interactions between three sets of nested parallel circulations (Figure 1).

Our understanding of the control of local renal tissue oxygen consumption is complicated by the fact that it is so heavily dependent upon tubular sodium reabsorption.<sup>20</sup> Renal oxygen consumption ( $VO_2$ ) can be approximated using the formula:

$$VO_2^{total} = VO_2^{basal} + VO_2^{Na+} = VO_2^{basal} + \frac{T_{Na+}}{\beta}$$

where  $VO_2^{basal}$  represents an assumed fixed rate of oxygen consumption required for processes independent of sodium reabsorption (~15% of  $VO_2^{total}$  under normal physiological

Accepted Article

conditions<sup>20</sup>), and  $VO_2^{Na^+}$  represents oxygen utilisation for the reabsorption of sodium.  $VO_2^{Na^+}$ , in turn, is dependent both on the molar quantity of sodium reabsorbed and the energetic cost of reabsorption of each mole of sodium ( $\beta$ ). This formula can be applied both across the whole kidney and at the local level. Given that the effects of vasoactive agents on local medullary tissue oxygenation cannot always be predicted based on their effects on local tissue perfusion and whole-kidney oxygen delivery and consumption,<sup>21</sup> local oxygen consumption probably plays a critical role in determining local tissue oxygen tension. Unfortunately, despite valiant attempts,<sup>22</sup> there are no available methods for quantifying renal oxygen consumption at the local tissue level *in vivo*. This represents a significant impediment in our understanding of renal oxygenation, since the value of  $\beta$  varies across the various segments of the nephron,<sup>23</sup> is highly dependent on the neuro-hormonal milieu and particularly the bioavailability of nitric oxide,<sup>24</sup> and likely changes markedly in the diseased<sup>25</sup> or injured<sup>26</sup> kidney. Furthermore, the quantity of sodium reabsorbed within each tubular segments varies with physiological state.<sup>23</sup> Given this uncertainty, we see an important role for computational models to provide a method for systematic data integration, a tool for evaluating 'what-if' scenarios, and so a translational pathway between basic research findings and improved clinical practice.

The power of computational modelling is that, by repeating the process of model calibration and validation, a model can cumulatively integrate data from all available experiments. This gives researchers a systematic method for taking into account all the available quantitative and qualitative anatomic and physiological data available, past and present, and putting this to work in the service of addressing the research question of interest. By nesting models within models, multiscale computational model can integrate data over a range of length scales, from cells up to tissues and organ systems. This approach is like a lever on experimental data, allowing re-assessment and reinterpretation of data, and suggesting new hypotheses as new predictions are made.

One example of this approach is our recently published papers on accounting for oxygen in the rat renal cortex.<sup>27, 28</sup> This model drew on detailed geometrical data that were gathered with a specific purpose in mind; to assess the importance of renal arterial-to-venous oxygen shunting. However, by integrating these new data in the context of data from another 20+ prior papers on renal anatomy and physiology in the rat, we were able to reveal a critical role for variations in the density of peritubular capillaries in determining renal tissue oxygenation (Figure 2). This may at least partly underlie the increased susceptibility of patients with CKD, a condition associated with capillary rarefaction, to development of AKI under conditions like CPB, when there may be mis-matched changes in renal oxygen delivery and oxygen consumption.<sup>27</sup>

#### **Evidence that medullary hypoxia is a common pathway in AKI of multiple aetiologies**

Here, we will begin to build the case that because renal medulla hypoxia is a common pathway to AKI, this is likely to also be true in AKI associated with CPB. We begin by

restating the argument linking AKI to hypoxia.

*The renal medulla is susceptible to hypoxia:* Despite the fact that the kidneys receive a quarter of the cardiac output, they are susceptible to hypoxia.<sup>29</sup> Multiple factors render the medulla particularly susceptible to hypoxia, including relatively low blood flow,<sup>18</sup> limitations in oxygen diffusion due to the relatively low capillary density in the kidney<sup>27</sup> and diffusive oxygen shunting in the renal cortex (from arteries to veins)<sup>28, 30</sup> and medulla itself (from descending to long ascending vasa recta).<sup>30, 31</sup> Furthermore, the outer medulla contains the thick ascending limbs of Henle's loop (mTALs), which reabsorb much of the filtered sodium, and so require a large amount of oxygen. Yet the mTALs are located at the periphery of the vascular bundles so have a comparatively meagre oxygen supply.<sup>32</sup> It is not surprising then, that in human AKI, tubular damage is most often seen in the outer medulla.<sup>33</sup>

*Medullary hypoxia is common to animal models of AKI,* including radiocontrast-induced nephropathy, ischaemia reperfusion injury, sepsis, and rhabdomyolysis.<sup>18</sup> Medullary hypoxia has even been observed in a clinically relevant ovine model of septic AKI in which global renal blood flow (RBF) and oxygen delivery are increased and renal cortical oxygenation is well maintained.<sup>34</sup> It is apparent that medullary hypoxia is not just a consequence of global renal ischaemia, but a specific event common to all forms of AKI where it has been investigated.

*Tissue hypoxia drives pathology:* Depletion of cellular ATP initiates signalling cascades leading to inflammation, apoptosis and necrosis.<sup>35</sup> Multiple downstream pathways then exacerbate tissue hypoxia. For example, oxidative stress and loss of Na,K-ATPase polarity and tight junctions between tubular cells reduces the efficiency of oxygen use, which increases oxygen consumption. Cellular protective mechanisms, driven by hypoxia inducible factors, protect the kidney when hypoxia is mild and/or brief, but fail when hypoxia is severe and/or protracted.<sup>35</sup> Hypoxia may also contribute to the progression from AKI to CKD.<sup>36</sup> For example, capillary rarefaction appears to be an early<sup>37</sup> and persistent<sup>38</sup> event after AKI, and is common to all forms of CKD.<sup>39, 40</sup>

*Medullary hypoxia should reduce glomerular filtration rate:* Unfortunately, the mechanistic links between tissue hypoxia and glomerular filtration rate have proved difficult to study. But from a theoretical perspective, we should expect that, as metabolism switches from aerobic to anaerobic, sodium reabsorption in the mTALs should be inhibited. This is predicted to activate the tubuloglomerular feedback (TGF) mechanism, causing afferent arteriolar vasoconstriction, reducing glomerular filtration and further reducing oxygen delivery to the medulla. Hypo-filtration might be exacerbated by oxidative stress and reduced nitric oxide bioavailability and hypoxic damage to tubular and vascular elements in the medulla.<sup>41</sup> Evidence that TGF is linked to renal oxygenation includes the observation of oscillations in glomerular capillary and tubular PO<sub>2</sub> that are dependent on TGF.<sup>42</sup> Nevertheless, the mechanistic links between tissue oxygenation and glomerular filtration

remain a major gap in our knowledge of the pathophysiological significance of hypoxia in AKI.

### **Evidence of renal ischaemia and hypoxia during and after cardiopulmonary bypass**

During CPB, perfusionists monitor mixed venous saturation of haemoglobin with oxygen ( $SvO_2$ ) and maintain it at 70-80%. This level of venous oxygenation is most commonly somewhat greater than that which would be experienced by a resting conscious human (65-75%), so should theoretically be adequate for oxygenation of all organs. However, one must also consider that the local circulations of the various organ systems are in parallel (Figure 1). Thus, what is adequate for some organs may not be adequate for others. During CPB the brain<sup>43</sup> and kidney<sup>44</sup> appear to be particularly susceptible to ischaemia and hypoxia, and thus subsequent damage and dysfunction.

Multiple factors associated with CPB would be predicted, purely on our understanding of circulatory physiology, to promote renal hypoxia. Haemodilution, a necessary consequence of priming the CPB circuit, blunts autoregulation of RBF.<sup>45</sup> Periods of low pump flow and/or arterial pressure would therefore be expected to result in renal ischaemia. Haemodilution also reduces the oxygen-carrying capacity of blood and therefore the quantity of renal oxygen delivery for any given level of RBF. Haemolysis and associated inflammation and oxidative stress would be expected to lead to renal vasoconstriction, as would activation of the sympathetic and renin-angiotensin systems. Loss of pulsatility of flow might also be expected to promote renal ischaemia.<sup>46</sup>

Known intraoperative risk factors for AKI after CPB would be expected to lead to renal hypoxia. These include excessive haemodilution<sup>47</sup> or relatively low pump flow leading to low whole body oxygen delivery,<sup>48, 49</sup> and low nadir arterial pressure during CPB.<sup>50</sup> All of these would be expected to reduce renal oxygen delivery. Many pre-operative risk factors are also likely to be associated with reduced oxygen delivery or increased oxygen consumption in the kidney, including chronic obstructive pulmonary disease, CKD, infection and inflammation, and diabetes.<sup>18</sup> Unfortunately, we have virtually no hard evidence regarding the influences of these various factors on RBF during CPB.

