

# Renal Hemodynamics, Function, and Oxygenation in Critically Ill Patients and after Major Surgery

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## Abstract

This review outlines the available data from the work of our group on renal hemodynamics, function, and oxygenation in patients who are critically ill with acute renal dysfunction, such as those with postoperative AKI, those in early clinical septic shock, in patients undergoing cardiac surgery with cardiopulmonary bypass, or in patients undergoing liver transplantation. We also provide information on renal hemodynamics, function, and oxygenation in patients with chronic renal impairment due to congestive heart failure. This review will argue that, for all of these groups of patients, the common denominator is that renal oxygenation is impaired due to a lower renal oxygen delivery or a pronounced increase in renal oxygen consumption.

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## Determinants of Renal Oxygen Delivery and Renal Oxygen Consumption

Renal oxygen ( $O_2$ ) availability is determined by the balance between renal  $O_2$  delivery ( $RDO_2$ ) and renal  $O_2$  consumption ( $RVO_2$ ).  $RDO_2$ , in turn, is dependent on renal blood flow (RBF) and arterial  $O_2$  content ( $CaO_2$ ) (Figure 1). RBF is determined by renal perfusion pressure (in the clinical situation, this is usually estimated as mean arterial pressure [MAP] minus central venous pressure). Pressure-flow autoregulation of RBF is well developed in the kidney, and is mediated by myogenic and tubuloglomerular feedback mechanisms (1). In severe hypotension, however, the renal autoregulatory capacity is exhausted and RBF becomes pressure dependent, with a risk of renal ischemia. In patients who are at high risk, a low MAP during surgery or in the intensive care unit (ICU) is directly correlated to an increase in serum creatinine, suggesting AKI (2–4). During surgery and in the postoperative period, many patients receive artificial solutions, such as colloids and crystalloids, which induce hemodilution and a reduction in blood  $O_2$  carrying capacity ( $CaO_2$ ), which, in turn, may affect  $RDO_2$  negatively. In a recent study, the differential effects of a colloid and a crystalloid fluid on systemic and renal hemodynamics were studied after cardiac surgery. Both fluids improved cardiac output and RBF, but none of the fluids increased  $RDO_2$ , due to hemodilution (5).

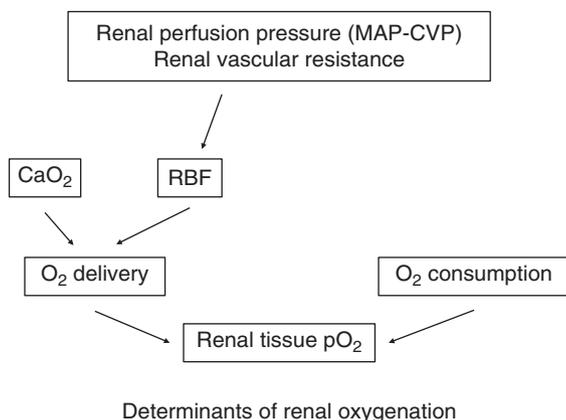
Active tubular sodium reabsorption accounts for 70%–80% of  $RVO_2$  (6). If you administer furosemide (bolus of 0.5 mg/kg followed by 0.5 mg/kg per hour) to postoperative patients,  $RVO_2$  will decrease by approximately 25%, and experimental studies have shown that furosemide causes an increase in medullary tissue  $PO_2$  (7), indicating an improved renal oxygenation. Tubular sodium reabsorption, in turn, is controlled by GFR (Figure 2). If GFR increases, tubular

sodium load will increase, causing tubular reabsorption to also increase. It has been shown in experimental studies (8) and in patients (9) that there is a close linear correlation between GFR, renal sodium reabsorption, and  $RVO_2$  (Figure 3). Thus, GFR is an important determinant of  $RVO_2$ . Infusion of atrial natriuretic peptide to postoperative patients, at a dose of 50 ng/kg per minute, has been shown to increase GFR by 15%, which was accompanied by a 25% increase in  $RVO_2$  (10). In the treatment of AKI, the aim is, obviously, to increase GFR, but one must bear in mind that any agent that increases GFR will also increase  $RVO_2$  and *vice versa*. It is also important to acknowledge that, unlike in other organs where an increase in blood flow will improve oxygenation, an increase in RBF augments GFR and the filtered load of sodium, resulting in an increased  $RVO_2$ . Due to this flow dependency of  $RVO_2$ , renal oxygenation will vary little, as long as RBF and GFR change in parallel.

The major determinants of GFR are the renal perfusion pressure and the pre-/postglomerular resistance ratio. A renal vasodilator that acts preferentially on the preglomerular resistance vessels increases both RBF and glomerular hydrostatic pressure and, thereby, GFR. Two vasodilatory agents have this renal vasodilatory profile: atrial natriuretic peptide, when used for treatment of AKI (11), and levosimendan in postoperative patients and in patients with cardiorenal syndrome (Figure 4) (12,13). Vasodilators—such as the inodilators dopamine, dobutamine, and milrinone—act on both pre- and postglomerular resistance vessels and will cause a substantial increase in RBF, with no major change in GFR, because dilation of the postglomerular vessels will increase the “runoff” of blood from the glomerulus, with minor changes in upstream glomerular hydrostatic pressure (13–15). The vasoconstrictor vasopressin has been introduced

