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

Sven-Erik Ricksten, Gudrun Bragadottir, Lukas Lannemyr, Bengt Redfors, and Jenny Skytte

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.

Determinants of Renal Oxygen Delivery and Renal Oxygen Consumption
Renal oxygen (O₂) availability is determined by the balance between renal O₂ delivery (RDO₂) and renal O₂ consumption (RVO₂). RDO₂, in turn, is dependent on renal blood flow (RBF) and arterial O₂ content (CaO₂) (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 tissue PO₂ (7), indicating an improved renal oxygenation. However, these solutions improved cardiac output and RBF, but none of the fluids increased RDO₂, due to hemodilution (5).

Active tubular sodium reabsorption accounts for 70%–80% of RVO₂ (6). If you administer furosemide (bolus of 0.5 mg/kg followed by 0.5 mg/kg per hour) to postoperative patients, RVO₂ will decrease by approximately 25%, and experimental studies have shown that furosemide causes an increase in medullary tissue PO₂ (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 RVO₂ (Figure 3). Thus, GFR is an important determinant of RVO₂. 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 23% increase in RVO₂ (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 RVO₂ 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 RVO₂. Due to this flow dependency of RVO₂, 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...
Renal oxygenation is defined as the ratio between RVO\textsubscript{2} and RDO\textsubscript{2}; i.e., the renal O\textsubscript{2} demand/supply relationship. It can easily be shown that this relationship is equivalent to the renal extraction of O\textsubscript{2} (RO\textsubscript{2}Ex; calculated as \([\text{CaO}_2 - \text{renal vein O}_2 \text{ content}/\text{CaO}_2]\), which requires measurements of arterial and renal vein O\textsubscript{2} saturations. An increase in RO\textsubscript{2}Ex means that RVO\textsubscript{2} has increased in relation to RDO\textsubscript{2} (i.e., renal oxygenation has been impaired), and \textit{vice versa}. When compared with other major organs, RVO\textsubscript{2} is relatively high, second only to the heart. It has been shown in patients who are sedated and mechanically ventilated that RVO\textsubscript{2} is two thirds (10 ml/min) that of myocardial O\textsubscript{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\textsubscript{2}Ex in the nonfailing kidney is low, 10\%, as compared with, e.g., the heart, in which O\textsubscript{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\textsubscript{2} consumption of the medullary thick ascending limbs, and the countercurrent exchange of O\textsubscript{2} within the vasa recta results in a poorly oxygenated outer medulla (7). The O\textsubscript{2} availability is, therefore, low in the outer medulla, with a tissue PO\textsubscript{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\textsubscript{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\textsubscript{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\textsubscript{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\textsubscript{2}/mmol reabsorbed sodium. Thus, the net reabsorption of a certain amount of sodium consumed 2.4 times more O\textsubscript{2} in the AKI group than in postoperative patients with no renal impairment (22). The correlation between GFR and RVO\textsubscript{2} in
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 RVO₂ 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, RVO₂ 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 O₂ 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 O₂ 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 O₂ for mitochondrial respiration, suggesting a basal modulatory role for NO in O₂ consumption (28). Laycock et al. (28) showed that blockade of NO synthase increased RVO₂ in dogs, while reducing GFR and renal sodium reabsorption. Indeed, inhibition of NO synthesis more than doubled the RVO₂/renal sodium reabsorption ratio in that study.

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).
The resetting of the relationship between GFR and RVO2 in clinical ischemic AKI (Figure 5) was accompanied by a severe impairment of the renal O2 demand/supply relationship, as demonstrated by the 70% higher RO2Ex, which was caused by a pronounced vasoconstriction and renal hypoperfusion at a maintained RVO2, compared with controls, despite a normalized cardiac output and MAP (Table 2) (13).

Renal Perfuson 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 (51Cr-EDTA). Renal oxygenation was estimated from RO2Ex (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 RDO2 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 increased arteriolar resistance caused by an increased renin-angiotensin system activity and arginine vasopressin levels, and an increased sympathetic activity, as observed in critically ill patients with AKI.

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

<table>
<thead>
<tr>
<th>Renal Variables</th>
<th>Kidney</th>
<th>Heart</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxygen consumption (ml/min)</td>
<td>10</td>
<td>15</td>
</tr>
<tr>
<td>Blood flow (ml/min)</td>
<td>750</td>
<td>250</td>
</tr>
<tr>
<td>Oxygen extraction (%)</td>
<td>10</td>
<td>55</td>
</tr>
</tbody>
</table>

Data obtained by permission from the authors (refs. 10 and 14).
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 O2 supply/demand relationship, as evidenced by an increased RO2Ex. 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 RDO2 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-β-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 RDO2 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 RDO2 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 O2 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, RDO2, GFR, RVO2, and the renal O2 supply/demand relationship (RO2Ex) 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 RDO2 by 20%, while GFR and RVO2 were unchanged (Figure 6). Thus, RO2Ex increased by 40%–45%, indicating a renal O2 supply/demand mismatch.