We are aware of only two studies in which RBF was estimated during CPB in humans, in both cases by measurement of the clearance of para-aminohippurate. Andersson and colleagues found that RBF was highly dependent on both pump flow and arterial pressure during hypothermic (28 °C) CPB.<sup>51</sup> They found that RBF was relatively normal at a high pump flow of 2.0-2.2 L min<sup>-1</sup>m<sup>2</sup> but was reduced by ~40% when pump flow was reduced to a level considered adequate for such hypothermic conditions (1.45-1.65 L min<sup>-1</sup>m<sup>2</sup>; note that pump flow is usually calculated as a function of body surface area; i.e. equivalent to the 'cardiac index'). Critically, they observed a complete absence of autoregulation of RBF. More recently, Lannemyr and colleagues found relatively well-maintained effective RBF during CPB (at 34-35 °C), but some redistribution of whole body blood flow away from the kidneys.<sup>52</sup> Nevertheless, because of the effects of haemodilution, while whole body oxygen

Accepted Article

delivery was well-maintained on CPB, renal oxygen delivery was still reduced by ~20%.<sup>52</sup>

Even if whole-kidney oxygen delivery is maintained during CPB, there is the potential for altered distribution of blood flow, via microvascular shunting, to induce renal tissue hypoxia by reducing tissue oxygen extraction. Koning and colleagues observed increased heterogeneity of flow in the sublingual circulation of patients during on-pump cardiothoracic surgery, but not during off-pump cardiothoracic surgery.<sup>53</sup> The existence of peri-glomerular shunt pathways in the renal circulation has long been a controversial proposition.<sup>54</sup> Nevertheless, it is noteworthy that Pathi and colleagues observed reduced renal vascular resistance in pigs during CPB (albeit measured by the flawed microsphere method), associated with reductions in glomerular size because of glomerular capillary narrowing.<sup>55</sup> These observations could indicate shunting of RBF away from glomerular capillaries during CPB. A similar mechanism has been proposed as a possible explanation for failure of glomerular filtration in hyperdynamic sepsis.<sup>56</sup>

Computational models predict the development of renal medullary hypoxia during CPB. Sgouralis and colleagues simulated hypothermic (28 °C) CPB using models of the kidney of the rat.<sup>57, 58</sup> Their findings indicate that the rewarming phase of CPB, prior to weaning from CPB, is a time of greatest risk of medullary hypoxia (Figure 3). Their models predict PO<sub>2</sub> in the vicinity of the mTALH to be less than 5 mmHg during re-warming, as a result of the increased metabolic activity and thus oxygen consumption caused by increased tissue temperature. These predictions accord with the clinical observation that rewarming on bypass increases the risk of AKI.<sup>59</sup> Excessive cooling also appears to promote AKI, since arterial perfusion temperature <27 °C during CPB was found to be associated with increased risk of AKI.<sup>60</sup> Thus, it may be that the rate of re-warming, rather than the perfusion temperature during hypothermic CPB, is a critical factor in determining risk of AKI. The impact of re-warming regimens on renal haemodynamics and oxygenation has not, to our knowledge, been systematically investigated in experimental animals or man.

Renal tissue PO<sub>2</sub> has been directly measured in experimental animals during CPB. In pigs, medullary and urinary hypoxia (PO<sub>2</sub> 1-5 mmHg for both) were observed during CPB.<sup>61</sup> In rats, CPB was associated with transient cortical and medullary hypoxia at a target blood haemoglobin concentration of 10 g/dL, but sustained hypoxia in both regions of the kidney when target haemoglobin was 6.5 g/dL.<sup>62</sup> Thus, evidence from experimental animals strongly supports the proposition that CPB is associated with intra-operative renal hypoxia that is exacerbated by anaemia.

Renal hypoxia also appears to be a hallmark of AKI after CPB.<sup>26</sup> In patients with AKI after CPB both renal blood flow measured by para-aminohippurate clearance (-40%) and renal oxygen delivery (-62%) were found to be markedly reduced<sup>63</sup>. In contrast, renal oxygen consumption was found to be maintained, despite reduced glomerular filtration rate (GFR) and thus the filtered load of sodium. These observations indicate that the metabolic



Accepted Article

efficiency of oxygen utilisation for sodium reabsorption is reduced in AKI. In pigs, medullary hypoxia was observed 24 h after CPB.<sup>64-66</sup> Furthermore, therapies instituted during CPB, that ameliorated post-CPB renal dysfunction, also ameliorated post-CPB medullary hypoxia. These included blockade of endothelin type A receptors,<sup>65</sup> inhibition of phosphodiesterase-5,<sup>66</sup> and reversal of intra-operative anaemia.<sup>64</sup> Thus, it appears likely that amelioration of post-CPB renal hypoxia can reduce the risk of renal dysfunction. A method to monitor intrarenal oxygenation intra-operatively may therefore provide a useful tool to manage the risk of AKI in patients during cardiac surgery.

#### **How could we detect intraoperative renal hypoxia?**

A measure of renal oxygenation during the operation could give a real-time assessment of risk of AKI and potentially justify and enable interventions during surgery (i.e. prior to injury). Unfortunately, it is not currently feasible to directly measure the oxygen tension ( $PO_2$ ) of renal tissue during cardi thoracic surgery. However, there have been indirect measurements. Choi and colleagues used near infrared spectroscopy to assess the regional saturation of intrarenal (and cerebral) haemoglobin with oxygen ( $rSO_2$ ) in 95 adult patients during cardiac surgery with CPB.<sup>67</sup> They found that both renal and cerebral  $rSO_2$  fell at the commencement of CPB. Renal  $rSO_2$  recovered during the initial stages of CPB but then slowly decreased. They also found that patients who developed AKI experienced longer periods during surgery during which saturation of intrarenal haemoglobin with oxygen was below thresholds of 70%, 65%, 60%, 55% and 50%. Furthermore, the odds of post-operative AKI were significantly greater as patients experienced more severe and longer periods of desaturation of renal haemoglobin. Similarly, infants who developed AKI after cardiac surgery on CPB experienced more severe intraoperative desaturation of renal tissue than those who did not develop AKI.<sup>68</sup> Thus, intra-operative monitoring of renal oxygenation could potentially be used to assess the risk of AKI at a time when it might not be too late to intervene to prevent kidney injury. Unfortunately, near infrared spectroscopy may not be an ideal method for this purpose, since it could not be applied in adult patients whose kidneys were more than 40 mm below the surface of the skin<sup>67</sup> or in paediatric patients older than 12 months or weighing more than 10 kg.<sup>68</sup>

We have recently proposed that continuous measurement of urinary  $PO_2$  could be used to estimate renal medullary tissue  $PO_2$ , and thus could be used as a 'physiological biomarker' of risk of AKI.<sup>69, 70</sup> Our argument was based on the observations that (i) the ascending vasa recta are closely associated with collecting ducts in the medulla so that pelvic urinary  $PO_2$  equilibrates with medullary tissue  $PO_2$  and (ii) the  $PO_2$  of urine in both the renal pelvis and the bladder varies in response to stimuli that would be expected to alter medullary tissue  $PO_2$ . More recently, we developed a computational model of oxygen diffusion across the urothelium of the ureter which predicts good agreement between medullary and bladder urinary  $PO_2$ , provided that urine flow is adequate (Figure 4).<sup>71</sup> Consistent with this proposition, we found good agreement between medullary tissue  $PO_2$  and bladder urinary  $PO_2$  in sheep during development of sepsis-induced AKI<sup>72</sup> and in rabbits when medullary

oxygenation was altered pharmacologically.<sup>71</sup>

Kainuma and colleagues measured bladder urine PO<sub>2</sub> during on-pump cardiac surgery in 98 patients, using a polarographic electrode inserted into the bladder catheter.<sup>73</sup> They found that urinary PO<sub>2</sub> fell during CPB and that failure of urinary PO<sub>2</sub> to increase/recover after CPB predicted later development of AKI. However, because polarographic electrodes are fragile and require repeated calibration, their approach is unlikely to be feasible in routine clinical practice. However, recent fibre optic methods for PO<sub>2</sub> measurement by luminescence lifetime oximetry, could provide a clinically translatable method.<sup>69, 70</sup>

### **Potential interventions to improve renal oxygenation during cardiopulmonary bypass**

#### *Off-pump surgery*

One potential solution to avoid CPB-associated renal hypoxia is to avoid CPB altogether. Off-pump cardiac surgery has been found to be associated with a lower risk of AKI than cardiac surgery on CPB.<sup>74, 75</sup> However, in a recent multicentre trial the investigators could detect no benefit of off-pump surgery in terms of loss of kidney function at 1 year.<sup>74</sup> Thus, significant benefits of off-pump surgery for the kidney have not been demonstrated. This apparent lack of benefit could be due to the common occurrence of haemodynamic instability during off-pump procedures.<sup>76</sup> There is also evidence of poorer outcomes in terms of completeness of revascularization during the surgical procedure and graft patency one year after coronary artery bypass graft,<sup>77</sup> and the need for repeat revascularization.<sup>75</sup>

#### *Anaemia and transfusion*

The established relationship between intra-operative anaemia and post-operative AKI (*vide supra*) provided the impetus for studies of the effects of correction of anaemia by blood transfusion. Available evidence from observational studies indicates that early transfusion to correct anaemia may exacerbate, rather than ameliorate, the risk of AKI.<sup>78</sup> Transfusion of more than two units of packed red blood cells was also found to be associated with increased levels of the urinary biomarkers interleukin-18 and neutrophil gelatinase-associated lipocalin.<sup>79</sup> A potential explanation for this apparent paradox is that stored red blood cells have reduced affinity for oxygen, are less deformable, have shorter lifespans compared with the patient's own red blood cells, and are prone to damage and thus liberation of free haemoglobin.<sup>78, 80</sup> However, the absence of well-designed randomised trials in this field remains a significant impediment to our understanding of the effects of blood transfusion. The results of an ongoing randomised trial comparing a restrictive versus a liberal transfusion strategy may clarify this issue (Transfusion Requirements in Cardiac Surgery III (TRICS-III; National Institutes of Health Clinical Trial Identifier NCT02042898).