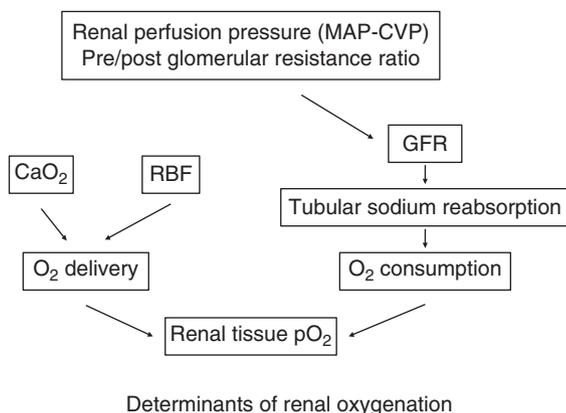
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**Figure 1.** | A schematic drawing of the determinants of renal oxygenation. Renal oxygen ( $O_2$ ) availability is determined by the balance between  $O_2$  delivery and  $O_2$  consumption. Renal oxygen delivery is dependent on renal blood flow (RBF) and arterial oxygen content ( $CaO_2$ ). RBF is determined by renal perfusion pressure and renal vascular resistance. In severe hypotension, the renal autoregulatory capacity is exhausted and RBF becomes pressure dependent. A low renal perfusion pressure (mean arterial pressure minus central venous pressure) during surgery or in the intensive care unit is directly correlated to an increase in serum creatinine. CVP, central venous pressure; MAP, mean arterial pressure.

in the clinical arena for treatment of vasodilatory shock, *e.g.*, in patients with septic shock (16). However, the use of vasopressin in shock treatment is a double-edged sword because, in postoperative patients, vasopressin increases GFR, and thereby  $RVO_2$ , by vasoconstriction of the postglomerular resistance vessels, which is accompanied by a reduction in



**Figure 2.** | Determinants of renal oxygen consumption ( $RVO_2$ ). Tubular sodium reabsorption accounts for 70%–80% of  $RVO_2$ . A continuous infusion of, *e.g.*, furosemide (0.5 mg/kg per hour), will decrease  $RVO_2$  by approximately 25%, and medullary tissue  $PO_2$  will increase. Tubular sodium reabsorption, in turn, is controlled by GFR. If GFR increases, tubular sodium load will increase and reabsorption will increase. Thus, GFR is a major determinant of  $RVO_2$ . GFR is determined by the renal perfusion pressure (MAP minus CVP) and the pre-/postglomerular resistance ratio. Atrial natriuretic peptide (ANP) at a dose of 50 ng/kg per minute increases GFR by 15% and thereby  $RVO_2$  by approximately 25%. In the treatment of AKI, the aim is to increase GFR, but this will also increase  $RVO_2$ .

RBF and  $RDO_2$ . Thus, vasopressin has the potential to induce a renal  $O_2$  supply/demand mismatch (17).

### Renal $O_2$ Extraction Is a Direct Measure of Renal Oxygenation

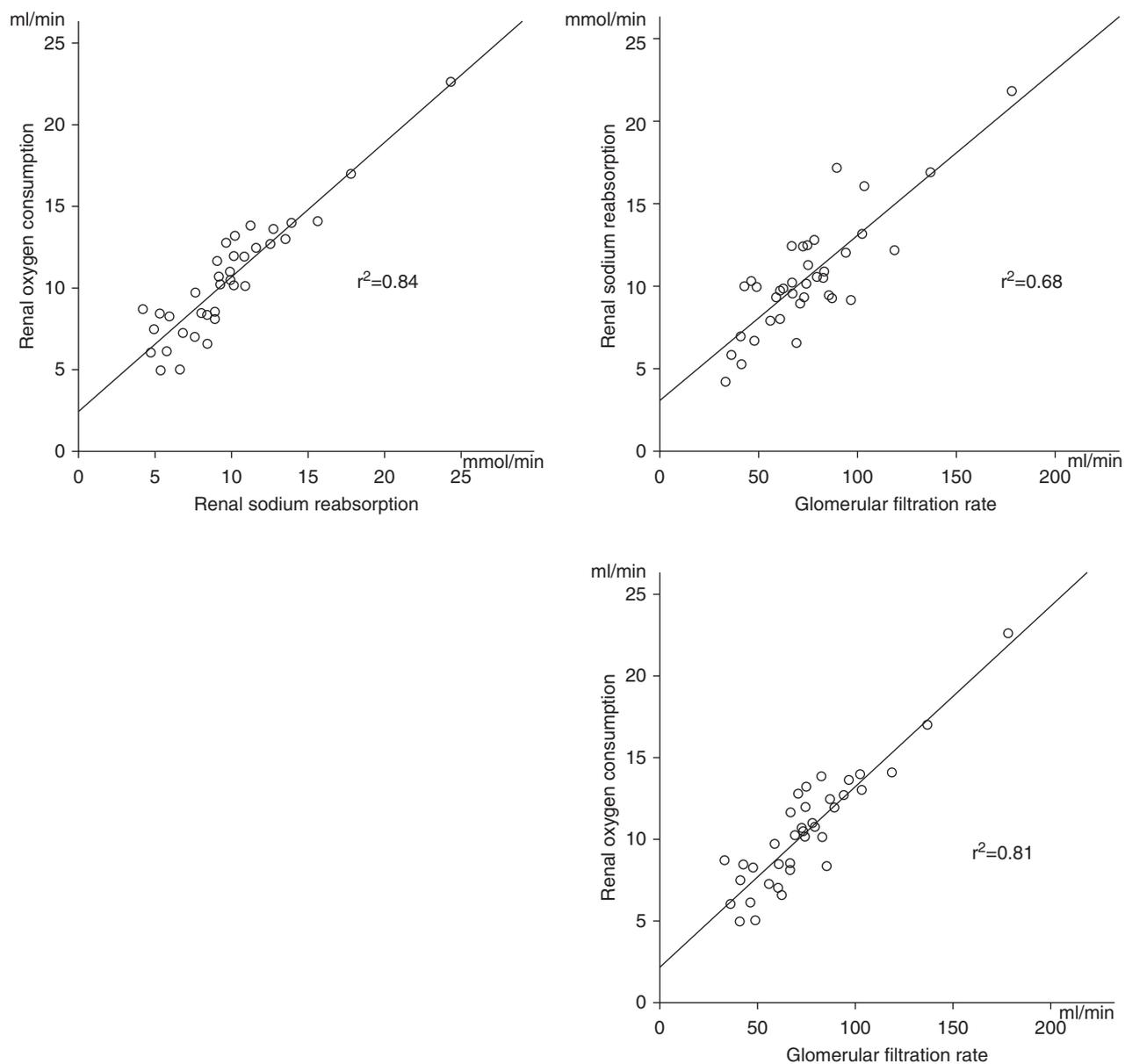
Renal oxygenation is defined as the ratio between  $RVO_2$  and  $RDO_2$ , *i.e.*, the renal  $O_2$  demand/supply relationship. It can easily be shown that this relationship is equivalent to the renal extraction of  $O_2$  ( $RO_2Ex$ ; calculated as  $[CaO_2 - \text{renal vein } O_2 \text{ content}] / CaO_2$ ), which requires measurements of arterial and renal vein  $O_2$  saturations. An increase in  $RO_2Ex$  means that  $RVO_2$  has increased in relation to  $RDO_2$  (*i.e.*, renal oxygenation has been impaired), and *vice versa*. When compared with other major organs,  $RVO_2$  is relatively high, second only to the heart. It has been shown in patients who are sedated and mechanically ventilated that  $RVO_2$  is two thirds (10 ml/min) that of myocardial  $O_2$  consumption (15 ml/min) (Table 1) (9). RBF, which accounts for approximately 20%–25% of cardiac output, is three times higher than myocardial blood flow in this group of patients. Therefore,  $RO_2Ex$  in the nonfailing kidney is low, 10%, as compared with, *e.g.*, the heart, in which  $O_2$  extraction is 55% (Table 1).