<p>| Table 2. Renal perfusion, filtration, and oxygenation in clinical AKI after cardiac surgery |</p>
<table>
<thead>
<tr>
<th>Systemic and Renal Variables</th>
<th>Control Group (n=37)</th>
<th>AKI Group (n=12)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>73.9±1.1</td>
<td>73.5±0.7</td>
<td>NS</td>
</tr>
<tr>
<td>Cardiac index (L/min per m²)</td>
<td>2.63±0.08</td>
<td>2.77±0.16</td>
<td>NS</td>
</tr>
<tr>
<td>Renal blood flow (ml/min)</td>
<td>758±40</td>
<td>477±54</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Renal vascular resistance (mm Hg/ml per min)</td>
<td>0.097±0.005</td>
<td>0.146±0.015</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>GFR (ml/min)</td>
<td>74.7±4.7</td>
<td>32.3±3.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sodium reabsorption (mmol/min)</td>
<td>9.7±0.7</td>
<td>4.0±0.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Renal oxygen consumption (ml/min)</td>
<td>10.4±0.6</td>
<td>11.0±1.1</td>
<td>NS</td>
</tr>
<tr>
<td>Renal oxygen extraction</td>
<td>0.097±0.004</td>
<td>0.163±0.009</td>
<td>&lt;0.001</td>
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Values are means±SEM. Data obtained by permission from the authors (ref. 22).
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 O2 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...
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 $^{51}$Cr-EDTA, and renal oxygenation was estimated from RO2Ex. 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 mechanical ventilation 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 RDO2 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).

RVO2 and RO2Ex were both higher in the liver transplant group (43% and 33%, respectively) when compared with the comparator group. The remarkably high RVO2 seen after liver transplantation could be explained by the production and release of reactive O2 species from the liver graft as a consequence of the ischemia/reperfusion injury (47). It has been shown that oxidative stress increases mitochondrial O2 consumption and reduces tubular epithelial sodium transport, both contributing to an increase in RVO2 (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 RVO2 was not met by a proportional increase in RDO2.

**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.

### 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>
<thead>
<tr>
<th>Table 4. The kidney in liver transplantation</th>
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<tr>
<td><strong>Systemic and Renal Variables</strong></td>
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<tr>
<td>-----------------------------------</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
</tr>
<tr>
<td>Cardiac index (L/min per m²)</td>
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<tr>
<td>Renal blood flow (ml/min)</td>
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<tr>
<td>Renal oxygen delivery (ml/min)</td>
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<tr>
<td>Renal vascular resistance (mm Hg/ml per min)</td>
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<tr>
<td>GFR (ml/min)</td>
</tr>
<tr>
<td>Renal oxygen consumption (ml/min)</td>
</tr>
<tr>
<td>Renal oxygen extraction (%)</td>
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</table>

Values are means±SD. Data obtained by permission from the authors (ref. 50).
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, RVO2, 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, RVO2, 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 m²). 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 51Cr-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%), RDO2 (−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, RVO2 was only 22% lower than in the comparator group. RO2Ex was 15% in the patients with HF, a number considerably higher than in the comparator group (10%). In other words, the pronounced reduction in RDO2 could not meet renal O2 requirements, causing

![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).](https://example.com/figure8)

<table>
<thead>
<tr>
<th>Renal Variables</th>
<th>AKI</th>
<th>Early Sepsis</th>
<th>CPB</th>
<th>Liver Transplantation</th>
<th>CKD</th>
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<td>Impaired</td>
<td>Impaired</td>
<td>Impaired</td>
<td>Impaired</td>
</tr>
<tr>
<td>Renal oxygen delivery</td>
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<td>Decreased</td>
<td>Increased</td>
<td>Decreased</td>
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<tr>
<td>GFR</td>
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<td>Decreased</td>
<td>Unchanged</td>
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</tr>
<tr>
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<td>Unchanged</td>
<td>Increased (after CPB)</td>
<td>Increased (after CPB)</td>
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<td>Increased</td>
<td>Increased</td>
<td>Not studied</td>
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</tbody>
</table>

CPB, cardiopulmonary bypass; RVO2, 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 O2 saturation (rSO2) (61). Although measurements of rSO2 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 rSO2 and the invasively measured renal vein O2 saturation has not been determined in an adult population. In a study by Tholén et al. (64), it was shown that renal rSO2 is correlated to, and predicts changes in, renal vein O2 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 rSO2, guiding interventions to prevent or treat a low renal rSO2, 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, RVO2, 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 RDO2 in all groups, except for patients undergoing liver transplantation, where impaired renal oxygenation was caused by a pronounced increase in RVO2. Finally, in all groups, there was an increased O2 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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