### *Cooling and rewarming on bypass*

Simulations using computational models indicate that cooling on bypass reduces renal oxygen consumption and so protects the renal medulla from hypoxia, but that rewarming on bypass promotes renal medullary hypoxia (Figure 3).<sup>57, 58</sup> Rewarming on bypass *per se*,<sup>59</sup> hyperthermic perfusion (arterial outlet temperature >37 °C),<sup>81, 82</sup> and higher ICU admission temperature<sup>81</sup> have been shown to be associated with increased risk of post-operative AKI. However, neither sustained intra-operative mild hypothermia (34 °C versus 37 °C)<sup>59</sup> nor sustained moderate hypothermia (28-30 °C versus 35.5-36.5 °C)<sup>83</sup> were found to be associated with reduced incidence of AKI after coronary artery bypass graft. Furthermore, a recent meta-analysis failed to detect a beneficial effect of therapeutic hypothermia on the incidence of AKI after CPB or in other settings (e.g. after cardiac arrest).<sup>84</sup> The lack of apparent benefit of therapeutic hypothermia on post-operative renal function after CPB may reflect both the eventual need for rewarming and the well-established effect of hypothermic perfusion to increase renal vascular resistance.<sup>85</sup>

### *Management of pump flow and arterial pressure on bypass*

Another approach to prevention of renal hypoxia during CPB could be to optimise haemodynamic conditions during perfusion (i.e. pump flow and arterial pressure) to maintain kidney oxygenation. Remarkably, this approach has been little-studied. There are at least three factors that complicate our ability to tailor perfusion conditions to optimize kidney oxygenation. Firstly, we must consider that the kidneys are arranged in parallel with other organs in the systemic circulation (Figure 1). Consequently, perfusion conditions that are adequate for some organs may not be adequate for the kidney (and *vice versa*). Secondly, we must consider that the renal medullary circulation is arranged in parallel with the bulk of the renal cortex (excluding the juxtamedullary cortex)<sup>19</sup> and the potential for redistribution of blood flow between the inner and outer medulla (Figure 1). Thus, perfusion conditions that are adequate for the renal cortex may not be adequate for the renal medulla (and *vice versa*). Thirdly, we must consider that tissue oxygenation is determined by the balance between local oxygen delivery and oxygen consumption. Below, we consider the evidence from clinical studies that perfusion conditions influence post-operative renal function, before considering the experimental evidence that manipulation of perfusion conditions might alter renal perfusion and oxygenation.

*Clinical observations:* Intuitively, one would expect that maintenance of both a relatively high pump flow and high MAP during CPB would optimise renal perfusion and oxygenation, and thus mitigate the risk of AKI. There is strong evidence that low pump flow on CPB increases the risk of AKI.<sup>86, 87</sup> However, the impact of arterial pressure during CPB on post-operative renal function remains a matter of controversy. Many observational studies have

failed to detect a relationship between MAP on CPB and post-operative renal function.<sup>88-90</sup> Furthermore, we are unaware of any prospective trials that have demonstrated a clear effect of CPB perfusion pressure on post-operative renal function. For example, Urzua and colleagues failed to detect differences in post-operative outcomes in small samples of patients in whom arterial pressure was maintained above 70 mmHg by infusion of noradrenaline (n = 7) compared with another group (n = 14) whose arterial pressure during CPB was 10-15 mmHg lower.<sup>91</sup> Creatinine clearance was greater during CPB, but not post-operatively, in the groups of patients with higher arterial pressure. Similarly, Sirvinkas and colleagues could not detect a relationship between MAP during CPB and post-operative serum creatinine in 122 elderly patients randomised to target levels of MAP of 45.0-59.9 mmHg, 60.0-69.9 mmHg or 70-95 mmHg.<sup>92</sup>

On the other hand, it may be that periods of intra-operative hypotension, and/or a failure to match MAP on bypass with pre-operative MAP, increase the risk of AKI, and might not be captured in studies in which MAP is averaged over the total period of CPB. For example, Fischer and colleagues, in a retrospective analysis, also could not detect a relationship between post-operative renal function and average MAP on CPB.<sup>86</sup> However, they did find that patients who developed post-operative acute renal failure (i.e. requiring hemofiltration/dialysis) or mild renal impairment experienced longer periods at MAP below 60 mmHg, and lower mean pump flow on CPB, than those who did not. Haase and colleagues were unable to reproduce this finding in a larger retrospective study of 920 patients.<sup>90</sup> However, they did identify a trend for intra-operative hypotension to exacerbate the increased risk of AKI associated with intra-operative anaemia. Furthermore, Kanji and colleagues found that the magnitude of the difference between pre-operative MAP and MAP on CPB was independently associated with risk of post-operative AKI in a group of 157 high-risk patients.<sup>87</sup> Thus, it remains possible that better management of MAP on bypass, including avoidance of periods of hypotension, particularly in anaemic patients, and better matching of MAP on bypass to the patient's normal resting level of arterial pressure, could mitigate the risk of AKI.

Both low haematocrit and low pump flow during CPB are predictors of AKI, but they are also the two major determinants of whole body oxygen delivery, an independent predictor of AKI.<sup>48, 93</sup> This has led to the suggestion that AKI might be avoided in patients with anaemia by increasing pump flow.<sup>94</sup> However, we are not aware of any interventional studies to directly test this hypothesis. Ranucci and colleagues also identified a critical value of whole body oxygen delivery, below which hyperlactaemia is more likely to develop ( $260 \text{ ml min}^{-1} \text{ m}^{-2}$ ). We note that these data relate to systemic lactate and whole body oxygen delivery.<sup>94</sup> Specific information on the relationship between renal oxygen delivery and the renal

arterio-venous lactate gradient might be useful for optimising pump flow for management of kidney oxygenation.

It is clear from the preceding discussion that optimisation of intrarenal oxygenation, and thus potentially the risk of AKI, requires a more evidence-based approach. What, then, can we glean from the available experimental observations?

*Experimental observations:* Mackay and colleagues assessed regional perfusion using microspheres in pigs during normothermic CPB.<sup>95</sup> They found that increasing pump flow, and thus perfusion pressure from 45 to 90 mmHg, increased renal and splanchnic perfusion but not cerebral perfusion. In another study, this group showed that increasing MAP by increasing pump flow was markedly more effective at increasing global RBF than was infusion of phenylephrine to achieve an equivalent MAP at a lower pump flow.<sup>96</sup> Remarkably, they were unable to detect autoregulation of RBF in either study. These experimental observations accord with the only available clinical observations of the effects of altered pump flow on RBF in human patients, showing a virtually linear relationship between RBF and both pump flow and MAP.<sup>51</sup> Thus, although it may be feasible and safe to manipulate MAP pharmacologically without altering pump flow,<sup>97</sup> it seems unlikely that RBF can be improved without some level of increased pump flow.

We are not aware of any studies in which the effects of altered MAP, induced by alterations in pump flow and/or vasopressor support, have been systematically investigated with the aim of determining their relative effects on RBF or local renal tissue perfusion and oxygenation. The choice of vasoactive agents and their doses, that could potentially be used to optimise renal tissue oxygenation, must be based on evidence from clinically relevant large-animal models. To this end, Calzavacca and colleagues recently assessed the effects of a range of vasoconstrictor factors on regional kidney perfusion and oxygenation in conscious sheep.<sup>21</sup> Rather surprisingly, they found that the effects of noradrenaline, angiotensin II and arginine vasopressin on renal cortical and medullary oxygenation could not be predicted based on their effects on total RBF, global renal oxygen delivery and renal oxygen consumption, or even regional perfusion as assessed by laser Doppler flowmetry. For example, even though noradrenaline had little effect on total RBF in this healthy ovine model, it greatly reduced both cortical and medullary tissue PO<sub>2</sub>. In contrast, cortical and medullary tissue PO<sub>2</sub> was relatively well-maintained during infusion of arginine vasopressin, even though it markedly reduced global renal blood flow. These observations are consistent with the concept that regional kidney oxygenation is determined by the complex interplay between local tissue perfusion (and thus oxygen delivery to tissue) and local tubular sodium reabsorption (and thus tissue oxygen consumption).<sup>18</sup> They also provide a strong rationale for studies of the effects of vasoactive agents on regional kidney oxygenation and perfusion in a clinically relevant large-animal model of CPB. We are not aware of any published reports of such

studies. Thus, we must conclude that we currently have virtually no directly relevant information to inform management of local renal tissue oxygenation through optimization of systemic haemodynamics during CPB.

#### *Pulsatile versus non-pulsatile flow*

CPB most often employs non-pulsatile flow. Available perfusion pump technology can at least partially restore pulsatility towards that achieved by the heart. The relative merits of partial pulsatile versus non-pulsatile flow remain controversial. The increased shear-stress and 'haemodynamic energy'<sup>98</sup> associated with partial pulsatile flow should theoretically aid tissue perfusion. In humans, partial pulsatile flow on CPB has been demonstrated to improve post-operative perfused vessel density in the sublingual circulation<sup>99</sup> and improve cerebral oxygenation in paediatric patients during CPB.<sup>100</sup> In experimental studies, partial pulsatile flow has also been shown to improve cerebral blood flow during CPB.<sup>101</sup> However, effects on RBF and regional kidney perfusion have been variable. Nakamura and colleagues demonstrated renal tissue perfusion (as assessed by coloured microspheres) improved more during partial pulsatile than non-pulsatile flow in sheep.<sup>102</sup> Similar observations were made in pigs by Undar and colleagues.<sup>101</sup> In contrast, in other experimental studies increased RBF during partial pulsatile CPB has either not been observed<sup>103, 104</sup> or been of marginal significance.<sup>105</sup> It has been argued that the continuing controversy regarding the effectiveness of partial pulsatile flow is a product of the diversity of equipment deployed to achieve pulsatility and its ability to simulate physiological patterns of pulsation.<sup>46</sup> Others have argued that this is not the case, and that the potential benefits of pulsatility are likely blunted by the accompanying greater haemolysis and capillary leak.<sup>104</sup> Clearly, more systematic efforts are required to resolve this long-standing controversy.