The relatively high RBF is directed preferentially to the cortex, which will optimize the filtration process and solute reabsorption. The proportion of the cortical flow that is conducted to the outer and inner medulla is only approximately 40% and 20%, respectively (18). The combination of low medullary perfusion, high  $O_2$  consumption of the medullary thick ascending limbs, and the countercurrent exchange of  $O_2$  within the vasa recta results in a poorly oxygenated outer medulla (7). The  $O_2$  availability is, therefore, low in the outer medulla, with a tissue  $PO_2$  of 10–20 mm Hg, as compared with 50 mm Hg in the cortex. Thus, because the outer medulla is already on the threshold of hypoxia under normal conditions, it is particularly sensitive to prolonged or intermittent episodes of low  $RDO_2$ , caused by hypoperfusion or hemodilution, as seen, *e.g.*, after major surgery (especially cardiac or vascular surgery) or severe heart failure (HF)—common causes of ischemic AKI.

### Renal Perfusion and Oxygenation in Clinical AKI

It has provocatively been stated that “acute renal failure is acute renal success” (19,20), because a reduction in GFR in AKI should lead to a reduction in the renal reabsorptive workload, thus preserving medullary oxygenation with a reduced risk of further aggravation of ischemia.

After surgery, in patients who are sedated, mechanically ventilated, without complications, and have no renal dysfunction,  $RVO_2$  is approximately 10–12 ml/min (see Table 1) (13); this value is slightly lower than that which has previously been reported in conscious, healthy volunteers. This corresponds to a mean of 0.82 ml  $O_2$ /mmol reabsorbed sodium, which is in line with findings from previous animal studies (21). In contrast, in high-risk cardiac surgery, complicated by AKI, patients consumed 1.9 ml  $O_2$ /mmol reabsorbed sodium. Thus, the net reabsorption of a certain amount of sodium consumed 2.4 times more  $O_2$  in the AKI group than in postoperative patients with no renal impairment (22). The correlation between GFR and  $RVO_2$  in

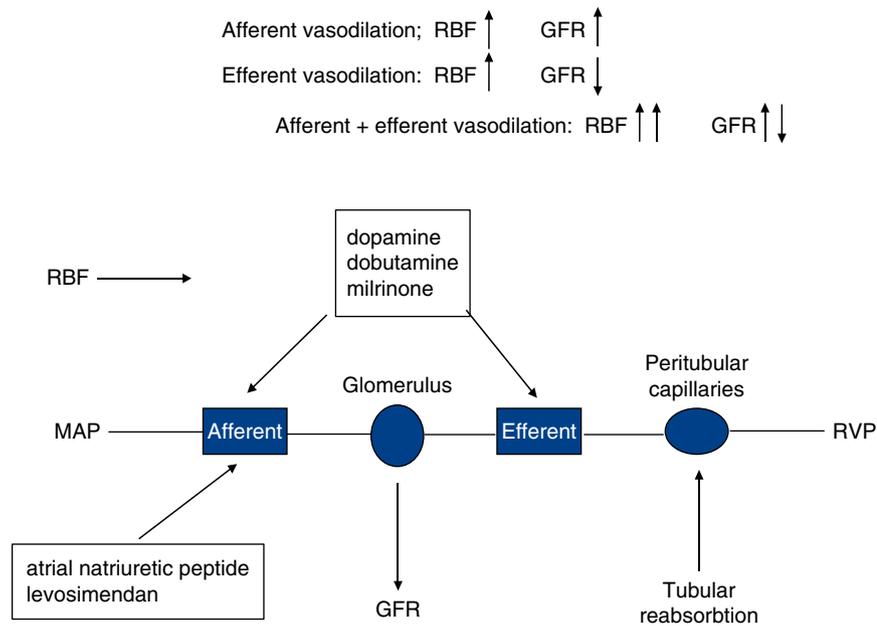


**Figure 3.** | The close relationships between renal sodium reabsorption, renal oxygen consumption, and GFR in postoperative patients undergoing uncomplicated cardiac surgery. Data obtained by permission from the authors (ref. 22).

patients with early AKI after cardiac surgery versus those undergoing uncomplicated surgery are shown in Figure 5. From this figure it can be seen that there is a close correlation between GFR and  $RVO_2$  in both groups of patients. According to the “acute renal failure is acute renal success” hypothesis (19,20), patients with AKI should fall on the lower part of the regression line of the control patients. However, the regression line of the patients with AKI is clearly shifted to the left, *i.e.*, at a certain level of GFR,  $RVO_2$  is higher (22). Thus, our findings do not support this hypothesis put forward by many investigators that acute renal failure is a renal success.