#### **Potential interventions to ameliorate the consequences of renal hypoxia during cardiopulmonary bypass**

If renal hypoxia cannot be avoided during CPB, perhaps we can find ways to ameliorate its consequences by prophylactic therapies? There has been great recent interest in the potential for remote ischaemic preconditioning (RIPC) to protect the heart and other organs during CPB. In a multi-centre clinical trial of 240 patients undergoing on-pump cardiac surgery, Zarbock and colleagues found that the simple manoeuvre of 3 cycles of 5 min ischaemia and 5 min reperfusion in one upper arm after induction of anaesthesia, reduced the absolute risk of AKI by 15%.<sup>106</sup> However, enthusiasm has been dampened somewhat by difficulties in replicating these findings in other studies. Two recent meta-analyses failed to find evidence that RIPC reduces the risk of post-operative AKI.<sup>107, 108</sup> Thus, if RIPC benefits the kidney in cardiac surgery, it might be only under rather specific conditions that remain to be precisely defined. There has also been considerable interest in the potential reno-

protective effects of pre-operative activation of hypoxia inducible factors.<sup>109</sup> However, no therapies have yet been translated into clinical practice.

There is also scope to tailor interventions in patients with post-operative AKI to optimise renal oxygenation.<sup>26</sup> Ricksten and colleagues have reported a series of carefully conducted clinical studies in which they assessed renal oxygen delivery and renal oxygen consumption in patients with and without AKI after cardiac surgery. They showed that patients with AKI after cardiac surgery have a deficit in renal oxygen delivery compared to patients without AKI, but that renal oxygen consumption is maintained at relatively normal levels, despite reduced GFR.<sup>63</sup> Thus, AKI after cardiac surgery is associated with increased renal fractional oxygen extraction, indicating a worsening of the renal oxygen supply/demand relationship in these patients. They have also tested the effects of a number of interventions, commonly used to aid resuscitation of the kidney (e.g. to increase GFR), on the renal oxygen supply/demand relationship. They found that low-dose vasopressin increased GFR (and thus renal oxygen consumption), but reduced RBF (and thus renal oxygen delivery), so increased the fractional extraction of oxygen by the kidney.<sup>110</sup> In contrast, levosimendan, a drug with both positive inotropic and vasodilator effects, increased both RBF and GFR, so had no detectable effect on the renal fractional extraction of oxygen.<sup>111</sup> Dopamine increased RBF without significantly altering GFR, so reduced renal fractional oxygen extraction.<sup>112</sup> Noradrenaline increased both GFR and RBF, while renal oxygen delivery increased but renal oxygen extraction did not change significantly, so renal fractional oxygen extraction was reduced.<sup>113</sup> They also tested the effects of the diuretics mannitol and furosemide in patients without AKI after CPB.<sup>114</sup> In patients without AKI after cardiac surgery, mannitol increased GFR (and thus renal oxygen consumption) without significantly altering RBF (and thus renal oxygen delivery). Thus, renal fractional oxygen extraction was increased. Combining an infusion of mannitol with furosemide inhibited sodium reabsorption so normalised renal fractional oxygen extraction. In patients with AKI, mannitol increased RBF and tended to increase GFR, so had no detectable effect on fractional renal oxygen extraction.<sup>115</sup> Thus, the effects of mannitol, if they exist, appear to be modulated by the presence of AKI. They also found, in patients without AKI, that crystalloid (Ringer's lactate) but not colloid (Venofundin®) increased renal fractional oxygen extraction, presumably by increasing GFR.<sup>116</sup>

Collectively, the observations described in the paragraph above show that therapies aimed at improving GFR in patients with post-operative AKI should be administered with caution, and with consideration of the likely effects of these treatments on the renal oxygen supply/demand relationship. These findings also provide important guidance for intensivists with regard to the appropriate choice of therapies to optimise global renal oxygenation. However, a note of caution should be added, since their measures of global renal oxygenation do not provide information on the relative oxygenation of the renal cortex and medulla. Noradrenaline infusion, for example, was found not to worsen the global renal oxygen supply/demand relationship in patients with post-operative AKI,<sup>113</sup> healthy

conscious sheep,<sup>21</sup> or in conscious sheep with hyperdynamic septic AKI.<sup>72</sup> But in both studies in sheep, in which it was possible to assess local renal tissue oxygenation, noradrenaline was found to induce localized medullary ischaemia and hypoxia. Thus, we really require a method to monitor medullary oxygenation in patients with AKI or at risk of developing AKI. Our recent studies in experimental animals indicate that continuous measurement of urinary PO<sub>2</sub> could provide this capability.<sup>71, 72, 117</sup>

### **Conclusions and future directions**

The aetiology of AKI after CPB is clearly complex. Nevertheless, there is considerable evidence that hypoxia, particularly in the renal medulla, plays some role. We believe at least three approaches are required to advance our understanding of this problem. Firstly, we require clinically relevant models for the study of renal oxygenation during CPB. Recent advances in our ability to monitor regional kidney perfusion and oxygenation in large animals make this feasible.<sup>118</sup> Secondly, we require methods to monitor renal medullary oxygenation in humans during cardiac surgery. Continuous measurement of urinary PO<sub>2</sub> could provide at least a partial solution to this problem.<sup>71, 72</sup> Thirdly, we require computational models of intrarenal oxygenation applicable to the human condition. Unfortunately, currently available models of kidney oxygenation are based exclusively on the kidney of the rat,<sup>119</sup> but a number of research groups are working towards addressing this deficiency. Combining these approaches could provide a translational pathway to develop ways to detect renal medullary hypoxia during cardiac surgery and develop rational interventions to ameliorate it.

### **Grants**

The authors' work was supported by grants from the National Health and Medical Research Council of Australia (GNT1050672 & GNT1122455), the National Heart Foundation of Australia (VG-2016-101377) and the Australian Research Council (DP140103045).

### **Conflict of Interest**

The authors declare they have no conflicts of interest with respect to this article. We also confirm that the submitted material conforms with Good Publishing Practice in Physiology.

### **References**

1. Hu, J, Chen, R, Liu, S, Yu, X, Zou, J, Ding, X: Global incidence and outcomes of adult patients with acute kidney injury after cardiac surgery: A systematic review and meta-analysis. *J Cardiothorac Vasc Anesth*, **30**: 82-89, 2016.
2. Lenihan, CR, Montez-Rath, ME, Mora Mangano, CT, Chertow, GM, Winkelmayer, WC: Trends in acute kidney injury, associated use of dialysis, and mortality after cardiac surgery, 1999 to 2008. *Ann Thorac Surg*, **95**: 20-28, 2013.
3. Karkouti, K, Wijeyesundera, DN, Yau, TM, Callum, JL, Cheng, DC, Crowther, M, Dupuis, JY, Fremes, SE, Kent, B, Laflamme, C, Lamy, A, Legare, JF, Mazer, CD, McCluskey, SA,



- Rubens, FD, Sawchuk, C, Beattie, WS: Acute kidney injury after cardiac surgery: focus on modifiable risk factors. *Circulation*, **119**: 495-502, 2009.
4. Coca, SG, Singanamala, S, Parikh, CR: Chronic kidney disease after acute kidney injury: a systematic review and meta-analysis. *Kidney Int*, **81**: 442-448, 2012.
  5. Chawla, LS, Eggers, PW, Star, RA, Kimmel, PL: Acute kidney injury and chronic kidney disease as interconnected syndromes. *N Engl J Med*, **371**: 58-66, 2014.
  6. Ng, SY, Sanagou, M, Wolfe, R, Cochrane, A, Smith, JA, Reid, CM: Prediction of acute kidney injury within 30 days of cardiac surgery. *J Thorac Cardiovasc Surg*, **147**: 1875-1883, 1883 e1871, 2014.
  7. Jiang, W, Teng, J, Xu, J, Shen, B, Wang, Y, Fang, Y, Zou, Z, Jin, J, Zhuang, Y, Liu, L, Luo, Z, Wang, C, Ding, X: Dynamic predictive scores for cardiac surgery-associated acute kidney injury. *JAMA*, **5**, 2016.
  8. Schley, G, Koberle, C, Manuilova, E, Rutz, S, Forster, C, Weyand, M, Formentini, I, Kientsch-Engel, R, Eckardt, KU, Willam, C: Comparison of plasma and urine biomarker performance in acute kidney injury. *PLoS one*, **10**: e0145042, 2015.
  9. Meersch, M, Schmidt, C, Van Aken, H, Martens, S, Rossaint, J, Singbartl, K, Gorlich, D, Kellum, JA, Zarbock, A: Urinary TIMP-2 and IGFBP7 as early biomarkers of acute kidney injury and renal recovery following cardiac surgery. *PLoS one*, **9**: e93460, 2014.
  10. 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*, **66**: 993-1005, 2015.
  11. Pickering, JW, Endre, ZH: Bench to bedside: the next steps for biomarkers in acute kidney injury. *Am J Physiol Renal Physiol*, **311**: F717-F721, 2016.
  12. Kellum, JA, Cerda, J, Kaplan, LJ, Nadim, MK, Palevsky, PM: Fluids for prevention and management of acute kidney injury. *Int J Artif Organs*, **31**: 96-110, 2008.
  13. Himmelfarb, J, Joannidis, M, Molitoris, B, Schietz, M, Okusa, MD, Warnock, D, Laghi, F, Goldstein, SL, Prielipp, R, Parikh, CR, Pannu, N, Lobo, SM, Shah, S, D'Intini, V, Kellum, JA: Evaluation and initial management of acute kidney injury. *Clin J Am Soc Nephrol*, **3**: 962-967, 2008.
  14. Rosner, MH, Portilla, D, Okusa, MD: Cardiac surgery as a cause of acute kidney injury: pathogenesis and potential therapies. *J Intensive Care Med*, **23**: 3-18, 2008.
  15. Schetz, M, Bove, T, Morelli, A, Mankad, S, Ronco, C, Kellum, JA: Prevention of cardiac surgery-associated acute kidney injury. *Int J Artif Organs*, **31**: 179-189, 2008.
  16. Patel, NN, Rogers, CA, Angelini, GD, Murphy, GJ: Pharmacological therapies for the prevention of acute kidney injury following cardiac surgery: a systematic review. *Heart Fail Rev*, **16**: 553-567, 2011.
  17. Murphy, GJ, Lin, H, Coward, RJ, Toth, T, Holmes, R, Hall, D, Angelini, GD: An initial evaluation of post-cardiopulmonary bypass acute kidney injury in swine. *Eur J Cardiothorac Surg*, **36**: 849-855, 2009.
  18. Evans, RG, Ince, C, Joles, JA, Smith, DW, May, CN, O'Connor, PM, Gardiner, BS: Haemodynamic influences on kidney oxygenation: clinical implications of integrative physiology. *Clin Exp Pharmacol Physiol*, **40**: 106-122, 2013.
  19. Evans, RG, Eppel, GA, Anderson, WP, Denton, KM: Mechanisms underlying the differential control of blood flow in the renal medulla and cortex. *J Hypertens*, **22**: 1439-1451, 2004.