One can only speculate on the mechanism behind the increased  $O_2$  utilization for sodium transport in patients with AKI. A potential explanation could be ischemia-induced loss of epithelial-cell polarization and loss of

tight-junction integrity in AKI, as has been shown in experimental studies and after human renal transplantation (23,24). The tubular cells, thus, lose their ability to pump efficiently in a specific direction, from one compartment to another. Another explanation for the increased  $O_2$  costs for sodium reabsorption in clinical AKI may be diminished renal generation of nitric oxide (NO) due to endothelial damage and downregulation of endothelial NO synthase (25–27). NO has been shown to directly compete with  $O_2$  for mitochondrial respiration, suggesting a basal modulatory role for NO in  $O_2$  consumption (28). Laycock *et al.* (28) showed that blockade of NO synthase increased  $RVO_2$  in dogs, while reducing GFR and renal sodium reabsorption. Indeed, inhibition of NO synthesis more than doubled the  $RVO_2$ /renal sodium reabsorption ratio in that study.



**Figure 4. | The effects of various renal vasodilators on RBF and GFR.** Note that dopamine, dobutamine, and milrinone act on both afferent and efferent arterioles, which will increase RBF with no effects on GFR, whereas atrial natriuretic peptide and levosimendan act preferentially on the afferent arterioles, which will increase both RBF and GFR. MAP, mean arterial pressure; RVP, renal venous pressure.

The resetting of the relationship between GFR and  $RVO_2$  in clinical ischemic AKI (Figure 5) was accompanied by a severe impairment of the renal  $O_2$  demand/supply relationship, as demonstrated by the 70% higher  $RO_2Ex$ , which was caused by a pronounced vasoconstriction and renal hypoperfusion at a maintained  $RVO_2$ , compared with controls, despite a normalized cardiac output and MAP (Table 2) (13).

### Renal Perfusion and Oxygenation in Early Clinical Septic Shock

Severe sepsis and septic shock is a common cause of ICU admission and is responsible for AKI (septic AKI) in approximately 40%–50% of the critically ill population. Furthermore, septic AKI is associated with a high risk of early hospital mortality (29,30). There are divergent theories regarding the pathophysiology of septic AKI. Schrier and Wang (31) proposed, on the basis of experimental models, that the predominant early pathogenetic factor is renal vasoconstriction caused by reflex activation of renal sympathetic activity, the renin-angiotensin system, and increased levels of arginine vasopressin, which thus decreases both RBF and GFR and is induced by constriction of afferent

arterioles. In contrast, in a hyperdynamic, experimental sepsis model, Langenberg *et al.* (32) showed that the reduction in creatinine clearance was accompanied by an increase in RBF, and this was, therefore, explained by dilation of efferent arterioles.

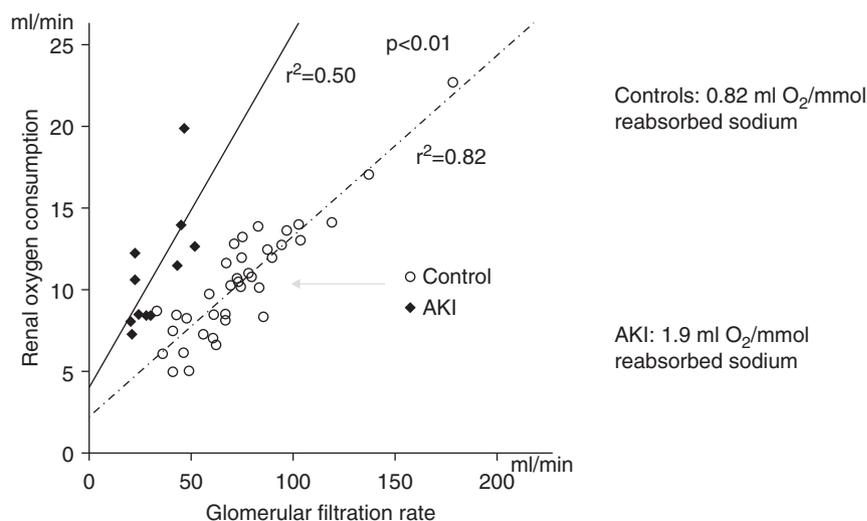
Recently, we measured renal perfusion, filtration, and oxygenation in patients within 24 hours after their arrival to the ICU due to early NE-dependent septic shock (33). Renal plasma flow was measured using the infusion-clearance technique for *p*-aminohippuric acid (PAH), corrected by renal extraction of PAH by a renal vein catheter. Filtration fraction was measured by renal extraction of chromium-51-labeled EDTA ( $^{51}Cr$ -EDTA). Renal oxygenation was estimated from  $RO_2Ex$  (Table 3). Patients undergoing uneventful major cardiac surgery served as a comparator group. We believe the comparison between these two groups is relevant because both groups were exposed to systemic inflammation. Furthermore, both groups were sedated and mechanically ventilated during the experimental procedure.

RBF and  $RDO_2$  were impaired, due to renal vasoconstriction and a redistribution of blood flow away from the kidneys, when compared with a comparator group (Table 3). This renal vasoconstriction could be explained by an

**Table 1. Renal and myocardial oxygen/demand supply relationship in postoperative patients who were mechanically ventilated**

Renal Variables	Kidney	Heart
Oxygen consumption (ml/min)	10	15
Blood flow (ml/min)	750	250
Oxygen extraction (%)	10	55

Data obtained by permission from the authors (refs. 10 and 14).