20. Evans, RG, Harrop, GK, Ngo, JP, Ow, CP, O'Connor, PM: Basal renal oxygen consumption and the efficiency of oxygen utilization for sodium reabsorption. *Am J Physiol Renal Physiol*, **306**: F551-F560, 2014.
21. Calzavacca, P, Evans, RG, Bailey, M, Bellomo, R, May, CN: Variable responses of regional renal oxygenation and perfusion to vasoactive agents in awake sheep. *Am J Physiol Regul Integr Comp Physiol*, **309**: R1226-1233, 2015.
22. Juillard, L, Lemoine, S, Janier, MF, Barthez, PY, Bonnefoi, F, Laville, M: Validation of renal oxidative metabolism measurement by positron-emission tomography. *Hypertension*, **50**: 242-247, 2007.
23. Gullans, SR, Hebert, SC: Metabolic basis of ion transport. In: *Brenner and Rector's The Kidney*. Fifth Edition ed. edited by Brenner BM, Philadelphia, WB Saunders Company, 1996, pp 211-246.
24. Adler, S, Huang, H, Wolin, MS, Kaminski, PM: Oxidant stress leads to impaired regulation of renal cortical oxygen consumption by nitric oxide in the aging kidney. *J Am Soc Nephrol*, **15**: 52-60, 2004.
25. Hansell, P, Welch, WJ, Blantz, RC, Palm, F: Determinants of kidney oxygen consumption and their relationship to tissue oxygen tension in diabetes and hypertension. *Clin Exp Pharmacol Physiol*, **40**: 123-137, 2013.
26. Ricksten, SE, Bragadottir, G, Redfors, B: Renal oxygenation in clinical acute kidney injury. *Crit Care*, **17**: 221, 2013.
27. Lee, CJ, Gardiner, BS, Ngo, JP, Kar, S, Evans, RG, Smith, DW: Accounting for oxygen in the renal cortex: A computational study of factors that predispose the cortex to hypoxia. *Am J Physiol - Renal Physiol*, **313**: F218-F236, 2017.
28. Lee, CJ, Ngo, JP, Kar, S, Gardiner, BS, Evans, RG, Smith, DW: A pseudo-three-dimensional model for quantification of oxygen diffusion from pre-glomerular arteries to renal tissue and renal venous blood. *Am J Physiol - Renal Physiol*, **313**: F237-F253, 2017.
29. Evans, RG, Gardiner, BS, Smith, DW, O'Connor, PM: Intrarenal oxygenation: unique challenges and the biophysical basis of homeostasis. *Am J Physiol Renal Physiol*, **295**: F1259-1270, 2008.
30. Ngo, JP, Ow, CP, Gardiner, BS, Kar, S, Pearson, JT, Smith, DW, Evans, RG: Diffusive shunting of gases and other molecules in the renal vasculature: Physiological and evolutionary significance. *Am J Physiol Regul Integr Comp Physiol*, **311**: R797-R810, 2016.
31. Chen, J, Edwards, A, Layton, AT: A mathematical model of O<sub>2</sub> transport in the rat outer medulla. II. Impact of outer medullary architecture. *Am J Physiol Renal Physiol*, **297**: F537-548, 2009.
32. Fry, BC, Edwards, A, Sgouralis, I, Layton, AT: Impact of renal medullary three-dimensional architecture on oxygen transport. *Am J Physiol Renal Physiol*, **307**: F263-272, 2014.
33. Heyman, SN, Rosenberger, C, Rosen, S: Experimental ischemia-reperfusion: biases and myths-the proximal vs. distal hypoxic tubular injury debate revisited. *Kidney Int*, **77**: 9-16, 2010.
34. Calzavacca, P, Evans, RG, Bailey, M, Bellomo, R, May, CN: Cortical and medullary tissue perfusion and oxygenation in experimental septic acute kidney injury. *Crit Care Med*, **43**: e431-439, 2015.
35. Heyman, SN, Evans, RG, Rosen, S, Rosenberger, C: Cellular adaptive changes in AKI: mitigating renal hypoxic injury. *Nephrol Dial Transplant*, **27**: 1721-1728, 2012.
36. Tanaka, S, Tanaka, T, Nangaku, M: Hypoxia is a key player in the AKI-to-CKD transition.

- Am J Physiol - Renal Physiol*, **307**: F1187-F1195, 2014.
37. Ehling, J, Babickova, J, Gremse, F, Klinkhammer, BM, Baetke, S, Knuechel, R, Kiessling, F, Floege, J, Lammers, T, Boor, P: Quantitative micro-computed tomography imaging of vascular dysfunction in progressive kidney diseases. *J Am Soc Nephrol*, **27**: 520-532, 2016.
  38. Basile, DP: The endothelial cell in ischemic acute kidney injury: implications for acute and chronic function. *Kidney Int*, **72**: 151-156, 2007.
  39. Babickova, J, Klinkhammer, BM, Buhl, EM, Djurdjaj, S, Hoss, M, Heymann, F, Tacke, F, Floege, J, Becker, JU, Boor, P: Regardless of etiology, progressive renal disease causes ultrastructural and functional alterations of peritubular capillaries. *Kidney Int*, **91**: 70-85, 2017.
  40. Kang, DH, Kanellis, J, Hugo, C, Truong, L, Anderson, S, Kerjaschki, D, Schreiner, GF, Johnson, RJ: Role of the microvascular endothelium in progressive renal disease. *J Am Soc Nephrol*, **13**: 806-816, 2002.
  41. Regner, KR, Roman, RJ: Role of medullary blood flow in the pathogenesis of renal ischemia-reperfusion injury. *Curr Opin Nephrol Hypertens*, **21**: 33-38, 2012.
  42. Schurek, HJ, Johns, O: Is tubuloglomerular feedback a tool to prevent nephron oxygen deficiency? *Kidney Int*, **51**: 386-392, 1997.
  43. Seco, M, Edelman, JJ, Van Boxtel, B, Forrest, P, Byrom, MJ, Wilson, MK, Fraser, J, Bannon, PG, Vallely, MP: Neurologic injury and protection in adult cardiac and aortic surgery. *J Cardiothorac Vasc Anesth*, **29**: 185-195, 2015.
  44. Mazzone, AL, Baker, RA, Gleadle, JM: Mending a broken heart but breaking the kidney. *Nephrology (Carlton)*, **21**: 812-820, 2016.
  45. Franchini, KG: Influence of hemodilution on the renal blood flow autoregulation during acute expansion in rats. *Am J Physiol*, **277**: R1662-1674, 1999.
  46. Undar, A, Palanzo, D, Qiu, F, Alkan-Bozkaya, T, Akcevin, A, Talor, J, Baer, L, Woitas, K, Wise, R, McCoach, R, Guan, Y, Haines, N, Wang, S, Clark, JB, Myers, JL: Benefits of pulsatile flow in pediatric cardiopulmonary bypass procedures: from conception to conduction. *Perfusion*, **26 Suppl 1**: 35-39, 2011.
  47. Karkouti, K, Beattie, WS, Wijeyesundera, 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*, **129**: 391-400, 2005.
  48. de Somer, F, Mulholland, JW, Bryan, MR, Aloisio, T, Van Nooten, GJ, Ranucci, M: O<sub>2</sub> delivery and CO<sub>2</sub> production during cardiopulmonary bypass as determinants of acute kidney injury: time for a goal-directed perfusion management? *Crit Care*, **15**: R192, 2011.
  49. Bennett, MJ, Rajakaruna, C, Bazerbashi, S, Webb, G, Gomez-Cano, M, Lloyd, C: Oxygen delivery during cardiopulmonary bypass (and renal outcome) using two systems of extracorporeal circulation: a retrospective review. *Interac Cardiovasc Thorac Surg*, **16**: 760-764, 2013.
  50. Magruder, JT, Dungan, SP, Grimm, JC, Harness, HL, Wierschke, C, Castillejo, S, Barodka, V, Katz, N, Shah, AS, Whitman, GJ: Nadir oxygen delivery on bypass and hypotension increase acute kidney injury risk after cardiac operations. *Ann Thorac Surg*, **100**: 1697-1703, 2015.
  51. Andersson, LG, Bratteby, LE, Ekroth, R, Hallhagen, S, Joachimsson, PO, van der Linden, J, Wesslen, O: Renal function during cardiopulmonary bypass: influence of pump flow