**Figure 5.** | The close correlation between GFR and RVO<sub>2</sub> in patients after uncomplicated cardiac surgery (controls, *n*=37) and in patients with postoperative AKI. Note the slope of the regression line is steeper in the AKI group. Thus, filtration and reabsorption of sodium consumes approximately 2.5 times more oxygen in the AKI group. Data obtained by permission from the authors (ref. 22).

increase, particularly, in the tone of the renal afferent arterioles, because renal filtration fraction (GFR/renal plasma flow) was not significantly different between the two groups, suggesting a balanced decrease in both GFR and RBF in the patients with septic shock. Such an increase in the tone of the afferent arterioles in sepsis has been demonstrated in endotoxemic animals (34). This redistribution of blood flow in septic shock impaired the renal O<sub>2</sub> supply/demand relationship, as evidenced by an increased RO<sub>2</sub>Ex. Thus, these results are not in line with data from previous studies on large animals, which showed that AKI in early septic shock is accompanied by renal vasodilation and an increase in RBF (32). The lower RDO<sub>2</sub> may explain the early signs of tubular dysfunction/injury seen in the septic group, which are expressed as a pathologic elevation of the tubular injury marker N-acetyl- $\beta$ -D-glucosaminidase (NAG).

### Effects of Cardiopulmonary Bypass on Renal Perfusion and Oxygenation

AKI is a prevalent complication after cardiac surgery with cardiopulmonary bypass (CPB). The incidence of post-cardiac surgery AKI ranges between 15% and 30%, depending on the complexity of the procedure (35,36). Dialysis-dependent

AKI, occurring in 2%–5% of patients who undergo cardiac surgery, carries a mortality of between 50% and 80% (37). Renal hypoperfusion and impaired RDO<sub>2</sub> have been considered important pathways in the development of post-cardiac surgery AKI (38,39). It has previously been shown that RBF correlates positively to MAP during hypothermic (28°C), non-pulsatile CPB, suggesting impaired autoregulation of RBF (40). A decreased RDO<sub>2</sub> may also be caused by hemodilution due to priming the CPB circuit with cellfree solution, usually a crystalloid. It has been shown that the degree of hemodilution (38,41) and a decreased systemic O<sub>2</sub> delivery (42) are independent risk factors for the development of postoperative AKI.

To increase our understanding of the renal effects of cardiac surgery with normothermic CPB, we measured RBF, RDO<sub>2</sub>, GFR, RVO<sub>2</sub>, and the renal O<sub>2</sub> supply/demand relationship (RO<sub>2</sub>Ex) before, during, and after open cardiac surgery using CPB (43). Despite a 33% increase in systemic perfusion flow rate compared with baseline cardiac output, CPB induced renal vasoconstriction, redistributing blood flow away from the kidneys, which, in combination with hemodilution, decreased RDO<sub>2</sub> by 20%, while GFR and RVO<sub>2</sub> were unchanged (Figure 6). Thus, RO<sub>2</sub>Ex increased by 40%–45%, indicating a renal O<sub>2</sub> supply/demand mismatch

**Table 2.** Renal perfusion, filtration, and oxygenation in clinical AKI after cardiac surgery

Systemic and Renal Variables	Control Group ( <i>n</i> =37)	AKI Group ( <i>n</i> =12)	<i>P</i> Value
Mean arterial pressure (mm Hg)	73.9±1.1	73.5±0.7	NS
Cardiac index (L/min per m <sup>2</sup> )	2.63±0.08	2.77±0.16	NS
Renal blood flow (ml/min)	758±40	477±54	<0.001
Renal vascular resistance (mm Hg/ml per min)	0.097±0.005	0.146±0.015	<0.01
GFR (ml/min)	74.7±4.7	32.3±3.6	<0.001
Sodium reabsorption (mmol/min)	9.7±0.7	4.0±0.4	<0.001
Renal oxygen consumption (ml/min)	10.4±0.6	11.0±1.1	NS
Renal oxygen extraction	0.097±0.004	0.163±0.009	<0.001

Values are means±SEM. Data obtained by permission from the authors (ref. 22).

**Table 3. The kidney in early clinical sepsis**

Systemic and Renal Variables	Comparator Group (postoperative patients; n=58)	Early Sepsis (n=8)	P Value
Mean arterial pressure (mm Hg)	73±7	76±2	NS
Cardiac index (L/min per m <sup>2</sup> )	2.8±0.5	3.3±0.6	NS
Renal blood flow (ml/min)	858±261	696±166	<0.05
Renal oxygen delivery (ml/min)	122±42	93±24	<0.05
Renal vascular resistance (mm Hg/ml per min)	0.082±0.023	0.098±0.023	<0.05
GFR (ml/min)	80±24	54±18	<0.01
RVO <sub>2</sub> (ml/min)	11.4±3.1	11.4±4.0	NS
Renal oxygen extraction (%)	9.7±2.7	12.4±3.9	<0.05
RVO <sub>2</sub> /sodium reabsorption (ml/mmol)	1.2±0.3	1.6±0.7	<0.05
Urinary NAG/creatinine	—	5.4±3.4 (<1.5)	—

Values are means±SD. RVO<sub>2</sub>, renal oxygen consumption; NAG, N-acetyl-β-D-glucosaminidase. Data obtained by permission from the authors (ref. 33).

during CPB. After weaning from CPB, renal oxygenation deteriorated further, because RO<sub>2</sub>Ex increased by 80% from baseline (Figure 7), due to hemodilution and an increase in RVO<sub>2</sub> (45% compared with baseline), accompanied by a peak sevenfold increase in the urinary NAG/creatinine ratio, indicating tubular injury. There was a positive correlation between the increase in RO<sub>2</sub>Ex and the urinary NAG/creatinine ratio, suggesting renal hypoxia may have a causative role in the release of the tubular injury marker. The increase in RVO<sub>2</sub> after CPB could be explained by a resetting of the relationship between renal sodium reabsorption and RVO<sub>2</sub>. Before CPB, a mean of 0.86 mmol O<sub>2</sub> was consumed per millimole of reabsorbed sodium. In contrast, after CPB, 1.31 mmol O<sub>2</sub>/mmol reabsorbed sodium was consumed. Thus, the net reabsorption of a certain amount of sodium consumed 52% more O<sub>2</sub> after CPB, as compared with before CPB. Such an increased O<sub>2</sub> utilization for tubular sodium transport has previously been described in patients with post-cardiac surgery AKI and most likely reflects hypoxia-induced tubular dysfunction (see above).