- and systemic blood pressure. *Eur J Cardiothorac Surg*, **8**: 597-602, 1994.
52. Lannemyr, L, Bragadottir, G, Krumbholz, V, Redfors, B, Sellgren, J, Ricksten, SE: Effects of cardiopulmonary bypass on renal perfusion, filtration, and oxygenation in patients undergoing cardiac surgery. *Anesthesiology*, **126**: 205-213, 2017.
  53. Koning, NJ, Simon, LE, Asfar, P, Baufreton, C, Boer, C: Systemic microvascular shunting through hyperdynamic capillaries after acute physiological disturbances following cardiopulmonary bypass. *Am J Physiol Heart Circ Physiol*, **307**: H967-975, 2014.
  54. Casellas, D, Mimran, A: Shunting in renal microvasculature of the rat: a scanning electron microscopic study of corrosion casts. *Anat Rec*, **201**: 237-248, 1981.
  55. Pathi, VL, Morrison, J, MacPhaden, A, Martin, W, McQuiston, AM, Wheatley, DJ: Alterations in renal microcirculation during cardiopulmonary bypass. *Ann Thorac Surg*, **65**: 993-998, 1998.
  56. Calzavacca, P, May, CN, Bellomo, R: Glomerular haemodynamics, the renal sympathetic nervous system and sepsis-induced acute kidney injury. *Nephrol Dial Transplant*, 2014.
  57. Sgouralis, I, Evans, RG, Gardiner, BS, Smith, JA, Fry, BC, Layton, AT: Renal hemodynamics, function and oxygenation during cardiac surgery performed on cardiopulmonary bypass: a modeling study. *Physiology Reports*, **3**: e12260 2015.
  58. Sgouralis, I, Evans, RG, Layton, AT: Renal medullary and urinary oxygen tension during cardiopulmonary bypass in the rat. *Math Med Biol*, **34**: 313-333, 2017.
  59. Boodhwani, M, Rubens, FD, Wozny, D, Nathan, HJ: Effects of mild hypothermia and rewarming on renal function after coronary artery bypass grafting. *Ann Thorac Surg*, **87**: 489-495, 2009.
  60. Kourliouros, A, Valencia, O, Phillips, SD, Collinson, PO, van Besouw, JP, Jahangiri, M: Low cardiopulmonary bypass perfusion temperatures are associated with acute kidney injury following coronary artery bypass surgery. *Eur J Cardiothorac Surg*, **37**: 704-709, 2010.
  61. Stafford-Smith, M, Grocott, HP: Renal medullary hypoxia during experimental cardiopulmonary bypass: a pilot study. *Perfusion*, **20**: 53-58, 2005.
  62. 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*, **28**: 504-511, 2013.
  63. Redfors, B, Bragadottir, G, Sellgren, J, Sward, 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*, **38**: 1695-1701, 2010.
  64. Patel, NN, Lin, H, Toth, T, Welsh, GI, Jones, C, Ray, P, Satchell, SC, Sleeman, P, Angelini, GD, Murphy, GJ: Reversal of anemia with allogenic RBC transfusion prevents post-cardiopulmonary bypass acute kidney injury in swine. *Am J Physiol Renal Physiol*, **301**: F605-614, 2011.
  65. Patel, NN, Toth, T, Jones, C, Lin, H, Ray, P, George, SJ, Welsh, G, Satchell, SC, Sleeman, P, Angelini, GD, Murphy, GJ: Prevention of post-cardiopulmonary bypass acute kidney injury by endothelin A receptor blockade. *Crit Care Med*, **39**: 793-802, 2011.
  66. Patel, NN, Lin, H, Toth, T, Jones, C, Ray, P, Welsh, GI, Satchell, SC, Sleeman, P, Angelini, GD, Murphy, GJ: Phosphodiesterase-5 inhibition prevents postcardiopulmonary bypass acute kidney injury in swine. *Ann Thorac Surg*, **92**: 2168-2176, 2011.
  67. Choi, DK, Kim, WJ, Chin, JH, Lee, EH, Don Hahm, K, Yeon Sim, J, Cheol Choi, I: Intraoperative renal regional oxygen desaturation can be a predictor for acute

- kidney injury after cardiac surgery. *J Cardiothorac Vasc Anesth*, **28**: 564-571, 2014.
68. Ruf, B, Bonelli, V, Balling, G, Horer, J, Nagdyman, N, Braun, SL, Ewert, P, Reiter, K: Intraoperative renal near-infrared spectroscopy indicates developing acute kidney injury in infants undergoing cardiac surgery with cardiopulmonary bypass: a case-control study. *Crit Care*, **19**: 27, 2015.
69. Evans, RG, Smith, JA, Wright, C, Gardiner, BS, Smith, DW, Cochrane, AD: Urinary oxygen tension: a clinical window on the health of the renal medulla? *Am J Physiol Regul Integr Comp Physiol*, **306**: R45-50, 2014.
70. Evans, RG, Smith, JA, Gardiner, BS, Smith, DW, Thrift, AG, Lankadeva, YR, May, CN, Cochrane, AD: Hypoxia as a biomarker of kidney disease. In: *Diseases of the Kidney Biomarkers of Disease: Methods, Discoveries and Applications*. edited by Preedy, VR & Patel VB, Springer-Verlag, 2016, pp 83-105.
71. Sgouralis, I, Kett, MM, Ow, CP, Abdelkader, A, Layton, AT, Gardiner, BS, Smith, DW, Lankadeva, YR, Evans, RG: Bladder urine oxygen tension for assessing renal medullary oxygenation in rabbits: Experimental and modelling studies. *Am J Physiol Regul Integr Comp Physiol*, **311**: R532-544, 2016.
72. Lankadeva, YR, Kosaka, J, Evans, RG, Bailey, SR, Bellomo, R, May, CN: Intrarenal and urinary oxygenation during norepinephrine resuscitation in ovine septic acute kidney injury. *Kidney Int*, **90**: 100-108, 2016.
73. Kainuma, M, Yamada, M, Miyake, T: Continuous urine oxygen tension monitoring in patients undergoing cardiac surgery. *J Cardiothorac Vasc Anesth*, **10**: 603-608, 1996.
74. Garg, AX, Devereaux, PJ, Yusuf, S, Cuerden, MS, Parikh, CR, Coca, SG, Walsh, M, Novick, R, Cook, RJ, Jain, AR, Pan, X, Noiseux, N, Vik, K, Stolf, NA, Ritchie, A, Favalaro, RR, Parvathaneni, S, Whitlock, RP, Ou, Y, Lawrence, M, Lamy, A, Investigators, C: Kidney function after off-pump or on-pump coronary artery bypass graft surgery: a randomized clinical trial. *JAMA*, **311**: 2191-2198, 2014.
75. 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, Olavegogeoascoechea, PA, Airan, B, Sulling, TA, Whitlock, RP, Ou, Y, Ng, J, Chrolavicius, S, Yusuf, S, Investigators, C: Off-pump or on-pump coronary-artery bypass grafting at 30 days. *N Engl J Med*, **366**: 1489-1497, 2012.
76. Couture, P, Denault, A, Limoges, P, Sheridan, P, Babin, D, Cartier, R: Mechanisms of hemodynamic changes during off-pump coronary artery bypass surgery. *Can J Anesth*, **49**: 835-849, 2003.
77. Shroyer, AL, Grover, FL, Hattler, B, Collins, JF, McDonald, GO, Kozora, E, Lucke, JC, Baltz, JH, Novitzky, D, Veterans Affairs Randomized On/Off Bypass Study, G: On-pump versus off-pump coronary-artery bypass surgery. *N Engl J Med*, **361**: 1827-1837, 2009.
78. 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*, **33**: 1749-1756, 2005.
79. Khan, UA, Coca, SG, Hong, K, Koyner, JL, Garg, AX, Passik, CS, Swaminathan, M, Garwood, S, Patel, UD, Hashim, S, Quantz, MA, Parikh, CR: Blood transfusions are associated with urinary biomarkers of kidney injury in cardiac surgery. *J Thorac Cardiovasc Surg*, **148**: 726-732, 2014.

80. Karkouti, K: Transfusion and risk of acute kidney injury in cardiac surgery. *Br J Anaesth*, **109 Suppl 1**: i29-i38, 2012.
81. Newland, RF, Tully, PJ, Baker, RA: Hyperthermic perfusion during cardiopulmonary bypass and postoperative temperature are independent predictors of acute kidney injury following cardiac surgery. *Perfusion*, **28**: 223-231, 2013.
82. Newland, RF, Baker, RA, Mazzone, AL, Quinn, SS, Chew, DP, Perfusion Downunder, C: Rewarming Temperature During Cardiopulmonary Bypass and Acute Kidney Injury: A Multicenter Analysis. *Ann Thorac Surg*, **101**: 1655-1662, 2016.
83. Swaminathan, M, East, C, Phillips-Bute, B, Newman, MF, Reves, JG, Smith, PK, Stafford-Smith, M: Report of a substudy on warm versus cold cardiopulmonary bypass: changes in creatinine clearance. *Ann Thorac Surg*, **72**: 1603-1609, 2001.
84. Susantitaphong, P, Alfayez, M, Cohen-Bucay, A, Balk, EM, Jaber, BL: Therapeutic hypothermia and prevention of acute kidney injury: a meta-analysis of randomized controlled trials. *Resuscitation*, **83**: 159-167, 2012.
85. Lazenby, WD, Ko, W, Zelano, JA, Lebowitz, N, Shin, YT, Isom, OW, Krieger, KH: Effects of temperature and flow rate on regional blood flow and metabolism during cardiopulmonary bypass. *Ann Thorac Surg*, **53**: 957-964, 1992.
86. Fischer, UM, Weissenberger, WK, Warters, RD, Geissler, HJ, Allen, SJ, Mehlhorn, U: Impact of cardiopulmonary bypass management on postcardiac surgery renal function. *Perfusion*, **17**: 401-406, 2002.
87. 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*, **5**: 71, 2010.
88. Abel, RM, Buckley, MJ, Austen, WG, Barnett, GO, Beck, CH, Jr., Fischer, JE: Etiology, incidence, and prognosis of renal failure following cardiac operations. Results of a prospective analysis of 500 consecutive patients. *J Thorac Cardiovasc Surg*, **71**: 323-333, 1976.
89. Slogoff, S, Reul, GJ, Keats, AS, Curry, GR, Crum, ME, Elmquist, BA, Giesecke, NM, Jistel, JR, Rogers, LK, Soderberg, JD, et al.: Role of perfusion pressure and flow in major organ dysfunction after cardiopulmonary bypass. *Ann Thorac Surg*, **50**: 911-918, 1990.
90. Haase, M, Bellomo, R, Story, D, Letis, A, Klemz, K, Matalanis, G, Seevanayagam, S, Dragun, D, Seeliger, E, Mertens, PR, Haase-Fielitz, A: Effect of mean arterial pressure, haemoglobin and blood transfusion during cardiopulmonary bypass on postoperative acute kidney injury. *Nephrol Dial Transplant*, **27**: 153-160, 2012.
91. Urzua, J, Troncoso, S, Bugeo, G, Canessa, R, Munoz, H, Lema, G, Valdivieso, A, Irazaval, M, Moran, S, Meneses, G: Renal function and cardiopulmonary bypass: effect of perfusion pressure. *J Cardiothorac Vasc Anesth*, **6**: 299-303, 1992.
92. Sirvinskas, E, Benetis, R, Raliene, L, Andrejaitiene, J: The influence of mean arterial blood pressure during cardiopulmonary bypass on postoperative renal dysfunction in elderly patients. *Perfusion*, **27**: 193-198, 2012.
93. Ranucci, M, Romitti, F, Isgro, G, Cotza, M, Brozzi, S, Boncilli, A, Ditta, A: Oxygen delivery during cardiopulmonary bypass and acute renal failure after coronary operations. *Ann Thorac Surg*, **80**: 2213-2220, 2005.
94. Ranucci, M: Perioperative renal failure: hypoperfusion during cardiopulmonary bypass? *Semin Cardiothorac Vasc Anesth*, **11**: 265-268, 2007.