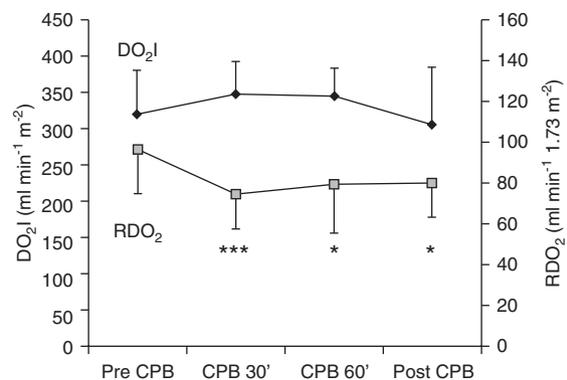
Theoretically, one way to improve renal oxygenation would be to perform CPB at a higher flow rate than the one traditionally used. This concept was tested by Lannemyr *et al.* (44), who studied the effects of varying CPB flow rates (2.4, 2.7, and 3.0 L/min per m<sup>2</sup>) on renal oxygenation in 17 patients with normal renal function undergoing cardiac surgery with normothermic CPB. At a flow rate of 2.7 and 3.0 L/min per m<sup>2</sup>, RO<sub>2</sub>Ex was 12% and 23% lower, respectively, compared with 2.4 L/min per m<sup>2</sup>. This corresponds to a 14% and 30% improvement, respectively, of the renal O<sub>2</sub> supply/demand relationship. One could, therefore, speculate that one way to protect the kidneys during CPB would be to use higher CPB flow rates than those conventionally used. Our group has recently launched a randomized trial evaluating the renal effects of a high (3.0 L/min per m<sup>2</sup>) versus a standard CPB flow rate (2.4 L/min per m<sup>2</sup>). The primary end points are RBF, RDO<sub>2</sub>, and tubular injury markers (ClinicalTrials.gov identifier, NCT04084301).

### Renal Perfusion and Oxygenation after Liver Transplantation

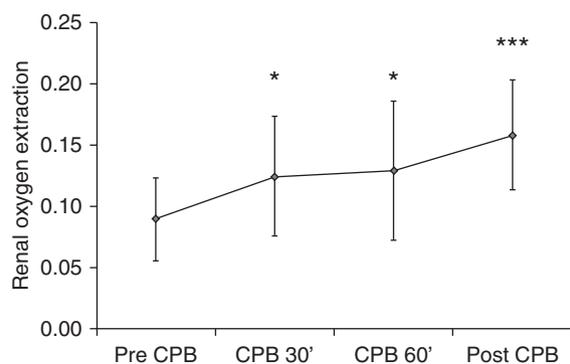
AKI is a common complication after liver transplantation, with a reported incidence of 10%–60% (45,46). Mortality

after liver transplantation is reported to be 45%–55% in patients developing AKI, compared with 2%–6% in patients not developing AKI (45). The etiology of AKI after liver transplantation is unknown, but is most likely multifactorial. Hypotension caused by intraoperative blood loss and postreperfusion syndrome (47) is presumably of importance. Furthermore, renal dysfunction may be present before transplantation, as seen in patients with hepatorenal syndrome. In patients with hepatorenal syndrome, a splanchnic vasodilation is seen. This vasodilation is accompanied by activation of the renin-angiotensin system and the sympathetic nervous system, resulting in increased renal vascular resistance. As a result, blood flow will be distributed away from the kidneys and, hence, the kidneys will receive a decreased O<sub>2</sub> delivery (48,49). This could be considered as a potential mechanism causing AKI after liver transplantation.

To gain more insight into the pathophysiologic mechanisms behind the development of AKI in liver transplanted patients, we studied renal hemodynamics, function, and



**Figure 6. | The effects of cardiopulmonary bypass (CPB) on systemic (DO<sub>2</sub>I) and renal (RDO<sub>2</sub>) oxygen delivery in patients undergoing cardiac surgery.** Note DO<sub>2</sub>I was well maintained whereas RDO<sub>2</sub> decreased on CPB (flow rate, 2.4–2.5 L/min per m<sup>2</sup>). The decrease in RDO<sub>2</sub> was caused by a decrease in arterial oxygen content, due to hemodilution, and renal vasoconstriction. Data obtained by permission from the authors (ref. 44).



**Figure 7. | The effects of CPB on renal oxygenation, *i.e.*, the renal oxygen demand/supply relationship, expressed as renal oxygen extraction.** Due to the decrease in renal oxygen delivery, even at 30 minutes after the start of CPB, renal oxygenation was impaired, as shown by an increase in renal oxygen extraction. Early after CPB (post CPB), renal oxygenation was further impaired due to a pronounced increase in renal oxygen consumption seen after CPB. Data obtained by permission from the authors (ref. 44). \* $P < 0.05$ ; \*\*\* $P < 0.001$ .

oxygenation early after liver transplantation in 12 patients who were mechanically ventilated and sedated (50). RBF was measured by the continuous retrograde renal vein thermodilution technique (51), filtration fraction was measured by renal extraction of  $^{51}\text{Cr-EDTA}$ , and renal oxygenation was estimated from  $\text{RO}_2\text{Ex}$ . Patients undergoing uneventful major cardiac surgery served as a comparator group. We believe the comparison between these two groups is relevant because both groups have been exposed to major surgery and both groups have had contact with material that is not endogenous, with a consequent systemic inflammation. Furthermore, both groups were sedated and mechanically ventilated during the experimental procedure, which occurred early after arrival in the ICU in both groups.

Cardiac output was considerably higher (65%), accompanied by a considerably lower systemic vascular resistance ( $-36\%$ ), in the liver transplanted patients as compared with the comparator group (Table 4). Despite this hyperdynamic circulation in the patients with liver transplants, RBF and  $\text{RDO}_2$  were only moderately elevated (15%). In other words, the ratio between RBF and cardiac output was almost 30% lower in the patients with liver transplants, suggesting a redistribution of RBF away from the kidneys. In the liver

transplant group, GFR decreased by 40% compared with the preoperative value. When compared with the comparator group, GFR and filtration fraction was 27% and 40% lower, respectively, in the liver transplant group. Serum creatinine increased by 41% and 48% from baseline on the first and second postoperative day in the liver transplant group, whereas serum creatinine decreased postoperatively in the comparator group. What is the mechanism behind this early reduction in GFR after liver transplantation? The physiologic control of GFR is mediated by the balance between the tone of the afferent and efferent arterioles. A decrease in GFR may be caused either by vasoconstriction of the afferent arterioles or a vasodilation of the efferent arterioles, which will be accompanied by a decrease or an increase in RBF, respectively. Thus, on the basis of our findings, we suggest that the decrease in GFR, together with the increased vasodilation and increased RBF after liver transplantation, is best explained by a preferential dilation of the efferent arterioles. Such a renal hemodynamic pattern has previously been described in animal models of hyperdynamic septic shock showing renal vasodilation and loss of GFR, which was, in turn, explained by efferent renal vasodilation (52,53).

$\text{RVO}_2$  and  $\text{RO}_2\text{Ex}$  were both higher in the liver transplant group (43% and 33%, respectively) when compared with the comparator group. The remarkably high  $\text{RVO}_2$  seen after liver transplantation could be explained by the production and release of reactive  $\text{O}_2$  species from the liver graft as a consequence of the ischemia/reperfusion injury (47). It has been shown that oxidative stress increases mitochondrial  $\text{O}_2$  consumption and reduces tubular epithelial sodium transport, both contributing to an increase in  $\text{RVO}_2$  (54).

Thus, after liver transplantation, there is an early decline in renal function despite hyperdynamic systemic circulation and renal vasodilation, which is most likely explained by an efferent arteriolar vasodilation. This is accompanied by an impaired renal oxygenation, because the pronounced elevation of  $\text{RVO}_2$  was not met by a proportional increase in  $\text{RDO}_2$ .

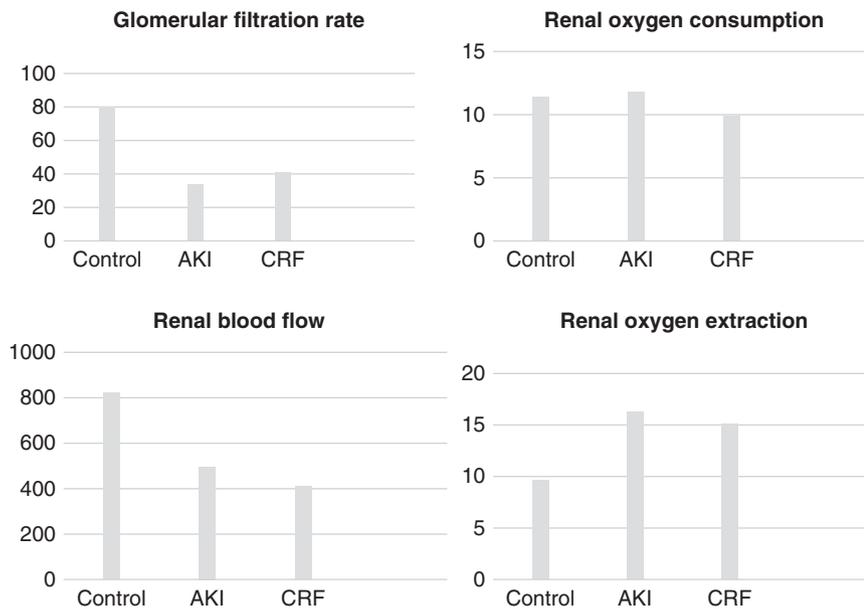
### Renal Perfusion and Oxygenation in Patients with Congestive HF and Chronic Renal Impairment

HF affects >26 million people worldwide and is a leading cause for hospitalization in Europe and the United States (55). Renal dysfunction caused by HF, also denoted as

**Table 4. The kidney in liver transplantation**

Systemic and Renal Variables	Comparator Group (postoperative patients; $n=58$ )	Liver Transplantation ( $n=12$ )	<i>P</i> Value
Mean arterial pressure (mm Hg)	74±9	74±2	NS
Cardiac index (L/min per $\text{m}^2$ )	2.6±0.5	4.3±1.0	<0.001
Renal blood flow (ml/min)	716±209	843±197	<0.05
Renal oxygen delivery (ml/min)	104±32	120±30	<0.05
Renal vascular resistance (mm Hg/ml per min)	0.100±0.03	0.085±0.02	0.05
GFR (ml/min)	71±23	51±30	<0.01
Renal oxygen consumption (ml/min)	10.0±3.2	14.4±4.8	<0.001
Renal oxygen extraction (%)	10.0±3.1	12.4±4.0	<0.05

Values are means±SD. Data obtained by permission from the authors (ref. 50).



**Figure 8.** | Compiled data on renal variables in patients undergoing cardiac surgery without (control) and with postoperative AKI, and from patients with chronic renal failure (CRF) secondary to congestive heart failure. Note that, in CRF, there is a pronounced reduction (–50%) in both RBF and GFR, suggesting a preferential increase in preglomerular vascular resistance. Despite the lower GFR, renal oxygen consumption is only marginally reduced. Thus, the pronounced reduction in renal oxygen delivery could not meet renal oxygen requirements, causing a chronic impairment of renal oxygenation in patients with CRF. Data obtained by permission from the authors (ref. 13).

cardiorenal syndrome, is independently associated with increased risk of hospitalization and cardiovascular death (56). Indeed, renal dysfunction is a stronger predictor of mortality than New York Heart Association functional class of left ventricular ejection fraction (56). However, data on renal hemodynamics, GFR, RVO<sub>2</sub>, and renal oxygenation in clinical HF are scarce, and the therapeutic options for treatment of cardiorenal syndrome are limited (57).