95. Mackay, JH, Feerick, AE, Woodson, LC, Lin, C-Y, Deyo, DJ, Uchida, T, Johnston, WE: Increasing organ blood flow during cardiopulmonary bypass in pigs: comparison of dopamine and perfusion pressure. *Crit Care Med*, **23**: 1090-1098, 1995.
96. O'Dwyer, C, Woodson, LC, Conroy, BP, Lin, CY, Deyo, DJ, Uchida, T, Johnston, WE: Regional perfusion abnormalities with phenylephrine during normothermic bypass. *Ann Thorac Surg*, **63**: 728-735, 1997.
97. Pirraglia, PA, Peterson, JC, Hartman, GS, Yao, FS, Thomas, SJ, Charlson, ME: The efficacy and safety of a pharmacologic protocol for maintaining coronary artery bypass patients at a higher mean arterial pressure during cardiopulmonary bypass. 1998. *J Extra-Corp Tech*, **45**: 198-206, 2013.
98. Wolfe, R, Strother, A, Wang, S, Kunselman, AR, Undar, A: Impact of pulsatility and flow rates on hemodynamic energy transmission in an adult extracorporeal life support system. *Artif Organs*, **39**: E127-137, 2015.
99. Koning, NJ, Vonk, AB, van Barneveld, LJ, Beishuizen, A, Atasever, B, van den Brom, CE, Boer, C: Pulsatile flow during cardiopulmonary bypass preserves postoperative microcirculatory perfusion irrespective of systemic hemodynamics. *J Appl Physiol*, **112**: 1727-1734, 2012.
100. Su, XW, Guan, Y, Barnes, M, Clark, JB, Myers, JL, Undar, A: Improved cerebral oxygen saturation and blood flow pulsatility with pulsatile perfusion during pediatric cardiopulmonary bypass. *Pediatr Res*, **70**: 181-185, 2011.
101. Undar, A, Masai, T, Beyer, EA, Goddard-Finegold, J, McGarry, MC, Fraser, CDJ: Pediatric physiologic pulsatile pump enhances cerebral and renal blood flow during and after cardiopulmonary bypass. *Artif Organs*, **26**: 919-923, 2002.
102. Nakamura, K, Harasaki, H, Fukumura, F, Fukamachi, K, Whalen, RL: Comparison of pulsatile and non-pulsatile cardiopulmonary bypass on regional renal blood flow in sheep. *Scand Cardiovasc J*, **38**: 59-63, 2009.
103. Cook, DJ, Orszulak, TA, Daly, RC: The effects of pulsatile cardiopulmonary bypass on cerebral and renal blood flow in dogs. *J Cardiothorac Vasc Anesth*, **11**: 420-427, 1997.
104. Voss, B, Krane, M, Jung, C, Brockmann, G, Braun, S, Gunther, T, Lange, R, Bauernschmitt, R: Cardiopulmonary bypass with physiological flow and pressure curves: pulse is unnecessary! *Eur J Cardiothorac Surg*, **37**: 223-232, 2010.
105. Lodge, AJ, Undar, A, Daggett, CW, Runge, TM, Calhoon, JH, Ungerleider, RM: Regional blood flow during pulsatile cardiopulmonary bypass and after circulatory arrest in an infant model. *Ann Thorac Surg*, **63**: 1243-1250, 1997.
106. Zarbock, A, Schmidt, C, Van Aken, H, Wempe, C, Martens, S, Zahn, PK, Wolf, B, Goebel, U, Schwer, CI, Rosenberger, P, Haeberle, H, Gorlich, D, Kellum, JA, Meersch, M, Renal, RI: Effect of remote ischemic preconditioning on kidney injury among high-risk patients undergoing cardiac surgery: a randomized clinical trial. *JAMA*, **313**: 2133-2141, 2015.
107. Zhou, C, Jeon, Y, Meybohm, P, Zarbock, A, Young, PJ, Li, L, Hausenloy, DJ: Renoprotection by remote ischemic conditioning during elective coronary revascularization: A systematic review and meta-analysis of randomized controlled trials. *Int J Cardiol*, **222**: 295-302, 2016.
108. Wang, S, Li, H, He, N, Sun, Y, Guo, S, Liao, W, Liao, Y, Chen, Y, Bin, J: Impact of remote ischaemic preconditioning on major clinical outcomes in patients undergoing cardiovascular surgery: A meta-analysis with trial sequential analysis of 32

- randomised controlled trials. *Int J Cardiol*, **227**: 882-891, 2017.
109. Andringa, KK, Agarwal, A: Role of hypoxia-inducible factors in acute kidney injury. *Nephron Clin Pract*, **127**: 70-74, 2014.
110. 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*, **53**: 1052-1059, 2009.
111. Bragadottir, G, Redfors, B, Ricksten, SE: Effects of levosimendan on glomerular filtration rate, renal blood flow, and renal oxygenation after cardiac surgery with cardiopulmonary bypass: a randomized placebo-controlled study. *Crit Care Med*, **41**: 2328-2335, 2013.
112. Redfors, B, Bragadottir, G, Sellgren, J, Sward, K, Ricksten, SE: Dopamine increases renal oxygenation: a clinical study in post-cardiac surgery patients. *Acta Anaesthesiol Scand*, **54**: 183-190, 2010.
113. Redfors, B, Bragadottir, G, Sellgren, J, Sward, K, Ricksten, SE: Effects of norepinephrine on renal perfusion, filtration and oxygenation in vasodilatory shock and acute kidney injury. *Intensive Care Med*, **37**: 60-67, 2011.
114. Redfors, B, Sward, 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*, **35**: 115-122, 2009.
115. Bragadottir, G, Redfors, B, Ricksten, SE: Mannitol increases renal blood flow and maintains filtration fraction and oxygenation in postoperative acute kidney injury: a prospective interventional study. *Crit Care*, **16**: R159, 2012.
116. 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*, **115**: 736-742, 2015.
117. Lankadeva, YR, Kosaka, J, Evans, RG, Bellomo, R, May, CN: Urinary oxygenation as a surrogate measure of medullary oxygenation during angiotensin II therapy in septic acute kidney injury. *Crit Care Med*, **in press (CCMED-D-17-00918R2)**, 2017.
118. Calzavacca, P, Evans, RG, Bailey, M, Lankadeva, YR, Bellomo, R, May, CN: Long-term measurement of renal cortical and medullary tissue oxygenation and perfusion in unanesthetized sheep. *Am J Physiol Regul Integr Comp Physiol*, **308**: R832-839, 2015.
119. Layton, AT: Recent advances in renal hypoxia: insights from bench experiments and computer simulations. *Am J Physiol Renal Physiol*, **311**: F162-165, 2016.



## Figure Legends

**Fig. 1 Schematic of the factors that influence renal oxygen delivery.** The renal medullary circulation is essentially arranged in parallel with both the extrarenal circulation and the cortical vascular bed. Because the resistance to blood flow in the renal circulation before the point where the juxtamedullary afferent arterioles branch from cortical radial (interlobular) and arcuate arteries is small, the renal circulation can be considered to consist of two resistors in parallel, the outer and mid-cortical vascular bed ( $R_C$ ) and the juxtamedullary and medullary vascular bed ( $R_M$ ). The resistance of all other vascular beds can be lumped together as the extrarenal vascular resistance ( $R_{ER}$ ). Although the relative levels of vascular resistance are not directly relevant to consideration of renal oxygenation, they have a profound impact on the oxygen delivery to other organs such as the brain and splanchnic organs that are also susceptible to damage during cardiopulmonary bypass. Other abbreviations: MAP = mean arterial pressure,  $P_{RV}$  = renal venous pressure, RBF = renal blood flow,  $R_R$  = renal vascular resistance. Note also that there is the potential for redistribution of blood flow between the inner and outer medulla (not shown).

**Fig. 2 Sensitivity of cortical tissue oxygenation to factors that influence renal oxygen delivery and oxygen consumption in a model of oxygen transport in the renal cortex of the rat.** Relative changes in renal blood flow (RBF), the partial pressure of oxygen in arterial blood ( $PaO_2$ ), blood haemoglobin concentration (Hb), glomerular filtration rate (GFR), the energetic cost of reabsorption of each mole of sodium ( $\beta$ ), and peritubular capillary surface area (PCSA), from their physiological base-case, are shown along the x-axis. Simulations were run under conditions of low (A; 15,000 mm<sup>2</sup>), normal (B; 30,000 mm<sup>2</sup>) and high (C; 45,000 mm<sup>2</sup>) PCSA. The numbers within each cell depict the predicted tissue  $PO_2$ . The cells are also colour codes to show the relative change in tissue  $PO_2$  from baseline (shown in white). Note, in panel B, that of all the variables, tissue  $PO_2$  is most sensitive to the effects of reducing PCSA. Note also, in panel A, that a deficit in PCSA renders the kidney highly susceptible to hypoxia when RBF,  $PaO_2$ , Hb or  $\beta$  are reduced, or GFR is increased. Figure reproduced, with permission, from Lee et al (2017).<sup>27</sup>

**Fig. 3 Renal medullary tissue and urinary oxygen tension during simulated cardiopulmonary bypass in a computational model of the upper urinary tract of the rat.**

Oxygen tension is shown for the interstitial fluid in the inter-bundle region of the lower inner stripe of the outer medulla ( $P_{O_2}^{\text{ext-VB}}$ , in the vicinity of the thick ascending limbs of the loop of Henle; top panel), urine at the outlet of the collecting duct ( $P_{O_2}^{\text{CD-out}}$ , inner medulla/renal pelvic urine, middle panel), and in urine in the bladder ( $P_{O_2}^{\text{bladder}}$ , lower panel). The various phases of cardiac surgery are simulated, including the period prior to induction of anaesthesia (baseline), after induction of anaesthesia but before commencing cardiopulmonary bypass (pre-CPB), during hypothermic (28 °C) CPB, during re-warming on CPB (CPB-rewarm) and after weaning from CPB (post-CPB). Three scenarios of are simulated with regard to autoregulation of medullary blood flow, ranging from perfect autoregulation, to partial (50%) autoregulation, to the complete absence of autoregulation. Note that medullary and urinary  $PO_2$  are predicted to fall on CPB, particularly during the re-warming phase. Note also that the discrepancy between the  $PO_2$  of urine in the bladder relative to that in the collecting ducts in part reflects the low using flow predicted from this computational model. Figure reproduced, with permission from Oxford University Press on behalf of the Institute of Mathematics and its Applications, from Sgouralis et al (2017).<sup>58</sup>

**Fig. 4 Predictions of a computational model of oxygen transport along the rabbit ureter.**

The model generates predictions of pelvic urinary oxygen tension ( $PO_2$ ), and by inference the  $PO_2$  of the inner medulla, from three input variables: (1) bladder urine  $PO_2$ , (2) arterial blood  $PO_2$ , and (3) urine flow. Simulations are shown for normoxia (arterial  $PO_2 = 95$  mmHg) and hyperoxaemic conditions (arterial  $PO_2 = 250$  mmHg) such as those that might be experienced during major surgery and cardiopulmonary bypass. Figure reproduced, with permission, from Sgouralis et al (2016).<sup>71</sup>

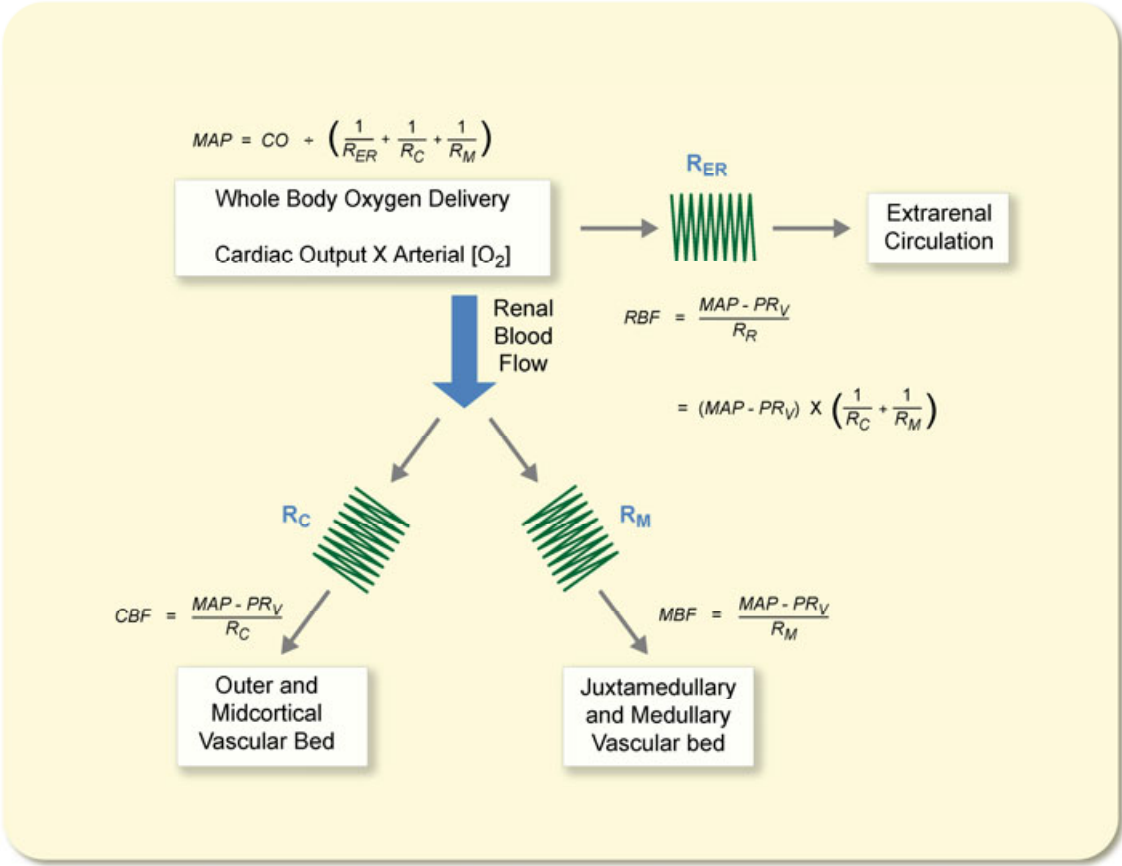


Figure 2

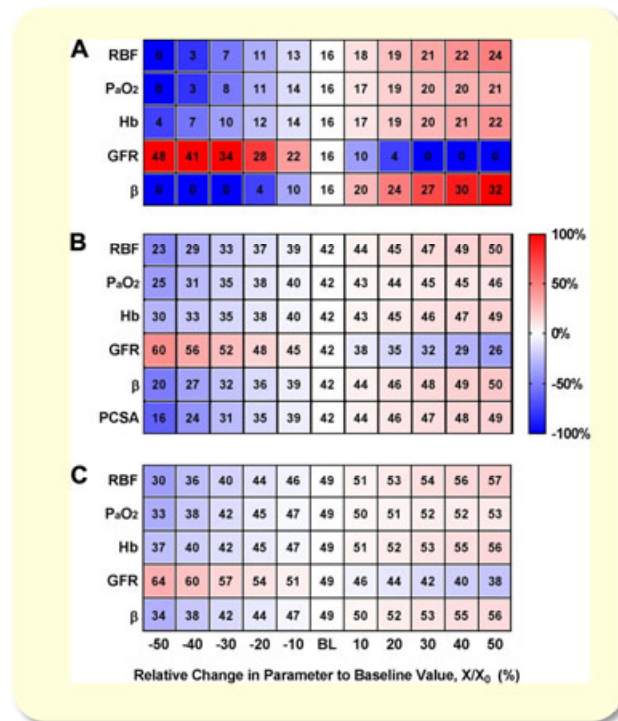


Figure 3

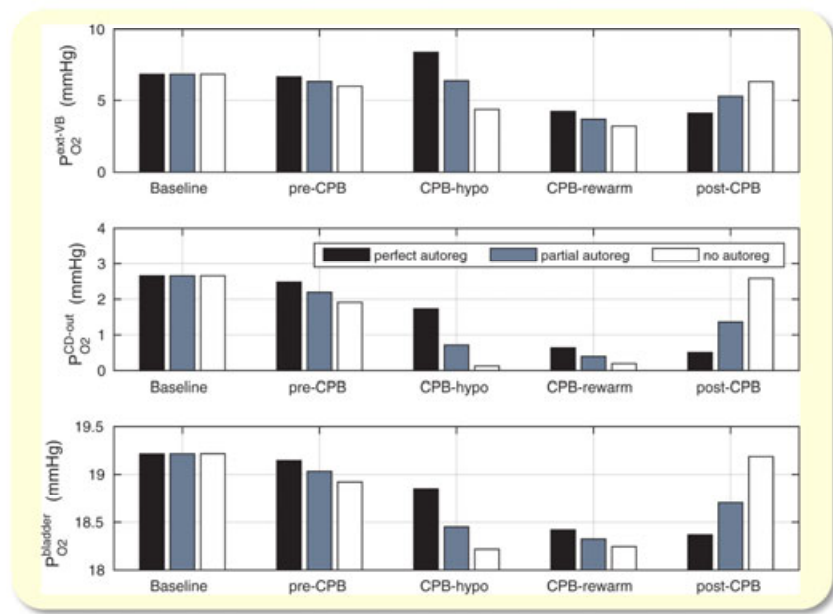


Figure 4