In a recent study, Lannemyr *et al.* (13) measured systemic and renal hemodynamics, GFR, RVO<sub>2</sub>, and renal oxygenation in 29 patients with chronic HF (left ventricular ejection fraction <40%) and impaired renal function (GFR <80 ml/min per 1.73 m<sup>2</sup>). A pulmonary artery catheter was used for measurements of systemic hemodynamics. The left renal vein was catheterized, and GFR and RBF were measured using the infusion-clearance technique for <sup>51</sup>Cr-EDTA and PAH (corrected for renal extraction of PAH), respectively.

When compared with a control group, with neither HF nor renal dysfunction (33), renal vascular resistance was 102% higher than in the comparator group, which could

explain the pronounced reduction in RBF (–52%), RDO<sub>2</sub> (–46%), and GFR (–48%) in these patients (Figure 8). The RBF/cardiac index ratio was only 18% in the patients with HF compared with 31% in the comparator group, suggesting a marked redistribution of RBF away from the kidneys. The lower RBF in these patients could be caused by an increased renal vascular resistance caused by, *e.g.*, increased renal sympathetic activity, activation of the renin-angiotensin-aldosterone system, and increased release of vasopressin, but also by increased central venous pressure (*i.e.*, increased renal venous back pressure). Filtration fraction was moderately elevated (17%) in the patients with HF when compared with the comparator group (14%), suggesting there is a preferential increase in preglomerular vascular resistance in patients with HF compared with controls.

Despite the much lower GFR, RVO<sub>2</sub> was only 22% lower than in the comparator group. RO<sub>2</sub>Ex was 15% in the patients with HF, a number considerably higher than in the comparator group (10%). In other words, the pronounced reduction in RDO<sub>2</sub> could not meet renal O<sub>2</sub> requirements, causing

**Table 5.** Renal oxygen delivery, function, and oxygenation in AKI, in early clinical sepsis, during and after cardiopulmonary bypass, after liver transplantation, and in chronic renal impairment

Renal Variables	AKI	Early Sepsis	CPB	Liver Transplantation	CKD
Renal oxygenation	Impaired	Impaired	Impaired	Impaired	Impaired
Renal oxygen delivery	Decreased	Decreased	Decreased	Increased	Decreased
GFR	Decreased	Decreased	Unchanged	Decreased	Decreased
RVO <sub>2</sub>	Unchanged	Unchanged	Increased (after CPB)	Increased	Unchanged
RVO <sub>2</sub> /sodium reabsorption	Increased	Increased	Increased (after CPB)	Increased	Not studied

CPB, cardiopulmonary bypass; RVO<sub>2</sub>, renal oxygen consumption.

a chronic impairment of renal oxygenation in the patients with HF. It has been suggested that renal hypoxia could be the common final pathway for progression to CKD (54), because chronic hypoxia induces oxidative stress, production of extracellular matrix, collagen deposition, vascular rarefaction, and interstitial fibrosis (54,58,59).

### Is It Possible To Measure Renal Oxygenation Noninvasively?

Impaired renal oxygenation measured by renal vein catheterization is associated with tubular injury and increased postoperative creatinine levels (50,60). However, invasive measurements may be technically challenging, and the method is not suitable for general use. Near-infrared spectroscopy is a noninvasive, optical technique that continuously measures the difference between oxygenated and deoxygenated hemoglobin within a regional tissue area, thus obtaining regional O<sub>2</sub> saturation (rSO<sub>2</sub>) (61). Although measurements of rSO<sub>2</sub> by the near-infrared spectroscopy technology for assessment of renal tissue oxygenation in pediatric patients (62,63) were found to be feasible, due to the proximity of the kidneys to the skin, the agreement with renal rSO<sub>2</sub> and the invasively measured renal vein O<sub>2</sub> saturation has not been determined in an adult population. In a study by Tholén *et al.* (64), it was shown that renal rSO<sub>2</sub> is correlated to, and predicts changes in, renal vein O<sub>2</sub> saturation, with a small bias and acceptable agreement. However, there was a drop-out rate of 25% because of a skin-to-kidney distance >4 cm, suggesting this technique for assessment of renal oxygenation is not suitable for all patients. There is a need for future studies to demonstrate that monitoring of renal rSO<sub>2</sub>, guiding interventions to prevent or treat a low renal rSO<sub>2</sub>, will improve renal outcome after cardiac surgery in suitable patients, before the technique is recommended for general use.

### Conclusions

In this review, we have presented data on renal hemodynamics, GFR, RVO<sub>2</sub>, and renal oxygenation from various groups of patients with renal dysfunction, such as in patients with AKI after cardiac surgery, in those with early sepsis, patients undergoing cardiac surgery with CPB, patients undergoing liver transplantation, and in patients with chronic renal failure. Irrespective of the cause of renal failure, for these groups of patients, the common denominator is that renal oxygenation is impaired (Table 5). This was caused by a lower RDO<sub>2</sub> in all groups, except for patients undergoing liver transplantation, where impaired renal oxygenation was caused by a pronounced increase in RVO<sub>2</sub>. Finally, in all groups, there was an increased O<sub>2</sub> utilization for tubular sodium transport, which most likely reflects hypoxia-induced tubular dysfunction.

### Disclosures

L. Lannemyr reports receiving honoraria from Orion Pharma, and having consultancy agreements with XVIVO Perfusion AB. All remaining authors have nothing to disclose.

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### Author Contributions

G. Bragadottir, L. Lannemyr, B. Redfors, and J. Skytte were responsible for methodology; S.-E. Ricksten wrote the original draft; and all authors reviewed and edited the manuscript.

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